CANNABIS IN THE CLINIC?
IN EPILEPSY

Investigators at the University of Utah have been actively pursuing research to examine the ability of cannabidiol (CBD), a non-psychoactive compound that can be extracted from marijuana plants, to safely and effectively stop seizures. Recent preclinical studies by Misty D. Smith, Ph.D., an Assistant Professor in the Department of Pharmacology and Toxicology in the College of Pharmacy and in the School of Dentistry at the University of Utah, was funded by the Epilepsy Foundation of America's Targeted Research Initiative for Cannabidiol in Epilepsy to investigate the nature of CBD interactions with traditional anti-seizure drugs and to determine how these drug interactions effect their therapeutic efficacy and safety.

Ongoing studies are now determining if the synergistic drug combination identified in acute preclinical studies will translate to improved efficacy and/or safety in a chronic model of viral infection induced epilepsy. The goal of this preclinical research is to ultimately inform CBD polytherapy in hopes of optimizing the therapeutic potential of CBD, while also determining CBD's potential disease-modifying effects on epilepsy-related histopathology, behavioral comorbidities, cognitive outcomes, and inflammation.

IN DRAVET SYNDROME

A form of CBD manufactured by GW Pharmaceuticals called Epidiolex was recently used in an open label clinical trial that sought to evaluate the effect of this compound in patients with Dravet Syndrome and other severe seizure-inducing syndromes. Dr. Francis Filloux, Professor of Pediatrics and Division Chief of Pediatric Neurology at the University of Utah, was actively involved in the study and was an author on a recent publication describing the results\(^1\). The majority of the families of the patients enrolled in the study have reported benefits either in terms of improved seizure control or in some other fashion and a significant portion of the patients enrolled in the study are continuing to receive CBD to aid in seizure control. As a consequence of these exciting preliminary outcomes, Dr. Filloux is also participating in additional GW Pharmaceuticals-sponsored clinical trials for Epidiolex. These new double-blind, placebo-controlled studies will evaluate the efficacy of this CBD compound in patients with Lennox Gastout Syndrome and patients who experience refractory seizures as a consequence of Tuberous Sclerosis. In addition, Dr. Filloux and his colleagues will continue to monitor the outcomes of patients who are continuing to take Epidiolex after the initial trial. Therefore, the combination of preclinical and clinical trials by University of Utah investigators will help determine the efficacy and safety of CBD for the treatment of refractory epilepsy.\(^\star\)

PHYSICIANS ARE EMPATHETIC TO the concerns of their patients and community. A strong social drive advocating the legalization of marijuana carries with it abundant anecdotal evidence for possible usage in treatment of several chronic diseases. As we move forward in evaluating possible marijuana usage in our communities, we need to have an evidence-based approach to make sure that we fulfill our primary responsibilities as physicians of protecting and serving our communities.

I think for the purposes of discussing marijuana and all of its components we need to divide the discussion into three different silos of information, which I will term medical, medicinal (Note - in order to avoid confusion medicinal will be now referred to as herbal throughout the remainder of the article), and recreational. Each of these different silos of discussion has their own considerations and consequences.

Before we can begin a discussion on marijuana we all need to have a basic understanding of the plant and its makeup. The marijuana plant, also known as cannabis, has over 400 chemicals with more than 60 of them being unique to the marijuana plant. The most famous of these is Tetrahydrocannabinol (THC). We can find a lot of information about marijuana and its active ingredients with simple research on the Internet. Most of the cannabinoids, the active compounds found in marijuana, are closely related and typically fall into at least 10 separate groups of related active ingredients. Marijuana is also known for its other non-pharmaceutical uses and is commonly called “hemp.” There are hundreds of slang words for Marijuana such as “weed,” “duby,” or “gange.” The diversity of slang words for Marijuana often denotes wide variety in its potency, additional ingredients, quality, delivery mechanism and harvest location. These issues all combine to make marijuana a very complicated issue.

MEDICAL

When considering the medical applications of a new drug, physicians need to know the common dosages, dosage forms, side effect profile, indications, contra-indications, and relative needed adjustments associated with other comorbidities. The information that we gain from bench and clinical research provides us with the information we need as physicians to treat our patients. Drug companies, the FDA and others help provide the research and evidence for us at each level of development for a new drug.

A new drug typically starts as a researcher investigates the chemical compounds in an herbal or other preparation that may be used by certain communities and cultures for treatment of certain conditions, in addition to synthetically altering current drugs to maximize effects and minimize side effects for treatment. Sometimes drugs are developed by understanding the underlying physiology and trying to match a chemical compound to a naturally occurring compound to mimic the effect. I’m sure there are also other ways that new ideas for new drugs begin.

Generally, each new drug goes through a typical process of working through four phases of research. The FDA polices this process to ensure that once a drug is released into our communities it is considered relatively safe and effective for the indications noted in the drug information. If a drug is considered urgent or emergent, the FDA does have a process to “Fast Track” the approval.

A good example of how this process has worked in the past is the drug Digoxin or Lanoxin. Digoxin can be found in a wildflower in the foothills of Oregon and Washington. It was known by American medicine men that you could grind up the plant and treat severe anxiety and heart palpitations. It is also rumored to have been used in some religious ceremonies to alter thinking and create a yellow/green perspective of the world. Through the research process they found the active ingredient in the plant called Digitalis and two isomers which are now called Digoxin...
and Digitoxin. These two drugs are well known by most physicians and there are still patients today who take them for atrial fibrillation and other indications.

Interestingly, the foxglove plant can provide as little as no drug or as much as a tenfold or more difference in concentration. As an emergency physician I’ve seen patients come in with digoxin toxicity. The patients can die from an overdose of this drug by causing severe blocks in their heart conduction. We have drugs to treat the overdose called FAB fragments. A pill manufactured in the United States delivers the same amount of drug in each brand name pill, and even generics are controlled within 10% above or below the bioavailability of the brand name drug. In short, the manufactured pill is much safer than grinding up a plant. And, the pill comes with the information physicians need to know to appropriately prescribe the medication.

For marijuana, therefore, the first real issue is the bypassing of safety and security measure in our society, having lay legislators or popular referendums releasing new drugs on the market for general consumption without the appropriate evidence and information. This creates an alternative pathway for drugs to simply bypass the entire research process that gives physicians the information they need to properly treat their patients.

The next issue for physicians is research and evidence for the treatment of conditions with marijuana or its derivatives. There have been many trials with marijuana around the world and the evidence points to possible efficacy in treatment of spasticity in multiple sclerosis patients, reduction in seizures for patients resistant to other available treatments, nausea/vomiting in cancer patients, and appetite stimulation. There are a lot of other discussions about anecdotal effectiveness in multiple other conditions, but research has yet to support these claims.

Currently there are several marijuana related drugs on the market in various countries. Here is a short summary with the most up to date information I could find on the drugs:

**Approved in the United States:**
- **Marinol (Dronabinol)** — synthetic THC first approved for use in the United States in 1985 and again in 1992. It was made a schedule three drug in 1999. The suggested use is for nausea and vomiting, appetite stimulation, and neuropathic pain in multiple sclerosis patients.
- **Cesamet (Nabilone)** — synthetic THC first approved in the United States in 1985, removed from the market, and reapproved in 2006 with appropriate safety labeling about alteration in the mental status of the patient. Suggested uses as an antiemetic and as an adjunct for neuropathic pain control.
- **Epidiolex (Cannabidiol)** — approved for limited use by the FDA for study and “compassionate” care for certain types of patients. The dosages are still indeterminate. Phase III trial results published out of England show to be promising for Dravet Syndrome based on a 20mg/kg/day dosage. U of U medical center is currently running an open-label trial.

**Approved Outside the United States:**
- **Sativex** - released in Europe for treatment of pain and spasticity but failed phase 3 trials in the United States by one manufacturer, but two additional trials were in progress in 2015. Suggested use to improve appetite.

**Failed or Bench level Research Drugs:**
- **Dexanabinol** — synthetic non-psychotropic cannabinoid NOT approved in the United States as of 2013.
- **CT-3 (ajulemic acid)** — synthetic, higher potency THC for MS patients, NOT approved in the United States as of 2013.
- **Cannabinor** (formerly PRS-211,375) — synthetic cannabinoid that FAILED in Phase IIa clinical trials as of 2013.
- **HU 308** — synthetic cannabinoid in laboratory trials as of 2013.
- **HU 331** — synthetic cannabinoid in laboratory trials as of 2013.
- **Rimonabant/Acomplia** — synthetic endocannabinoid receptor blocker for obesity. Approved then REMOVED from the European union as of 2006.
- **Taranabant/MK-0364** — synthetic endocannabinoid receptor blocker. Research STOPPED in 2008 due to overwhelming side effects.

The drugs listed above are actual or synthetic analogs of isolated compounds from the marijuana plant. Many have failed phase 2 clinical trials or beyond. The process to date has shown how important it is to isolate out the chemical compounds and test them instead of simply using the whole plant and hoping for the best.

The New England Journal of Medicine published an article in June 2014 that outlines the adverse effects of marijuana that are well known in the literature and community. With a HIGH level of confidence marijuana is linked to addiction and other drugs; diminished lifetime achievement; motor vehicle accidents and chronic bronchitis. In addition, with a MEDIUM level of confidence it has been associated with abnormal brain development, schizophrenia, depression and anxiety.
Therefore, from a Medical perspective let me summarize the positive and negative aspects of “medical” marijuana:

Positive

• Current synthetic alternatives are on the market for treatment if needed for nausea/vomiting, pain, and appetite enhancement.

• New drugs are being researched and show promise for treatment of seizure disorders.

Negative

• Legislative and popular actions that may circumvent the FDA research review and security process for the development of new drugs.

• Release of marijuana in any form for medical use without the appropriate information for a physician to use to treat patients.

• Significant concerns about patients utilizing marijuana without an understanding of how it will interact with their comorbidities, medications, and other treatments.

• No known use for the whole plant and unknown complications from whole plant usage.

HERBAL

In our world today herbal and naturopathic remedies make up billions of dollars in business. Herbal remedies are not reviewed, researched, or controlled in any fashion. Herbal remedies do not have to show any quality control in the amount of drug or the bioavailability of a drug using various dosage forms. The result is patients can never be sure how much of an active ingredient they are actually receiving with each batch of an herbal remedy.

Herbal remedies have been used for thousands of years and today still make up the primary treatment process in some cultures. However, most of the time the active ingredient is not known. This can make it very difficult for someone using herbal remedies to treat conditions or medical problems.

The FDA has stepped in to manage the use and abuse of certain herbal remedies that are considered to be dangerous to the population and highly addiction prone. Examples of this include opioids, cocaine, and marijuana. Opium has a long cultural history and is used freely in some cultures as a recreational drug and herbal treatment. Cocaine, in its herbal form, has been used in some cultures to stimulate their workers to work longer hours and harder. As physicians we are very familiar with the complications caused by heroin, cocaine, and marijuana.

As physicians we have a responsibility to understand how herbal remedies may affect the current treatment regimens of our patients. For instance, patients who consume lots of broccoli, with high levels of vitamin K, can affect their protime/INR when treated with Coumadin.

Marijuana has many known side effects, but we are still learning how it interacts with other drugs and treatment protocols for patients. The research is being done on isolated cannabinoids which will eventually give us an understanding of the side effects it might have on our patients. However, the use of the whole plant, with over 10 categories of related compounds, will be difficult to determine how it’s going to interact with our patients.

Herbal use of marijuana will ultimately be a decision made by the government, influenced by legislators and the popular vote. The best thing physicians can do is to provide available information and concerns about the effects on the general public and public health concerns.

RECREATIONAL

The recreational use of marijuana has many implications for public health and for the citizens in our communities. Marijuana has long been known as a gateway drug for other drugs in the community, which has implications for behavioral health and addiction issues. The impact of marijuana on activities such as jobs, driving, operating heavy machinery, and other situations that could become dangerous with the use of a mind-altering drug are of grave concern to physicians and their patients.

Ultimately recreational use of marijuana once again becomes a government, legislator, and popular vote decision. We as physicians can provide some insight to the public health concerns of marijuana that may mimic alcohol in our communities.

Much like alcohol, marijuana has an effect on an individual’s ability to complete simple tasks. The implication of widespread use is it may become a public health concern. Every user will be asked to be responsible, as are the alcohol drinkers in our community, but I think we can estimate that the irresponsible use will follow a similar bell curve to the use of alcohol.

HERBAL AND RECREATIONAL PUBLIC HEALTH CONSIDERATIONS

States that have already legalized marijuana in some form and amount are experiencing new social concerns and consequences for their choices.

Smoking, with legislation that has been limited primarily to tobacco products, has had to be re-addressed in most states to see if smoking marijuana in a non-smoking area is considered legal and appropriate. Much like smoking tobacco, people can experience secondhand smoke affects, much like some people have been
exposed to in the past at certain concerts. Legislators have had to decide how they will modify their smoking/tobacco legislation to protect the public from marijuana smoking much as they have done with tobacco smoking throughout the years.

Driving under the influence of marijuana will also have to be addressed. In our communities we have laws that address what alcohol concentration in your blood can be tolerated before you are not able to operate a vehicle, heavy machinery or be in a dangerous situation. In addition, we have multiple ways to test for the presence of alcohol in your blood and breath so that officers can enforce the laws. It is difficult to get quantitative measurements for marijuana in your breath or blood. Marijuana has a long half-life in your blood, which means that qualitative tests can be positive for up to 1 to 2 months after usage. We know that marijuana can certainly affect your ability to drive and make you a public health risk if you use and drive but there is not enough research to date to decide at what level you’re still safe to be on public roads.

Protecting children is always a high priority. In many states where marijuana has become legalized there are now forms of marijuana that include common candies, baked goods, drinks, and other easily available products for purchase. There are currently no protective measures in place to protect our children from accidentally or purposely consuming any of these products. Marijuana has significant effects on children (particularly on their developing brains) and we have to protect them.

CONCLUSIONS

While we attempt to be empathetic with patients who have anecdotal response to marijuana for their medical conditions, we are obligated to fulfill our responsibilities as physicians to protect our patients and their children. We need to make sure that any drug released on the market goes through a well-designed and secure process to ensure that physicians are armed with the appropriate evidence-based information to treat our patients. We need to protect against lay legislators and popular referendums creating an alternative pathway to treatments for medical conditions. Further evaluation of marijuana and its components is needed to find which compounds can be used effectively and safely for the treatment of our patients. Marijuana for herbal or recreational use ultimately will be a decision made by the public and government. As physicians we need to help them prophylactically address the public health concerns that may be a consequence of global acceptance and usage of this mind-altering, addictive drug. Medical marijuana at this time is an oxymoron because there is not enough research and evidence for the use of the whole plant. However, there is hope that perhaps some individual components of the plant may be effective for treatment for some patients for certain medical conditions. We need to make sure that barriers to legitimate research are removed so we may discover those treatments which are both safe and effective.

We have the knowledge, expertise, experience and solutions that create high-performing healthcare organizations.

Our consulting team is well versed in the top trends, best practice techniques, and solutions that optimize financial management needed to energize practices and organizations.

Navigate effectively through healthcare change!

Consulting Services:
- Revenue Cycle Management Analysis
- Billing & Coding Analysis/Compliance
- Operational Assessment & Review
- Productivity & Quality Care Improvement
- Benchmarking & Financial Management
- Regulatory Compliance & Audits
- Compensation Planning
- Strategic & Business Planning/Development
- Practice Formation - Mergers - Acquisitions
- Valuations & Appraisals
- Managed Care Contracting & Negotiation
- Interim & Long-Term Management
- Marketing & Market Research
- Professional Staff Recruitment
- Governance & Leadership
- Compliance Audit & Training

Jackie Coult, CHBC
Board Certified Healthcare Consultant
P: 801.550.5058 - E-Mail: jgc.coult@comcast.net
Healthcare Consulting with Results
Over 28 years of experience
MEDICAL MARIJUANA HAS TAKEN on a false persona. There seems to be a belief that it is some type of super drug that will cure almost anything. While further study is warranted, we possess multiple studies providing insight into what it really is, and what it has the potential to treat. Studies that have been performed regarding its analgesic properties show it to be about as effective as NSAIDs. States that use marijuana for pain now have many patients using both marijuana and opioids to treat their pain. No studies to date show that marijuana use for chronic, non-malignant pain is an effective treatment, or a replacement for opioids.

Until recently - because of its Class I schedule, it has been difficult to study. Our current administration has alleviated some of the burden to studying marijuana. Certainly more studies are forthcoming.

In the meantime, marijuana seems to have an endless stream of anecdotal stories of its almost miraculous properties. The anecdotal should hold no place in science. While the stories can be heartwarming, they only influence our emotions. They have absolutely no way of controlling multiple variables, bias, and many other confounding factors. This will only harm scientific progress. It’s difficult to separate our personal experiences or influences from molding our opinions, but we need to let facts speak for themselves. Personal influences are not required, nor welcome.

But there is another influence at play here: the all-mighty dollar. Legal marijuana is already a $4 billion industry (this does not include illicit sales). That’s $4 billion, with limited market penetration, with less than half of the United States using some form of legal marijuana. Some of those who are most strongly supporting a marijuana initiative are mostly interested in their own financial prosperity. It is estimated to be over a $20 billion industry in the next five years. Expect increased pressure to legalize marijuana here and elsewhere as the industry grows in financial strength and influence.

Marijuana is widely believed to be benign, compared to other medications we are currently prescribing. However, marijuana does have serious side effects, the full impact of which we do not yet understand due to a lack of quality studies. We do know that marijuana can increase heart rates as much as two times for up to three hours, leading to a significantly increased risk of heart attack almost immediately after using it. We also know that smoking marijuana is more irritating to lung tissue than smoking tobacco, and users are more likely to have an ongoing cough and higher rates of lung-related health issues like chest colds and lung infections. It is believed to have higher carcinogenic risk than smoking tobacco, and higher risk of lung disease when smoked (although, again, these risks are not fully understood due to lack of scientific data).

Reaction time is significantly decreased. Driving after using marijuana more than doubles your risk of being in a car accident. These and other side effects can be exaggerated in patients with comorbidities like lung disease, liver disease, diabetes, and mental health disorders. Research shows a link between marijuana use and depression, anxiety, suicidal thoughts, short-term psychosis and schizophrenia. While it is not clear if marijuana causes these conditions, it can make them worse.

The US has an opioid epidemic. In 2010 the US consumed more than 90 percent of the world’s hydrocodone supply. This was partly due to its schedule III status. This was changed in October 2015; it is now a schedule II medication. The current "crisis" began in the early 90’s in a court of law. A physician was successfully sued for not properly treating a patient’s pain. The court and a patient advocacy group thereby created the belief that “Patients have the right to not have pain,” thus forcing physicians’ prescribing practices. The problem was further fueled by pharmaceutical companies marketing to physicians, hospitals, and patient advocacy groups. Soon thereafter, pain was named the 5th vital sign (Ironically, pain is neither vital, nor is it a sign. It’s a symptom). Doctors were told we were under-treating pain, and we were horrible people for not prescribing more opioid-based pain medications.

Our current opioid crisis was indeed fueled by public opinion, just as the medical marijuana issue is today. It is public opinion that is advocating its use. To my knowledge, no professional medical society endorses wide use of marijuana for medical purposes.
The opioid movement proceeded without proper scientific studies to legitimize not only prescribing practices, but dose and regimen schedules. Is the marijuana revolution repeating the unreasonable opioid movement of the early 90's? There are multiple similarities. We now have almost 30 years of retrospective data to look at regarding opioids. No doubt prescribing practices would have been different had we waited for the science.

Every medication I prescribe must have a dosing schedule. What is the dosing schedule for marijuana? How often? How much? For how long? We do not give prescriptions for a free pass to other medications, allowing patients to use as much and as frequently as desired; Nor should we for marijuana.

Other powers (politicians, courts, public opinion, lawyers, marketing, pharmaceutical companies, to name a few) deem their views more important than basic science. Again, let the facts speak for themselves. If we had done this in the 90's, physicians' prescribing practices with opioids would have been far different, and we may have avoided our current dilemma. One hundred percent of states using any form of legal marijuana have all experienced unanticipated complications with marijuana legalization. It appears to me that these complications haven't been properly vetted due to the public's strong emotional and anecdotal experiences.

I have spoken with multiple state senators and state representatives. They feel that public opinion is simply moving faster than science on this issue. While that is true, we need to learn from our previous mistakes. Medical marijuana is following the same disastrous path that opioid-based pain medications did in the 90's.

If public opinion is going to force the state to legalize marijuana, our medical community needs to be proactive in setting guidelines to help protect our patients as best we can. There may be a sponsored bill for the unrestricted use of medical marijuana introduced in the next legislative session. It would be pushed without the backing of the medical community. This reckless process, if successful, will harm patients. If public opinion is going to force some form of legalization, UMA should back a bill that has reasonable, science-based expectations, use parameters, and strict limits on who can prescribe. The following might be considered:

PATHOLOGY ELIGIBLE FOR TREATMENT

**Cancer and HIV** — This is where the best data for medical marijuana lies. Not for its pain relieving properties, but as an anti-emetic, and appetite stimulant for cachectic patients.

**Multiple Sclerosis** — While data is a little lacking, the American Academy of Neurology includes marijuana in their treatment algorithm. I would suggest strict adherence to their guidelines

**Epilepsy** — Current studies and data do not support its use. Studies have shown that THC compounds have been detrimental to the pediatric population. THC is a psychoactive compound. Early data appears that developing brains should not be exposed to THC. Multiple children are being treated for PTSD after being exposed to THC containing compounds.

**Chronic Pain** — Data does show marijuana to have analgesic properties. Studies suggest it is equivalent to Ibuprofen. Marijuana has been touted as a replacement for opioids, but data does not support this. While there may be patients who may benefit from marijuana, patient selection is key. Clear guidelines need to be in place prior to anyone initiating therapy.

GUIDELINES

1. Utah would need to employ the controlled substance database and reporting system for marijuana, just as it does with opioids and all controlled substances.

2. Opioids and marijuana should not be used together. This is also the American Medical Association’s recommendation.

3. Anyone using marijuana may not operate a motor vehicle. NO EXCEPTIONS! Colorado has seen a spike in death and injury due to motorists using marijuana.

4. A clear dosing schedule. Legalization of marijuana in Utah should not be a free pass to use as much marijuana or as often as the patient deems. If this is a prescription medication, it needs to follow the same standards as all prescription medications. Even OTC’s have dosing schedules.

Last year’s bill sponsored by Rep. Daw attempted to create a new specialty, a medical marijuana physician, who would be able to prescribe marijuana to anyone. The only requirement was to complete a state-mandated training course. This is not enough. Prescribers should be limited to certain board certified specialists ONLY:

- Oncologists — only for cancer patients
- Neurologists — only for multiple sclerosis
- Pain Management Specialists — only under strict guidelines and controls for chronic pain

The opinions expressed in this article are those of the author and do not necessarily reflect the policies or positions of the Utah Medical Association.