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FROM THE EDITOR

In this issue of SGIM *Forum*, our lead associate editors, Tanu Pandey and Farah Kaiksow, engaged a diverse group of writers to develop a varied perspective on the social, political, and medical controversies of medical marijuana. It is beyond the scope of *Forum* to provide a definitive technical review of the pharmacologic properties of marijuana, and for that we refer you to the well-referenced bibliographies that accompany each article. Additional material is available online at: http://www.sgim.org/publications/sgim-forum.

The opinions of the authors do not represent the position of the Society of General Internal Medicine or of the editors of *Forum* and should not be interpreted as medical recommendations or used to make medical decisions for patient care. The publication of this material should not be interpreted as an endorsement of marijuana use by any of the involved parties.

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—Karen R. Horowitz,* Forum *Editor

INTRODUCTION

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Medical Marijuana: Myth or Magic?

Tanu S. Pandey, MD, MPH

Dr. Pandey is a member of the SGIM Forum *editorial board and can be reached at tanumd@gmail.com.*

Marijuana use in the United States is a controversial subject that polarizes health care providers and patients alike and has garnered immense attention recently for many reasons—legalization, decriminalization, medical uses, and abuse as a "gateway" drug. Irrespective of personal opinions, it remains a mystery to many primary care physicians and should be addressed with scientific evidence (as well as subjective experience). In this themed edition of SGIM *Forum*, we have convened a group of pioneers and experts to discuss current medical and societal aspects of marijuana.

Marijuana, a mixture of the dried leaves and flowers from the plant *Cannabis sativa*, is the most common illegal recreational drug in the world. It can be smoked, eaten, brewed as tea, or administered in tablet or liquid form. Globally, 3.5% of the population has used marijuana at least once. It has conventionally been labeled as a schedule 1 drug in the United States, indicating that it is a drug of addiction with no known medicinal value, on par with heroin and cocaine. In the last couple of decades, however, attention has shifted to its medicinal properties. Proponents of medical marijuana claim that the premise of labeling it as an addictive drug is based on *insufficient* evidence regarding its pharmacological properties, that the prevalence of addiction to marijuana is less than 10%, and that—as opposed to alcohol, cocaine, or heroin—neither intoxication nor withdrawal is life threatening.[1]

Of all the different cannabis compounds, tetrahydrocannbinol (THC) is the psychoactive ingredient that causes altered mood; impairment in

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Arresting People for Marijuana Use is Bad for Their Health

Aaron D. Fox, MD, MS

Dr. Fox is assistant professor of medicine at Albert Einstein College of Medicine/Montefiore Medical Center in New York City.

Medical marijuana dispensaries will open in New York City in 2016, creating an opportunity for practitioners to prescribe marijuana after completing a four-hour online course and paying a $249 fee. My primary care practice in the Bronx includes patients with painful HIV-related neuropathies and other conditions that could benefit from medical marijuana. As an addiction medicine specialist, however, I also worry about the small but significant proportion—approximately 9%—of marijuana users who will develop dependence. I also worry whether changes in societal perceptions about the drug's safety will increase the likelihood of marijuana use by adolescents, whose developing brains are particularly susceptible to the drug's negative effects.

Our incomplete understanding of the safety and efficacy of medical marijuana makes the assessment of risks and benefits for patient care challenging. The many varieties of marijuana that are available make dosing unpredictable because of differences in potency among the different products. Federal law still prohibits marijuana use. Lastly, I as a physician am uncomfortable endorsing a smoked product as healthful. (The New York law only pertains to non-smokable forms of marijuana.) Many have argued that, at a policy level, medical marijuana is just a backdoor way of allowing recreational marijuana use, in which case the medical community should not be involved. However, the legal prohibition of marijuana has had negative health consequences, so perhaps decriminalization is a policy position that physicians should consider.

I remain unconvinced that (smoked) marijuana will be useful as medication, but I am also quite certain that the "War on Drugs" has been a disaster for the health and wellness of my patients and their communities. Years of attacks on the drug's supply chains have done little to suppress demand for marijuana in the United States, which has continued to increase over the past decade. The United States incarcerates more of its citizens than any other country in the world. As violent crime has decreased over the past two decades, drug-related arrests have increased, mostly driven by arrests related to marijuana. (This burden predominately falls upon communities of color.)

The mass incarceration of people of color is not just a political or criminal justice issue—it is also a health issue. As medical providers have increasingly been challenged to contextualize biomedical models of illness with an understanding of the social determinants of health, it has become clear that the collateral consequences of incarceration are far reaching. The violence and chronic stress of incarceration have been the-

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Research and Leadership in Cutting-edge Issues

Marshall H. Chin, MD, MPH

…we've realized that academic publication is just the start of the dissemination process. Research gives us a platform to teach about broader issues in disparities.

One of SGIM's six strategic priorities is leadership in cutting-edge issues. I'd like to reflect on the role of research in leading improvements in patient care and outcomes. I'll use as an example the field I know best: achieving health equity through research on health disparities and quality of care. First, I'll take the perspective of a researcher and then a user of research. I'll end by discussing what SGIM is doing in the research innovation space.

My wife, son, and I like road trip vacations. We pile our gear into our Subaru Outback and head out in any direction from Chicago. We've gotten into the habit of listening to books on tape during these long car rides and try to pick books that have something to do with our trip. On our winter 2015 driving trip to Michigan's ski slopes (Yes, Michigan has mountains!), we listened to *Whistling Vivaldi: How Stereotypes Affect Us and What We Can Do*, a book written by the eminent social psychologist Claude Steele, PhD. At the time, I was struggling to write an essay about how movement advocacy could integrate with personal relationships to help end health care disparities, and so my colleague Monica Vela recommended that I read this book.

Written for the lay public, *Whistling Vivaldi* is the story of how Dr. Steele and his colleagues around the world developed the concept of stereotype threat, which elucidates how our social identities impact our behavior and performance. The book unfolds like a good mystery novel, describing how each research study supplied a piece of the puzzle and left intriguing clues for the next set of studies. This incremental approach to research is the classic paradigm. When we write a research paper, we honor and acknowledge the prior work that informs our study and explain how our project advances the field. One of the great joys of SGIM meetings is interacting with colleagues, sharing our latest discoveries, and discussing future directions for our fields of study.

I have published a couple of articles in *JGIM* that attempted to synthesize the existing knowledge about disparities and guide our next steps. One article presents a roadmap to reduce disparities, and the other describes how to create the business case to achieve health equity. SGIM investigators stand out as the leaders in this field. In those two articles, I cited the SGIM Disparities Task Force that developed recommendations for health disparities curricula (Wally Smith, Joe Betancourt, Matt Wynia, Jada Bussey-Jones, Valerie Stone, Christopher Phillips, Alicia Fernandez, Liz Jacobs, Jacqueline Bowles); Tom Sequist and John Ayanian for an important article demonstrating that cultural competency training and clinical performance data stratified by race are helpful but not sufficient to improve clinical outcomes; Elbert Huang and David Meltzer for disparity cost studies; Monica Peek for interventions that integrate health care system and community to reduce diabetes disparities; Michael McWilliams and Bruce Landon for research on accountable care organizations and primary care; and John Goodson for research on primary care physician reimbursement. There are many more SGIM investigators I could have cited. These examples demonstrate the breadth of SGIM research relevant for achieving health equity, the importance of each piece of evidence we create, and the collective power of the work of so many fine investigators.

Over the past 15 years, I have participated in multi-stakeholder national committees in which I was primarily a user of research. As a researcher, these experiences have taught me the importance of communicating my findings clearly by putting myself in the shoes of stakeholders with different interests. It is critical to think carefully about the policy implications of our research and the most effective framing of papers.

For the past three years I have been a member of the Centers for Disease Control and Prevention's Community Preventive Services Task Force, the public health equivalent of

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The Medical Cannabis Evaluation

Jean Talleyrand, MD, and John S. Abrams, PhD

Dr. Talleyrand is the vice chairman and chief medical officer and Dr. Abrams is the chairman and chief scientific officer of the non-profit research organization Clinical Endocannabinoid System Consortium (CESC).

I first began recommending cannabis regularly in 2004. That year, a federal District Court decision (Conant vs. Walters) upheld an appeal allowing physicians the freedom to recommend cannabis as medical treatment.[1] We could recommend cannabis use to patients as long as we performed a good faith evaluation and didn't "aid and abet" in the still-illegal procurement of cannabis. An occasional patient would request cannabis to relieve pain, nausea, or the side effects of prescription medication. The process was not foreign to me. Proposition 215, the Compassionate Use Act, had made medical cannabis recommendations a possibility as early as 1996. The occasional request was a refreshing change to patient desires for opiates or benzodiazepenes. To prescribe cannabis, our hospital had a form letter that simply required my signature and date.

I attended medical school at Boston University (class of '95). We were taught very little about cannabis. The curriculum did not allow for an in-depth understanding of the clinical and pharmacological effects of botanical therapies. When we approached the topic in 1992, my second-year pharmacology professor described cannabis simply as a Drug Enforcement Agency (DEA)-classified schedule I substance with a high potential for abuse and no medicinal uses. There was no mention of the recent discovery of endocannabinoids, their relationship to phytocannabinoids or the CB1 and CB2 receptors, nor the therapeutic significance of those discoveries. The many levels of missing information struck a chord of concern with me. However, there was too much to learn and not much time for debate.

Table 1. Cannabis-based Medical Products

Flower (Plant)
Oil, Extracted
Capsules
Tinctures
Creams/Lotions
Patches

In 1996, California was the first state to allow its patients to use cannabis as medicine. The epicenter of this movement was the San Francisco Bay Area. At the time, I was completing a residency program at the San Francisco General Hospital. Our community had seen many young people die of AIDS. As a physician, requests for compassionate care at the end of life were a regular occurrence. HIV-positive and AIDS patients would confide to the more open-minded doctors that they used cannabis primarily to ameliorate prescription medicine side effects—sometimes for pain or to increase appetite—and often to relieve the stress and anxiety associated with living with a terminal diagnosis.

In 1997, UCSF professor Donald Abrams, MD, received funding from the National Institute on Drug Abuse (NIDA) to conduct clinical trials of the short-term safety of cannabinoids in HIV infection.[2] Then, as is still true today, NIDA typically funded studies that elucidated the abuse potential of drugs. In this instance, NIDA's concerns focused on whether cannabis use would alter the concentration and effectiveness of anti-retroviral drugs through drug interactions. Dr. Abrams' study countered these concerns by concluding that there was no evidence that smoked and oral cannabinoids were unsafe for people with HIV infection with respect to HIV RNA levels, CD4+ and CD8+ cell counts, or protease inhibitor levels over a 21-day treatment. His research also suggested that some cannabis users suffering from HIV wasting syndrome seemed to improve. Dr. Abrams' clinical trial, among others, provided the earliest evidence of cannabis' medical and therapeutic potential.

Dr. Abrams' clinical trial, among others, provided the earliest evidence of cannabis' medical and therapeutic potential.

After the Conant vs. Walters decision, I established MediCann, a group practice that focused on evaluating cannabis-using patients. The demand was nearly instantaneous, and our practice grew to a network of offices throughout California. Many physicians observed the symptom relief and beneficial effects of cannabis and became advocates for its therapeutic use. Almost 12 years later, MediCann has evaluated more than 200,000 patients. MediCann physicians learned about the efficacy of cannabis from this experience, and some eventually went on to create their own medical cannabis evaluation practices.

Ninety-five percent of patients who present to our practice have already used cannabis. They have experimented with the plant and observed a benefit. They describe this benefit in detail and present with a practiced treatment plan. Unlike most pharmaceutical treatments, compliance in this situation is not an

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Cannabis Implicated in a Case of Hypersensitivity Pneumonitis

Sarah Shangraw, MS3 (presenter); Caroline McCulley, MD (discussant, in italic); and Ruben Halperin, MD (discussant, in italic)

Ms. Shangraw is a third-year medical student at Oregon Health & Science University School of Medicine; Dr. McCulley is with the Internal Medicine Residency Program at Providence Portland Medical Center; and Dr. Halperin is faculty in the Division of General Internal Medicine at Providence Portland Medical Center.

A previously healthy 40-year-old man presents with acute onset dyspnea. He has had four similar episodes over the past two months. These episodes begin with 30 minutes of dyspnea followed by an hour of diaphoresis, high fevers, and full-body myalgias. These symptoms resolve spontaneously, though the patient is fatigued for several hours afterward. The patient denies other symptoms as well as tobacco or IV drug use. Household members have not experienced similar symptoms. He has not traveled outside the Northwestern United States or internationally. He is febrile at 100.9°F, with pulse 123 bpm, BP 166/106, respiratory rate 26, and SpO2 90%. The physical exam is unremarkable except for an inspiratory bibasilar "squeak and pop" in his lungs and intermittent nonproductive cough.

Our diagnostic approach to a patient with episodic dyspnea begins with a broad differential of both cardiac and pulmonary etiologies. From a cardiac standpoint, we need to rule out acute coronary syndrome, acute decompensated heart failure, and flash pulmonary edema. Pulmonary conditions that can cause episodic dyspnea include reactive airway disease, recurrent pulmonary emboli (PE), pneumonitis, and (less likely) pneumonia. Panic attacks are also in the differential, although this would be a diagnosis of exclusion. Finally, thinking specifically about this otherwise healthy young patient, the episodic nature of acute dyspnea, fevers, and myalgias also raises the possibility of a "zebra" diagnosis, the hereditary autoinflammatory disease Familial Mediterranean Fever. An initial evaluation would include a chest X-ray, CBC, troponin, EKG, ABG, and a D-dimer or CT pulmonary angiogram depending on the pre-test probability of a PE.

The patient previously presented to his primary care physician with these symptoms. Previous chest X-rays obtained after two prior episodes do not demonstrate any acute cardiopulmonary process. He was treated with guaifenesin then erythromycin for presumed bronchitis and atypical pneumonia, respectively. These treatments gave modest but short-lived improvement. Given the recurrent nature of these episodes, previously negative chest X-rays, unexplained hypoxemia, and the fact that a pneumonitis was on our differential, we obtain a CT chest that reveals numerous small (3 to 8 mm) ground-glass granulomatous opacities scattered throughout the lungs and some para-aortic lymphadenopathy.

The granulomas and the clinical symptoms of systemic inflammatory response syndrome (SIRS) help narrow our differential. Mycobacterial infections, fungal infections, and recurrent aspiration pneumonia can cause this pattern of lung disease. Non-infectious etiologies include hypersensitivity pneumonitis, sarcoidosis, granulomatosis with polyangiitis, talc granulomatosis, and hot-tub lung. This patient denied any travel to regions endemic to coccidiomycosis or histoplasmosis and likewise denied risk factors for TB. With a more refined differential, one needs to return to the patient and ask specific questions related to recurrent exposures that may cause hypersensitivity pneumonitis, including work exposures, pets, unusual activities, and systemic symptoms (i.e. rashes, nose bleeds, arthralgias, weight loss) associated with the vasculitides.

We obtain a CBC, CMP, UA, CK, TSH, ANA/ANCA, and D-dimer; all are within normal limits except for a slight eosinophilia to 8%. An infectious workup, including a respiratory viral panel and procalcitonin, is similarly benign.

With infectious and autoimmune pathology excluded, hypersensitivity pneumonitis is now at the top of our differential. This is typically caused by contaminated water, aerosols used in agriculture, birds, or rodents. Our patient does not have any traditional exposures on initial questioning.

On more detailed exploration of the hours preceding the episodes, he reports episodically vaping hash oil. He had purchased a new strain of marijuana and a water-based filter shortly before his first episode. He typically smokes marijuana daily with his asymptomatic wife.

We can now diagnose this patient with cannabis-induced hypersensitivity pneumonitis based on the detailed history, episodic nature, negative infectious and autoimmune work-up, and findings on CT imaging. Hypersensitivity pneumonitis occurs when an antigen elicits an inflammatory response within the lungs. In this case, contaminants in marijuana or related smoking devices can introduce antigens directly into the lungs. The patient in our case had recently started smoking from a water-based filter, which was possibly contaminated and causing his symptoms. Typical contaminants are Aspergillus *and other fungi, mycobacterium found in the soil and water, and agricultural chemicals like insecticides. The diagnosis is typically made by the detailed history, CT imaging, and biopsy if non-invasive testing is inconclusive. The mainstay of treatment is removal of the offending agent and a course of systemic corticosteroids.*

This patient was prescribed a short course of steroids and asked to abstain from smoking marijuana.

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Medical Marijuana and the Opioid Epidemic

Marcus A. Bachhuber, MD

Dr. Bachhuber is assistant profesor of medicine at Albert Einstein College of Medicine/Montefiore Medical Center in New York City.

On November 1, 2011, the Centers for Disease Control and Prevention declared overdoses involving prescription opioid analgesics to be an "epidemic." In the decades prior, the concerted efforts of federal agencies, accreditation organizations, specialty societies, state medical boards, and the pharmaceutical industry had driven a massive increase in opioid analgesic prescribing for pain.[1-5] By 2007, the United States consumed 83% of the world's oxycodone and more than 99% of the world's hydrocodone.[6] In parallel to this increase in supply, morbidity and mortality have escalated. Between 2002 and 2012, the number of addiction treatment admissions involving opioid analgesics more than tripled.[7] By 2013, overdoses involving opioid analgesics had become a leading cause of injury and accidental death in the United States, killing 16,235 individuals in that year alone.[8]

While concerns over the safety of opioid analgesics have been mounting, access to medical marijuana has been exploding across the United States. As of January 2015, 23 states and the District of Columbia had legalized marijuana for medical use. While not all states specify chronic pain as a qualifying indication, in states that do, this is by far the most common condition reported. In Michigan, for example, 93.7% of people who registered with the medical marijuana program cited severe and chronic pain.[9]

Despite their increasingly common intersection, the relationship between medical marijuana and opioid analgesic use is not well understood. In surveys from medical marijuana states, a majority of people attending medical marijuana assessment clinics or dispensaries report substituting marijuana for prescription drugs.[10-13] Furthermore, many attendees report interest in alternatives to chronic opioid analgesic therapy.[13] In one clinical study, patients taking opioid analgesics chronically had decreased pain with the addition of vaporized marijuana.[14] However, patients in the treatment arms of two clinical trials (i.e. smoked marijuana for HIV neuropathy and a cannabinoid spray for cancer pain) did not have decreased opioid analgesic use, though the studies were not specifically designed or powered to detect a difference in this outcome.[15,16] Furthermore, the role of marijuana in potentially causing the use of other illicit drugs remains hotly debated.

Given these potential connections between medical marijuana and opioid analgesic use, I co-authored a study in 2014 seeking to estimate the impact of medical marijuana laws on fatal overdoses involving opioid analgesics.[17] Using death certificate data from the Centers for Disease Control and Prevention from 1999 to 2010, the study team and I found that the presence of a medical marijuana law was associated with a 24.8% lower rate of fatal overdoses involving opioid analgesics relative to pre-law trends and trends in non-law states. A recent follow-up study incorporating more years of data and using more complex methods found similar results but reported this association to be limited only to states allowing dispensaries (versus those allowing only home cultivation).[18]

While the results of these studies are compelling, they should be interpreted in light of certain limitations. As we and others have noted, these are ecological studies at the state level, and inferences about individual outcomes or the precise mechanisms underlying our findings cannot be made. Fundamentally, they also rely on observational data, with the attendant risks of confounding.

While policy research can guide policymakers, clinical research is needed to guide clinicians. The overwhelming consensus among health care providers is that more research is needed on the safety and efficacy of medical marijuana. In particular, information on the safety and efficacy of marijuana relative to opioid analgesics would be useful. While many have noted that chronic marijuana use has a host of risks, these are risks of marijuana relative to using nothing. Perhaps a more relevant question for many patients is: What are the risks of marijuana relative to the risks of opioid analgesics? While many aspects of this question are uncertain, few would dispute that the overdose fatality risk of marijuana by itself is essentially nil.

Given federal and state limitations, many have found such clinical research to be exceedingly challenging. But this may be changing. Colorado's statute legalizing marijuana included a provision to fund medical marijuana research. Currently approved projects include a comparative effectiveness trial of marijuana versus oxycodone for pain—an incredibly timely study.

In view of the overwhelming support for medical marijuana among the American public, it seems likely that the number of states legalizing it will continue to increase in the coming years. Therefore, providers will be increasingly asked to make difficult clinical decisions about medical marijuana, either by itself or in combination with other medications. Some have advocated that refusing to recommend medical marijuana is the "safest" route, but what if receiving medical marijuana prevents a patient from being prescribed opioid analgesics chronically? Or what if medical marijuana allows a patient to lower the dose or discontinue opioid analgesics altogether?

Many health care providers remain skeptical about marijuana as medicine. While it is too early to know if marijuana will ultimately fulfill this role, we can all agree on the clear need to expand the number of

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A Cardiologist Becomes a Cannabinologist

Joe D. Goldstrich, MD, FACC

Dr. Goldstrich is medical director at Zelda Therapeutics.

It was 2012, and I had recently turned 74. I had retired from a satisfying career in preventive cardiology, nutrition, integrative medicine, and clinical lipidology. I was bored and depressed. Still fit and able to think clearly, what was I to do with the rest of my life? All my medical licenses except for California and Missouri were now inactive.

I saw an ad for a job in Pomona, California, to work in a medical marijuana clinic. I wasn't exactly sure what this entailed, so I investigated and found that it was a job providing recommendations for the use of medical marijuana, which had been legal in California since 1996. I thought this might provide relief from my doldrums and malaise, so I signed on. I saw about 25 patients a day—mostly young men with purported low back pain who were looking for a legal way to smoke marijuana. There were a few interesting patients who told me how cannabis relieved their migraine headaches,[1] Crohn's disease,[2] low back pain, [3] glaucoma,[4] multiple sclerosis spasms,[5] and insomnia.[6] One woman was looking for cannabis to relieve the side effects of chemotherapy.[7]

Some, but not all the applicants, brought medical records documenting their diagnosis.

I lasted six days because providing the recommendation without supporting medical records, a requirement of the California medical board, was too stressful for me. I was fortunate enough to find other interesting work as the medical director of a nutritional supplement company. I remembered those interesting medical marijuana patients and continued to follow the medical marijuana job opportunities in California.

In late 2013, I saw an ad for a medical marijuana clinic in Oakland, California. This clinic was part of a group of clinics belonging to Jean Talleyrand, MD, founder and president of MediCann. Dr. Talleyrand advertised that his clinics were "highly professional, ethical …founded and run by physicians." I flew to California and spent three days seeing patients with Dr. Talleyrand. I was impressed with his professionalism and extensive experience with Medi-Cann in providing medical marijuana recommendations to more than 300,000 California patients. I signed on again, and over the next nine months interviewed close to 3,000 patients seeking a recommendation for medical cannabis.[8]

During this period of time, my list of medical conditions for which patients found cannabis useful grew to include attention deficit hyperactivity disorder,[9] asthma,[10] anxiety, [11] seizures,[12] depression,[13] post-traumatic stress disorder,[14] erectile dysfunction,[15] and cancer.[16] (Regarding cancer, cannabis not only provided relief from chemotherapy but also appeared to treat the tumor—more on this later.)

It gradually dawned on me that while I had been providing the legal mechanism for patients to use medical cannabis to treat their medical condition, I had little to no first-hand knowledge or experience in guiding patients on using cannabis to treat their conditions. It was then that I decided to become a *bona fide* cannabinologist.

More to learn.

In 2014, I joined the Society of Cannabis Clinicians,[17] a professional society devoted to the exploration and investigation of medical and scientific applications of cannabis medicine. Shortly after joining, Mara Gordon, a layperson who had been making cannabis oil for medical purposes, spoke to the society. She had been advising patients on how to use cannabis medicinally for several years.

In September 2014, while attending a continuing medical education program on medical cannabis in Denver, Colorado, I heard Mara present again. Mara was supplying medical cannabis oil to really sick people—people with cancer, people who were deemed incurable after exhausting traditional medical therapy. She had supplied medical cannabis to hundreds of patients over several years and had more experience in advising patients on the use of medical cannabis than anyone else that I had encountered. I asked Mara to teach me what she knew about the use of medical cannabis—to let me learn from her experience. This was not an easy thing for a physician to do, but I was willing to do whatever was needed to gain this knowledge. That was the spring of 2015.

Most of the patients I have consulted on have had cancer. I have followed the tumor markers and radiologic scans. Some tumors have shrunk and even disappeared, some have stopped growing, and some have continued to grow unabated. Cannabis is not an oncologic panacea, but I've seen enough success to remain cautiously optimistic about the role of cannabis in the treatment of cancer.

In a nutshell, here are some of the most important things I have learned about the use of cannabis in the treatment of cancer:

1. Cannabis may work synergistically with chemotherapy[18] and radiation.[19]
2. Cannabis may induce autophagy and subsequent apoptosis resulting in programmed cancer cell death.[20]
3. Tumor ID-1 gene expression facilitates cancer cell growth, survival, and metastases.[21]

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ESSAY: PART II

Practical Issues in Medical Cannabis Use: A Mother and Scientist Weighs in on the Issues Facing Medical Cannabis Use and the Future of Research

Catherine Jacobson, PhD

Dr. Jacobson is the director of clinical research at Tilray, a federally licensed producer of medical cannabis in Canada.

The political and health controversies surrounding medical cannabis have exploded over the last three years. This has been due in large part to the discovery that it may benefit children with severe treatment-resistant epilepsy—a debilitating brain disease with no effective treatment.

My son has a severe form of epilepsy. Three years ago another parent told me that cannabis was alleviating the severity of his child's seizures. I searched the Pubmed database and found a reasonable number of studies[1-3] supporting anti-seizure effects of one specific cannabinoid, Cannabidiol (CBD). CBD is a non-psychoactive cannabinoid; that is, it does not induce a "high." Though there were no definitive data on dose, side effects, or efficacy, there was enough promise in the studies I reviewed to encourage me toward further investigation into whether CBD might lessen the frequency and severity of my son's seizures. Uncontrolled epilepsy in children is a cruel disease that can lead to significant cognitive, motor, and behavioral delays. Neither the patient nor the caretaker knows when the next seizure will strike or how much damage it will cause. In fact, sudden unexplained death in epilepsy (SUDEP) is responsible for 34% of all sudden deaths in children.[4] The percentage of patients with epilepsy who have untreatable seizures has remained the same (at about 30% to 35%) since the approval of phenytoin in 1953, despite the development of 40 second- and third-generation anti-seizure drugs over the last 60 years. I believe that any therapy with the potential to reduce seizure frequency or severity in this difficult-to-treat and constantly suffering population must be explored.

I searched medical cannabis dispensaries in San Francisco, where I live, for CBD. As the parent of a child with a serious brain disease, I suddenly found myself consulting "bud-tenders" who had no medical training for advice on how to transform raw cannabis, which contains hundreds of cannabinoids and terpenes, into an appropriate medication for my son. I was not alone. In every state in which medical cannabis was legal, other parents were doing the same thing. I decided to survey these parents to find out how they were solving what seemed to me an insurmountable problem. How were they deciding what to give their children? How did they calculate dosage? How did they administer the cannabis? The results of this survey were published in late 2013 in *Epilepsy and Behavior*.[5] My motivation for publishing the results of the survey was not to establish proof of efficacy. Indeed, establishing efficacy is impossible with a survey, and the reasons for this are clearly explained in the paper. Instead, my goal was to focus the attention of the medical community—both clinicians and researchers—on the experience of these parents in order to prompt further research into the safety, tolerability, and efficacy of specific cannabinoids in the treatment of epilepsy.

The survey results were astonishing. Parents reported incredible benefits to their children. Their willingness to experiment with preparations of cannabinoids obtained from unknown sources without medical guidance was disturbing, yet understandable, given the severity of this disease. It attests to the desperation a parent feels in the face of watching one's child slowly deteriorate. Importantly, however, it also attests to the lack of support these families received from their physicians and the researchers in the community. Support might have come in the form of following the child medically, with routine blood work to document effects on organ function, dangerous drug-drug interactions, and serious adverse events. Documentation of data from a large enough number of patients over the past two years could have provided some insight that would inform future treatment of pediatric epilepsy patients with cannabinoids. For these data to be meaningful, however, the chemical content of the cannabis that the children are ingesting must be defined. There is enormous variability in the cannabinoid content of artisanal preparations of medical cannabis. Trying to decipher the effects of an undefined preparation is tantamount to trying to decipher the effects of a handful of drugs taken together, without knowing which drugs they are or in what amount they are given. To collect interpretable data, cannabinoid content of the preparations being administered must be known.

For many frustrating months I attempted to find a reliable and safe source of CBD. I could not. Available samples were only provided in small artisanal batches and were not reproducible. They were often inaccurately labeled. What bud-tenders were calling CBD was always a mixture of many components of the plant, including the psychoactive cannabinoid, tetrahydrocannabinol (THC). The preparations also contained contaminants such as heavy metals, solvents, and pesticides—facts we discovered when we tested these preparations at medical cannabis testing facilities.

At the end of that discouraging search, we desperately wanted a preparation that met Food and Drug Administration (FDA) requirements for safety, would be supplied reliably, and could be administered in a clinical setting with oversight by our pediatric epileptologist. Together with another family, we approached the only pharma company we could find working in the cannabinoid field, GW

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OPINION

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orized to lead to acceleration in the aging process. Exposure to infectious diseases may be more common in correctional facilities than in the community. Security practices, such as solitary confinement, can have deleterious mental health effects, especially for adolescents and individuals with pre-existing mental health conditions. Criminal justice involvement can lead to legal restrictions on housing, public benefits, students loans, voting rights, and access to employment. At our community health center in the South Bronx, more than half of surveyed patients reported that they or a family member had been arrested in the past, and many respondents believed that this experience directly impacted their health.

As the co-director of the Bronx Transitions Clinic (BTC), which provides a medical home to individuals with criminal justice involvement, I often see patients who have been harmed more by laws regulating marijuana than by the drug itself. In my primary care practice, it is rare for me to see a healthy 22-year-old man for a check-up, but at the BTC we often get referrals to see drug court clients who have been sentenced to drug treatment. I clearly remember a young African-American man who had been working as a commercial driver, was expecting his first child with his domestic partner, and was then arrested for marijuana possession. He was mandated to participate in an outpatient drug treatment program, which he dutifully attended, but because of the time commitment necessary he lost his job. When I assessed him for medical or mental health needs that may not have been met at the drug treatment program, I didn't think he met criteria for cannabis use disorder. He had maintained a job and healthy social relationships. Not surprisingly, when threatened with jail time, he was able to stop using marijuana. Still, I doubt that he required drug treatment. When I asked him if he would start smoking again when his period of criminal justice supervision was over—also not surprisingly—he stated that he would. To me, this "treatment" seemed futile.

In the United States, our urge to punish often becomes irrational. With millions of American who actually have substance use disorders lacking access to effective treatment, I question the wisdom in directing limited resources toward non-dependent individuals who use marijuana recreationally. I also question the wisdom in taking away a man's ability to provide for his family in the name of justice. Four states and the District of Columbia have already legalized recreational marijuana use, demonstrating that many believe the harms of marijuana use do not justify prohibition. Possession of small amounts of marijuana has been decriminalized in New York City since 1977, yet thousands continue to be arrested for "possession of marijuana in public view," which often happens when people are stopped and told by officers to empty their pockets. Because these arrests are disproportionately targeted toward communities of color, the urge to punish seems to be less about the fear of marijuana and more about structural racism, which is also harmful for health.

Medical providers usually avoid debates that appear to be political or outside our realm of expertise. I, however, feel compelled to advocate for the health and wellness of my patients. In Portugal in 2001, all drugs were decriminalized, and a robust system of treatment and social support was targeted to individuals with substance use disorders. This effort was spearheaded by a family physician, João Goulão, and was followed by an overall reduction in substance use. Certainly, Portugal is a much smaller and less diverse country than the United States, and we cannot be certain that their experience with decriminalization can be replicated here. I believe, however, that the voices of physicians highlighting the health-related harms of the "War on Drugs" and advocating for a system that emphasizes treatment and support over punishment need to be part of the debate.

Ultimately, if well-designed randomized controlled trials demonstrate the safety and efficacy of marijuana for common medical conditions, I am certain that I will learn to prescribe marijuana like any other therapeutic modality. For now, though, it's hard for me to see marijuana as a medication. Like alcohol, it is a substance that is consumed recreationally and probably can be consumed responsibly. But unlike alcohol, its legal status confers health risks that may exceed the actual risks of consumption. ***SGIM***

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Pharma, which is based in the United Kingdom. We asked if they would be willing to produce a pure CBD medication for our children that met FDA standards for safety. To our amazement, they agreed and found an FDA mechanism by which our physician could administer CBD legally through our hospital's pharmacy. The FDA's Expanded Access (or Compassionate Use) Program was established to allow patients access to potentially beneficial investigational drugs in the case of "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning of the patient" and for which there are no effective treatment options.[6] Obtaining the investigational drug via this mechanism required an enormous amount of work. First, our physician had to get FDA and institutional approval of the protocol. Second, DEA approval for importing and storing a schedule 1 substance was required. Six months

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movement, thinking, and problem solving; and hallucinations and paranoia. Cannabidiol (CBD) is believed to have medicinal properties. These include neuroprotective, anxiolytic, anti-convulsant, anti-inflammatory, and sedative effects. It has been suggested that a form of cannabis with a higher proportion of CBD and low amounts of THC can be beneficial in several debilitating conditions for which traditional medications prove ineffective, although many find it challenging to promote a drug that traditionally has had only recreational uses. The current medical literature regarding the potential medicinal applications for this drug is inadequate and scientifically weak. However, case reports and case series have been described that are compelling.

Acknowledging that research on marijuana has been difficult due to regulatory limitations, here are a few conditions for which medical marijuana may be of benefit when traditional treatments have been ineffective:

1. *Multiple sclerosis (MS).* There is definite evidence that marijuana reduces spasticity in multiple sclerosis and spasm-related pain (attributed to its anti-inflammatory properties) as shown in 12 trials with 1,600 patients.[2] Urinary bladder symptoms, depression, constipation, insomnia, fecal incontinence, and defecation urgency have also been relieved. The American National MS Society supports patients who are interested in exploring this option. Marijuana does not reduce tremors, neuropathic pain, or disease progression and may elevate the risk for cognitive impairment. An oral spray (Sativex) is available for prescription use.
2. *Chronic pain syndromes*. This is the most common use of medical marijuana. Evidence from six small clinical trials (325 patients)[2] suggests that it can be used with negligible side effects or addiction in labor pain, migraines, arthritis, cancer pain, pain from spasticity, endometriosis, and fibromyalgia. After robust review of existing literature, the Institute of Medicine (IOM) has deemed that marijuana in any form can cause mild to moderate pain relief on par with codeine.
3. *Cachexia/wasting syndrome*. This is usually seen in patients with AIDS, cancer, or advanced dementia whose poor appetite results in weight loss and failure to thrive. Several small clinical trials have demonstrated that marijuana in inhaled or oral form stimulates appetite, arrests weight loss, causes weight gain, and reduces nausea more than placebo in patients with AIDS, cancer, or advanced dementia.[3] These effects were found to be long term. It is usually well tolerated and has few side effects. Based on this moderate evidence for marijuana, the Food and Drug Administration (FDA) has approved the use of dronabinol (i.e. a synthetic form of cannabis, trade name Marinol) for use in AIDS patients with weight loss.
4. *Severe nausea and vomiting*. Dronabinol and nabilone are synthetic forms of cannabis used for treatment of intractable chemotherapy-related nausea and vomiting.[3] Dronabinol is FDA approved for this indication. According to the American Society of Clinical Oncology, however, it should not be a first-line treatment.
5. *Amyotrophic lateral sclerosis (ALS).* Cannabis can relieve muscle spasm and pain, improve breathing through relaxation of bronchial muscles, reduce drooling by inhibiting saliva, stimulate appetite and sleep, and reduce depression.[4] It improves speech, swallowing, and sexual dysfunction. Cannabis may slow the progression of ALS but can aggravate the already-compromised respiratory system and cause death by respiratory failure. It is legally available for use in ALS in six states. The ALS Association supports further research related to the use of cannabis for ALS but also issues a cautious approach to the use of marijuana as a drug of choice based on current evidence.
6. *Crohn's disease (CD).* Due to its anti-inflammatory properties, patients with Crohn's disease report a reduction in symptoms with marijuana as proven in one clinical trial.[5] Crohn's disease is one of the few diseases for which a human clinical trial has been conducted with cannabis. In this study, subjects were given inhaled marijuana twice daily for eight weeks. The trial concluded that cannabis can resolve symptoms of pain and nausea, improve appetite and sleep, have minimal side effects, and be steroid sparing. Unfortunately, the effects are short term, with all symptoms returning after two weeks.
7. *Seizure disorder.* Twenty percent of adult patients with epilepsy in the United States smoke marijuana and report reduction in seizures. Childhood intractable seizure syndromes like Dravet syndrome may respond to marijuana dramatically.[6] Large clinical trials are needed to conclusively demonstrate its anti-convulsant efficacy, and several are ongoing. Anecdotal reports, as seen in the Cable News Network "Weed" documentaries by Dr. Sanjay Gupta, are impressive. The well-known product Charlotte's Web has a waiting list of almost 10,000.
8. *Glaucoma*. Smoking marijuana reduces pressure within the eyes, but this effect is of short duration, and no clinical trials have been conducted. Side effects include sedation, dry mouth, dizziness, depression, confusion, and weight gain. The American Glaucoma Society position statement on the use of marijuana for glaucoma is that

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"although marijuana can lower the IOP, its side effects and short duration of action, coupled with a lack of evidence that its use alters the course of glaucoma, preclude recommending this drug in any form for the treatment of glaucoma at the present time."

9. *Post-traumatic stress disorder (PTSD).* Many patients with PTSD smoke marijuana to improve their sleep, appetite, and depression. A single study showed reduction in nightmares in PTSD patients. Reconsolidation is a process in which latent memories persist by being repeatedly reawakened. If reconsolidation is blocked, then there is a weakening of the original memory. Research suggests that one of the cannabinoid chemicals may block negative memories or fear associated with psychological trauma, a process called reconsolidation blockage.
10. *Movement disorders and dementia.* Marijuana may ameliorate a few symptoms in Parkinson's, Huntington's, and Alzheimer's disease patients. No large clinical trials have been reported, though several are currently ongoing with Sativex spray.

Regardless of one's personal beliefs, it is clear that the safety as well as the medical applications for marijuana will continue to be a hot topic for years to come. It is therefore critical that health care providers enhance their knowledge about marijuana with an open mind.

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4. Cannabidiol (CBD), a non-psychoactive cannabinoid, expresses antitumor activity[22] in part through inhibition and down regulation of ID-1 expression.[23]

How can this information be used to formulate a therapeutic protocol to treat patients?

Many people envision the medical cannabis patient as someone who sits around the house smoking a joint all day long. That's not usually the case. Smoking might be an effective way to prevent a migraine headache or deal with a flare-up of chronic pain, but for most chronic diseases a concentrated form of cannabis is necessary and is best delivered by the transmucosal route. Accurate laboratory testing of the cannabis material is mandatory. This testing would include not only the percentage of the cannabinoids present in the material (i.e. THC, CBD) but also the absence of pesticides and toxic solvents and the presence of the full cannabinoid and terpene profile so as to take advantage of the entourage effect.[24]

Once the percentage of the cannabinoids are known, a prescription can be formulated in terms of milligrams of THC and/or CBD. Typical prescriptions for cancer patients will contain from 50 to 300 mg per day of THC and, depending on the status of the ID-1 gene for their particular tumor, from 50 to 300 mg per day of CBD. Specific strains, over and above their THC and CBD content, are chosen for their secondary effects (i.e. wakefulness, appetite stimulation, sleep). Most patients are seeking to avoid the psychoactivity associated with THC, and for that reason it is of paramount importance to start with extremely low doses (i.e. 1 to 5 mg) of THC and build up slowly, taking advantage of the known tolerance that develops with continued THC use. CBD, having little psychoactivity, can usually be advanced more quickly.

That's what I have learned so far. My experience convinces me that cannabis should be removed from its schedule 1 status so placebo controlled, double-blind studies can be carried out. Only then will we realize the full potential of this remarkable medicine.

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the US Preventive Services Task Force. The task force performs systematic literature reviews, and thus its work is dependent on the rigorous research studies that form the basis for its reviews and recommendations. A few years ago I chaired the subcommittee that wrote the translation research chapter for the national diabetes research strategic plan, a subcommittee that included star SGIM diabetes researchers Ron Ackermann, Monica Peek, and Tom Sequist. The literature was crucial for defining the existing knowledge base, identifying research voids, and ultimately creating requests for applications for the National Institutes of Health's efforts in diabetes translation research. Similarly, I have seen how organizations such as the Robert Wood Johnson Foundation, Merck Foundation, America's Essential Hospitals, and The Joint Commission establish their equity agenda. The existing research literature is crucial for understanding where we are and where we might go.

Research evidence is particularly important for multi-stakeholder committees that have many perspectives and interests. The research base forms the facts upon which policies are based. For example, I have been a member of the National Quality Forum's (NQF) committees. NQF is a non-profit organization that brings together diverse stakeholders to make recommendations about the clinical performance measures to be used in payers' quality assessment and value-based purchasing programs, and it advises on how to improve quality of care and outcomes. Not surprisingly, NQF's technical expert panels, such as the one on risk adjustment for sociodemographic factors in performance measurement, tend to have evidence-based discussions very similar to academic meetings. Other NQF committees with more general charges and broader representation (e.g. health care organizations, payers, consumer groups, unions, specialty societies, and academia), such as the ones that recommend specific clinical performance measures to the Centers for Medicare and Medicaid Services.

Research plays a key role in educating the lay public about disparities. Researchers used to think their responsibilities had been fulfilled once they published their papers in academic journals and presented their findings at scientific meetings. Increasingly, we've realized that academic publication is just the start of the dissemination process. Research gives us a platform to teach about broader issues in disparities. Media interviews, whether on one's own work or the research of others, give us important opportunities to educate the public about equity issues and make recommendations for reform. Similarly, panel discussions at academic and community meetings provide wonderful opportunities to reach important stakeholders. Two of my Chicago colleagues, Vinny Arora and Monica Peek, are particularly gifted communicators who are seamless in their transition between the academic and media worlds. They have the uncanny ability to explain anything to anybody in understandable terms and use multiple venues for disseminating their work, including social media, Twitter, blogs, and community events. (Monica is featured in the January 25, 2016, issue of *Time* magazine—with David Bowie on the front cover!)

It is critical that we educate policymakers about potential reforms to reduce disparities. At the annual SGIM Hill Day in Washington, DC, advocacy for research funding is usually one of the priority issues. Examples of outstanding research that has improved patient outcomes are gold. One of the leaders of the Friends of AHRQ (Agency for Healthcare Research and Quality) coalition that fought for continued funding of AHRQ recently told me that SGIM's advocacy was critical for AHRQ's survival in the most recent budget cycle. Your examples of important research were vital in making the case for AHRQ.

So what is SGIM doing to support research and leadership at the cutting edge? Our core activities remain the annual national and regional meetings, which provide important opportunities for members to interact, learn, and disseminate research findings. The 2016 annual meeting is focused on the cutting-edge topic of population health and aims to give members the knowledge and skills necessary to be at the forefront of this critical emerging field. In the future, SGIM plans to offer multi-year career development programs. Some topics (e.g. research methodology) will be specific to investigators. Other potential programs, including leadership development, media training, and writing workshops, will be of interest to all.

SGIM is a leader in cutting-edge issues. Our research strength is one of the primary reasons we have been a leader in health care reform and improving clinical outcomes. As a society, we will continue to build on this legacy. I hope you will continue with us on this journey to strengthen general internal medicine and improve health care for all. SGIM

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issue. The physician's role focuses on observing the course of illness and educating the patient on the best use of medical cannabis. The understanding of best use comes through anecdotal cases shared among patients and practicing cannabis-recommending physicians. What is conspicuous in its absence is a clearly defined dose in mg per kg of delta-9-tetrahydrocannibinol (THC), cannabidiol (CBD), or the other cannabinoids in the plant. Typically, a physician advises patients to initiate treatment with low doses and titrate up to relieve symptoms. Larger doses can have unpleasant side effects including somnolence, anxiety, or paranoia; however, no one has died from an overdose of cannabis alone. Toxicology studies have been inconclusive and may suggest a high LD50 for this drug.

The problem in determining appropriate dosage has other considerations. Many patients mistakenly titrate their dose to the psychoactive "high" rather than symptom relief. New users may reject cannabis, as they suffer either no effect or unwanted side effects from inappropriate doses. As a result, a community of scientists, clinicians, and cannabis-industry experts has formed a nonprofit research group called the Clinical Endocannabinoid System Consortium (CESC). This is where I first met and teamed up with John Abrams, PhD, a biochemist who has had a successful career specializing in immunology. Our first program, The Dosing Project, aims to determine appropriate symptom-relieving doses. We believe that by incorporating analytical laboratory data for phytocannabinoid concentrations in specific medicinal cannabis products voluntarily selected for use by participating subjects we can determine statistically significant weight-based dosing regimens. In this initial proof-of-concept study, subjects will self-report clinical outcomes for a narrow range of indications. There are many patients who successfully use cannabis in a consistent manner. An observational study like The Dosing Project is expected to provide clinically useful information.

As with most medical visits, the physician begins the medical cannabis evaluation with a history of the presenting medical condition and a physical exam. Subjective and objective measures of the current symptoms should be charted. The clinical record becomes even more valuable in documenting a course of illness and determining what medicinal trials should be attempted. Together, physician and patient are discovering the effect of cannabis as it is being used rather than expecting predetermined results. A good medical cannabis evaluation evolves into a discussion of cannabis use patterns. The patient is asked what type of cannabis product is being used, a preferred mode of administration (i.e. inhale, ingest, apply), and frequency of use. Follow-up visits are scheduled as needed. Some patients feel comfortable with their use pattern while others may want to discuss adverse outcomes or success stories. The California Medical Association requires follow-up visits at least annually.

Some states may have a mandatory patient registry. California has a voluntary registry. The physician produces a recommendation form letter, and the patient uses that letter to access cannabis dispensaries, grow his/her own plants, or register with the state. Aside from growing your own plants, the process of obtaining medical cannabis is not completely clear. States are still developing laws for cultivating, manufacturing, distributing, transporting, and storing marijuana.

Pharmaceutical companies are also participating in the development of cannabis as medicine. Dronabinol is the first product introduced by the pharmaceutical industry. It is a synthetic THC suspended in sesame oil and presented as a capsule. However, since cannabis contains a multitude of chemicals that act in synergy, the second-generation pharmaceutical products are plant based. Sativex is a cannabis plant extract in sub-lingual spray that has been approved for the treatment of spasticity from multiple sclerosis. Interestingly, GW Pharmaceuticals, the English company that created Sativex, is considered the largest cultivator of cannabis in the United Kingdom.

Recommending cannabis is on its way to becoming a standard part of physician practice. The effect of phytocannabinoids and terpenoids on the endocannabinoid system is emerging in the curriculum at some medical schools. Physicians now have another option that I believe can reduce pain and moderate inflammation, prevent seizures, improve diabetic glucose control, and possibly even treat cancer. An endocannabinoid specialty is in the nascent stages of development. Discussion is emerging among experts of a possible endocannabinoid deficiency as an underlying component of irritable bowel syndrome and fibromyalgia.[3] In the same way that most physicians are able to treat thyroid disease or control blood pressure, they should also now be able to appropriately recommend cannabis. It's been 20 years since California's Proposition 215 was passed as a compassionate act. Medical cannabis use has transitioned from a social act to scientific endeavor. As always, the wellness of our patients is our first priority. There is still much to learn.

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non-opioid options for the millions of Americans with chronic pain.

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MORNING REPORT

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He continues to use edible marijuana and has remained symptom-free since September 2015.

Take Home Points

1. Acute hypersensitivity pneumonitis (HP) is a challenging diagnosis due to nonspecific signs and symptoms and a large differential. A thorough history of possible exposures is essential for the diagnosis.
2. There are more than 300 known antigens that trigger HP, and novel exposures like cannabis have been described in the literature. Due to increasing popularity of recreational marijuana use and related smoking devices, cannabis-associated HP could become a more common diagnosis.
3. A thorough marijuana-use history should include the following: type of cannabis used, route of administration, storage, frequency and timing of use, and evaluation of all smoking devices, particularly those that use water.

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of applications and permits later, permission by all parties was granted. The speed with which we were granted permission is a testament to GW Pharma and their hard work and commitment to our children. Word spread fast, and they were soon asked to open additional Expanded Access programs at dozens of hospitals and clinics for hundreds of children. After evaluating the safety, tolerability, and potential efficacy of CBD in pediatric patients with severe treatment-resistant epilepsy through essentially an open-label trial (i.e. data gathered via the Expanded Access programs), GW Pharma decided to

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SGIM FORUM

Society of General Internal Medicine
1500 King Street Suite 303
Alexandria, VA 22314
202-887-5150 (tel)
202-887-5405 (fax)
www.sgim.org

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continue its clinical investigation with formal Phase 2 and 3 FDA trials. Results from the first Phase 3 trial are expected later this year.[7]

Unfortunately, most of the 200,000 pediatric patients with treatment-resistant epilepsy in the United States have not had access to GW's pure CBD, Epidiolex, over the past two years. Consequently, distressed parents have continued to test artisanal preparations. Some say THC is also needed for full benefits. Some say it's a specific strain that is most useful. Despite two years of the use of artisanal cannabinoid preparations, we still lack information on how to treat pediatric epilepsy with medical cannabis. We do not have analyses of the chemical composition of these preparations nor any documentation of basic safety and tolerability issues. Have there been any serious adverse events? What dose is most appropriate? Are there drug-drug interactions to be aware of? These remain unanswered questions for any physician who would like to recommend medical cannabis to improve his/her patient's quality of life. This is relevant not just for epilepsy patients but also for patients suffering from a host of other ailments who entrust medical cannabis to improve their disease and disease-related symptoms and overall quality of life.

How should we proceed with a scientifically valid exploration of the benefits and risks of medical cannabis for all of these patients? For the benefit of patients who are eager for guidance by their physicians and for the physicians who are eager for information to provide that guidance, I would argue for the unrestricted gathering of methodologically sound clinical data. This type of observational study would provide important information about whether the investigational drug is beneficial—and for whom.

While clinical research is complicated in the case of medical cannabis by patients' access to non-FDA-approved forms of the drug under investigation, the potential still exists to create valid methodologically sound research protocols that would provide meaningful and interpretable data. This research must begin, however, with a critical step: defining the drug under investigation. Whether patients are ingesting capsules or oils or vaporizing raw flowers, accurate documentation of the chemical components of the preparations and the dose administered is essential. Prospective open-label trials as well as randomized placebo-controlled trials can contribute to this knowledge base. Together, these data can guide informed treatment with a variety of defined medically appropriate cannabinoid preparations in a number of diseases. I hope that two years from now, how to treat seizures with cannabinoids will no longer be a mystery. We will have actual data.

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