



Is marijuana  
*medicine?*



Pennsylvania  
MEDICAL SOCIETY®

# IS MARIJUANA MEDICINE?

## Introduction

The idea of marijuana as medicine is not new. Historians tell us that the ancient Chinese, Egyptians and Greeks used cannabis to treat a variety of conditions, ranging from constipation to hemorrhoids, nosebleeds, tapeworms, and even hair loss. More recently, cannabis was included as an ingredient in many patent medicines sold in the United States during the 1800s.

In the 1970s, research suggested that marijuana might be useful in reducing intraocular pressure in glaucoma patients, and today advocates of legalization assert that it can be used to treat conditions like muscle spasms, pain and nausea. To date two oral synthetic marijuana medications – Marinol and Cesamet – have been approved for use in the United States.

However, even the ancients recognized that cannabis has a darker side, and they were well aware of its psychoactive properties. It is that darker side that led the U.S. government, after enactment of the Controlled Substances Act in 1970, to classify marijuana as a Schedule I drug. Under the Act, a Schedule I drug is one that:

1. Has a high potential for abuse.
2. Has no currently accepted medical use in treatment in the United States.
3. Lacks accepted safety for use of the drug or other substance under medical supervision.

Marijuana's status as a Schedule I drug presents barriers to researchers who wish to study its possible medical uses, as prospective investigators must successfully navigate a time consuming regulatory gauntlet in order to gain the necessary permission to go forward. Those hurdles have resulted in a dearth of credible research demonstrating the safety and efficacy of "medical marijuana."

For the past several years there has been growing pressure on the U.S. Food and Drug Administration (FDA) to relax marijuana's Schedule I status to facilitate medical research, with organizations like the American Medical Association (AMA) and Pennsylvania Medical Society (PAMED) calling on the government to open the door to studies of the drug's possible use to treat various diseases and conditions.

Despite the lack of adequate studies, public support for legalization of medical marijuana has increased significantly since the 2013 release of the CNN documentary, “Weed.” In that documentary, Dr. Sanjay Gupta related the success some parents reported in treating children suffering from severe epileptic seizure disorders with oil containing cannabidiol (CBD), the main non-psychoactive component of marijuana.

Currently eleven states have legalized CBD for medical use, while 23 others have gone farther and, at least to some degree, approved both CBD and delta-9-tetrahydrocannabinol (THC), marijuana’s psychoactive component. To date Pennsylvania is among the remaining states that have not legalized medical marijuana.

Given the known dangers of marijuana, PAMED does not currently support legalization of medical cannabis, though we believe there is sufficient evidence to warrant a relaxation of its Schedule I status to facilitate vigorous controlled, double-blinded studies for a number of disease and conditions, particularly CBD for seizure disorders in children.

In this paper we will first provide a brief overview of what we know and don’t know about the chemical components of the cannabis plant, and why what we know is of concern. Second, we will discuss the lack of credible medical marijuana research, and the reasons for that deficiency. Third, we will outline some of the ancillary risks associated with legalized medical marijuana, such as increased recreational use and diversion. Fourth, we will provide an overview of state medical marijuana laws, and position statements of key health care organizations. The paper will close with a list of important unanswered questions that reinforce the need for credible scientific research and clinical studies before medical marijuana should be legalized.

Specific concerns addressed in the paper include the following:

- We don’t know enough about what’s in marijuana, though we do know it contains toxic chemicals.
- The lack of credible studies supporting anecdotal reports that CBD aids children with epileptic seizure disorders.
- Legal barriers that continue to impede needed research and clinical trials.
- Approved medications exist, but they can have significant side effects.
- Dosing difficulties and known health risks associated with smoked marijuana.
- Diversion and increased recreational use and abuse in states with legalized medical marijuana.

## **What is in marijuana?**

Much of the attention focused on marijuana is directed toward two of its cannabinoid components: THC and CBD. THC is the psychoactive component of marijuana, responsible for both its mind-altering effect and its suggested benefit in treating some conditions like nausea in cancer patients. CBD is thought to have little, if any, psychoactive effect, and its possible use to treat children with severe epileptic seizure disorders, such as Dravet syndrome, has been well publicized in the popular media.

However, there's much more to marijuana than THC and CBD. Indeed, to say that cannabis is a complex substance would be an understatement. There are more than 400 known chemicals in marijuana, and between 60 and 80 of them are unique to the cannabis plant. Those chemicals are called cannabinoids, and many of them have been little studied and are poorly understood, one of PAMED's causes for concern.

We do know that marijuana and tobacco smoke contain many of the same chemical constituents, including carcinogenic chemicals known to be toxic to respiratory tissue. The major difference between the tar particulates found in marijuana and tobacco smoke is that only marijuana smoke contains THC, while only tobacco smoke contains nicotine.

### **Cannabidiol and seizure disorders – promising, but where's the data?**

Many Americans are familiar with the story of Charlotte Figi, the young girl featured in Dr. Sanjay Gupta's CNN documentary, "Weed." Charlotte suffers from a rare and severe form of epilepsy known as Dravet syndrome, and according to her parents was experiencing 300 grand mal seizures per week before treatment with CBD oil reduced that number to single digits. Other parents have reported similar results, and there is a growing belief that CBD-based medications may be a viable option for those severely ill children.

Nevertheless, hard proof of efficacy remains lacking, and as reported in Medpage Today, two surveys presented at the 2014 annual meeting of the American Epilepsy Society demonstrate the risk of approving medications based on anecdotal evidence.

In those surveys parents of children with severe seizure disorders reported high rates of efficacy from treatment with CBD-based products. However, the lead investigator in one of the surveys found what he called a fairly clear indication of parental bias in reporting responses to treatment, and said he had seen children seizing in his office despite parents' assurance that

they were now seizure free. And in chart reviews, parent-reported responders with EEG data available showed no objective improvement.

The lead investigator of the second study called the parents' reported positive response rates "astronomical," and "too good to be true." Both researchers concluded that well-controlled, randomized studies are needed.

Reinforcing that need, a new technical report from the American Academy of Pediatrics states that "there are no published studies on the use of cannabinoids or marijuana to treat health conditions in children or adolescents."

### **Epidiolex – answers are coming**

Those studies are under way. In 2013 the FDA granted approval for GW Pharmaceuticals, a United Kingdom-based pharmaceutical company, to conduct studies on a CBD medication for use in treating children with severe forms of epilepsy. The drug, Epidiolex, is reported to be a pure form of CBD, the non-psychoactive component of marijuana that has generated positive anecdotal evidence of efficacy.

Early open label studies of Epidiolex have been promising (an open label study is one in which researchers and patients know that patients are receiving the drug and not a placebo). One of those open label Phase 1/2 studies is being conducted at the Children's Hospital of Philadelphia.

As a result, in October 2014 the company announced that it was commencing a Phase 2/3 randomized double-blind, placebo-controlled (RDBPC) study of the medication - medicine's "gold standard" of research design. Additional Phase 3 studies are planned for this year in both Dravet syndrome and Lennox-Gastaut syndrome, another severe childhood epileptic seizure disorder.

Hopefully, these studies will produce much needed hard evidence of the safety and efficacy of CBD-based seizure medications. They may also answer questions that have arisen from earlier studies regarding the effect of CBD-based medications on blood levels of other anti-epileptic drugs (AEDs) that a patient is taking, an important factor to be considered by a treating physician.

### **Legal impediments - why research on safety and efficacy is lacking**

Proponents of legalization point to dozens, if not hundreds of studies that have been conducted around the world demonstrating marijuana's benefit in treating various maladies. However, precious few of them have met medicine's "gold standard" of large randomized, double-blinded placebo-control (RDBPC) studies, in which participants, investigators and study staff are all blinded to assure a lack of bias in the study results.

According to J. Michael Bostwick, MD, a psychiatrist at the Mayo Clinic and author of a review of medical marijuana research, few of these studies followed such a controlled clinical trial, and most of them had fewer than 200 patients. So doubt continues about marijuana's value and who it really can help, he says.

The website ProCon.org lists a total of 61 peer reviewed studies conducted worldwide between 1990 and 2014, spread over 16 different diseases or conditions. Of those 61 studies, only 27 were double-blinded, and only 17 were double-blinded with positive results. Of those 17, six short-term studies (some as short as two weeks) suggested reduced spasticity in Multiple Sclerosis, clearly warranting further examination.

In addition to being predominantly short-term, many of those 17 positive, peer reviewed, double-blinded studies involved a small number of participants, were not Phase 3 trials, or used terms like "might" or "may" to describe their results, suggesting the need for further research. Especially lacking are studies of the long-term effects of marijuana use to treat chronic conditions.

Much of the data in existence today comes from surveys of patients who were using marijuana, studies involving small numbers of patients, and open label studies in which investigators and patients knew what the patients were taking. These surveys and studies are generally considered to be less reliable than RDBPC studies, due to the increased potential for patient bias and subjectivity. As previously noted, the lead researcher of one such recent survey was skeptical of the results, calling them too good to be true.

The paucity of reliable research into the safety and efficacy of medical marijuana is a direct result of marijuana's status as a Schedule I drug. As such, would-be researchers must go through a strenuous review process conducted by the U.S. Department of Health and Human Services (HHS). Once an application has been scientifically evaluated and approved, researchers must then complete paperwork necessary for projects involving both human participants and a Schedule I controlled substance. When the above steps have been

completed, investigators then contact the National Institute on Drug Abuse (NIDA) Drug Supply Program to place an order for marijuana with specific THC concentrations. Currently NIDA, an agency within the National Institutes of Health (NIH), is the only legal source of marijuana for medical research in the United States.

Many nations, including the United States, are signatories to the Single Convention on Narcotic Drugs, a 1961 treaty whose principal objective is to limit the possession, use, trade in, distribution, import, export, manufacture and production of drugs exclusively to medical and scientific purposes and to address drug trafficking through international cooperation to deter and discourage drug traffickers.

The Convention lists cannabis as a Schedule I drug, in the same category as drugs like cocaine and heroin, and requires signatory nations to place the cultivation and control of cannabis in the hands of a single government agency. As a result, conducting medical marijuana research in many other nations has been hampered in the same manner as it has been in the United States.

### **FDA-approved cannabinoid medicines exist – but they have risks**

Despite the regulatory hurdles, two drugs containing cannabinoid compounds have been approved by the FDA and are available in the U.S. in prescription form. Both have been available since the 1980s.

Marinol is a Schedule III drug that comes in pill form, though it is being studied by researchers for delivery in other forms, such as via inhaler or patch. Marinol's active ingredient is a synthetic form of THC, and it is prescribed to relieve nausea associated with cancer chemotherapy and loss of appetite in AIDS patients.

Cesamet is a Schedule II drug, available in capsule form by prescription. Like Marinol, it utilizes a synthetic THC-like cannabinoid and is also used to treat chemotherapy-associated nausea.

A review of the risk information associated with Cesamet provided by its maker, Meda Pharmaceuticals, reveals much about the need for caution in approving marijuana for medical use. According to Meda, Cesamet can cause patients to see and hear things that are not real and can affect a patient's mental state. For this reason the company recommends that other drugs should be tried before Cesamet is prescribed. Further, Meda warns that Cesamet can be abused, and states that prescriptions should only last for a few days.

## **Risks associated with marijuana as a smoked medication**

Currently there are no FDA-approved marijuana medications that are smoked. In addition to the difficulty in administering standardized, regulated dosages, smoking marijuana exposes patients to many of the same carcinogens found in tobacco cigarettes.

According to the American Lung Association, marijuana smoke, like tobacco smoke, contains 33 cancer-causing chemicals. Marijuana smoke also deposits tar into the lungs. Worse, the Lung Association asserts that when equal amounts of marijuana and tobacco are smoked, marijuana deposits four times as much tar into the lungs, because marijuana joints are un-filtered and often more deeply inhaled than cigarettes.

The National Institute on Drug Abuse (NIDA) states that marijuana smoke is an irritant to the lungs, and frequent marijuana smokers can have many of the same respiratory problems experienced by tobacco smokers, such as daily cough and phlegm production, more frequent acute chest illness, and a heightened risk of lung infections. One study referenced by NIDA found that people who smoke marijuana frequently but do not smoke tobacco have more health problems and miss more days of work than those who don't smoke marijuana, mainly because of respiratory illnesses.

According to the American Thoracic Society, marijuana smoking can cause other problems in the lungs. Large air sacs in the lung, called bullae can develop. This often happens in younger marijuana smokers (less than 45 years old). Bullae can cause marijuana smokers to be short of breath, and if they rupture they can be life-threatening.

## **Marijuana edibles and the risk of diversion**

According to a January 23, 2015 Associated Press story, marijuana-related calls to poison control centers in Washington and Colorado have spiked since those states began allowing legal sales of marijuana. And while both states have now legalized recreational marijuana, the article makes it clear that in Washington those calls “began rising steadily several years ago as medical marijuana dispensaries started proliferating in the state.”

Alex Garrard, clinical managing director of the Washington Poison Control Center, said in the article that many of the products involved in the state's exposure cases are found at the state's

unregulated medical marijuana dispensaries, and not in licensed recreational shops, which are prohibited from selling the kinds of edibles that might appeal to children.

Last year a Colorado fourth grader brought a marijuana edible to school and gave it to a classmate, and more recently, in February 2015 nine students at a Colorado high school admitted being involved in marijuana-infused edibles being distributed and used at their school. Those edibles included marijuana-infused cookies and gummies.

And, a 2011 Colorado study reached this disturbing conclusion: "Diversion of medical marijuana is common among adolescents in substance treatment. These data support a relationship between medical marijuana exposure and marijuana availability, social norms, frequency of use, substance-related problems and general problems among teens in substance treatment. Adolescent substance treatment should address the impact of medical marijuana on treatment outcomes."

These findings are particularly worrisome in light of a review in the February 2015 *Journal of Developmental & Behavioral Pediatrics*, the official journal of the Society for Developmental and Behavioral Pediatrics, stating that a growing body of evidence links cannabis to "long-term and potentially irreversible physical, neurocognitive, psychiatric, and psychosocial adverse outcomes."

Given these concerns, policymakers should strongly consider the significant downside associated with marijuana edibles, even if only intended for medical use.

### **Medical marijuana and increased recreational use/abuse**

In addition to the risk of diversion, legalization of marijuana for medical use has been demonstrated to increase recreational use and abuse of the drug.

A 2011 study by researchers at Columbia University used two national surveys – the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), and the National Survey on Drug Use and Health (NSDUH) – to measure past-year cannabis use. Together the two surveys obtained responses from over 100,000 individuals.

The results showed that the odds of marijuana use were 1.92 times higher among residents of states with medical marijuana laws than in states without such laws. The odds of marijuana

abuse/dependence were 1.81 times higher in states with legalized medical marijuana than in states where medical marijuana has not been legalized.

And, a new Rand Corporation study shows that states that allow dispensaries (as does Senate Bill 3) face a greater risk of increased recreational use and related negative consequences relative to other medical marijuana law policy frameworks.

Thus, policymakers must recognize that legalization of medical marijuana is likely to have a spillover effect, with resulting higher rates of recreational use, abuse and dependence than currently exist in the Commonwealth.

### **State laws**

Currently 23 states have enacted laws legalizing, at least to some degree, medical marijuana containing both CBD and THC. Those states are: Alaska, Arizona, California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont and Washington.

Another 11 states have passed more limited, low THC/high CBD, medical marijuana laws. Those states are: Alabama, Florida, Iowa, Kentucky, Mississippi, Missouri, North Carolina, South Carolina, Tennessee, Utah and Wisconsin.

States allowing recreational marijuana use are Alaska, Colorado and Washington, to be joined by Oregon on July 1, 2015.

### **The Pennsylvania Medical Society position on medical marijuana**

The Pennsylvania Medical Society's position on medical marijuana closely mirrors that of the American Medical Association (AMA). Like the AMA, PAMED has called for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy.

PAMED has also joined the AMA in urging that marijuana's status as a federal Schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods, though both organizations have emphasized that this should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific

evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product.

And like the AMA, PAMED has called on the National Institutes of Health (NIH) to implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research into the medical utility of marijuana.

PAMED has additionally gone on record as specifically expressing support for clinical trials using CBD oil to treat children with seizure disorders.

However, until well-controlled studies of safety and efficacy have been completed, PAMED believes that legislation legalizing medical marijuana would be premature.

#### **Other organizations on medical marijuana**

Several key physician specialty societies, whose members treat patients for whom medical marijuana has been suggested, have weighed in on legalization. Following is a sampling of those organizations' policy statements.

The American Academy of Pediatrics policy (updated January 2015) includes the following recommendations. The Academy:

*Opposes marijuana use by children and adolescents;*

*Opposes the use of medical marijuana outside the regulatory process of the Food and Drug Administration but recognizes that marijuana may be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate;*

*Supports studying the effects of recent laws legalizing the use of marijuana to better understand the impact and define best policies to reduce adolescent marijuana use;*

*Recommends changing marijuana from a Schedule I to a Schedule II drug to facilitate research and development of pharmaceutical cannabinoids;*

The American Psychiatric Association position (approved December 2013) states:

*There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.*

*Further research on the use of cannabis-derived substances as medicine should be encouraged and facilitated by the federal government. The adverse effects of marijuana, including, but not limited to, the likelihood of addiction, must be simultaneously studied.*

*Policy and practice surrounding cannabis-derived substances should not be altered until sufficient clinical evidence supports such changes.*

*If scientific evidence supports the use of cannabis derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA.*

*Medical treatment should be evidence-based and determined by professional standards of care; it should not be authorized by ballot initiatives.*

*No medication approved by the FDA is smoked. Marijuana that is dispensed under a state-authorized program is not a specific product with controlled dosages. The buyer has no way of knowing the strength or purity of the product, as cannabis lacks the quality control of FDA-approved medicines.*

*Prescribers and patients should be aware that the dosage administered by smoking is related to the depth and duration of the inhalation, and therefore difficult to standardize. The content and potency of various cannabinoids contained in marijuana can also vary, making dose standardization a challenging task.*

*Physicians who recommend use of smoked marijuana for “medical” purposes should be fully aware of the risks and liabilities inherent in doing so.*

The American Academy of Neurology position statement (2014) also urges caution and additional research:

*The AAN supports all efforts to conduct rigorous research to evaluate the long-term safety and effectiveness of marijuana-based products. The AAN, for research purposes,*

*requests the reclassification of marijuana-based products from their current Schedule 1 status so as to improve access for study of marijuana or cannabinoids under IRB-approved research protocols. The AAN does not advocate for the legalization of marijuana-based products for use in neurologic disorders at this time, as further research is needed to determine the benefits and safety of such products. This is of paramount importance when marijuana-based products are used in patients with underlying neurologic disorders, or in children whose developing brains may be more vulnerable to the toxic effects of marijuana.*

*The AAN recognizes that there may be potential use for these agents in the treatment of some neurologic disorders. However, there is not sufficient evidence to make any definitive conclusions regarding the effectiveness of marijuana-based products for many neurologic conditions. Many of the cannabis preparations used in studies are not available in the United States. It is not appropriate to extrapolate the results of trials of standardized preparations to other, non-standardized, non-regulated cannabis products which may be commercially available in states with laws supporting the use of medical marijuana. Effectiveness of a non-standardized product is not equal to that of standardized products that are studied in clinical trials. Additionally, most currently available marijuana-based products are not regulated by any agency and may not contain the products mentioned by labeling. Quality control is therefore impossible, raising further safety questions. Each product and formulation of cannabis should demonstrate safety and effectiveness via scientific study similar to the process required by the Food and Drug Administration (FDA).*

The American Academy of Ophthalmology position (June 2014) states:

*Based on analysis by the National Eye Institute and the Institute of Medicine, the Academy finds no scientific evidence that marijuana is an effective long-term treatment for glaucoma, particularly when compared to the wide variety of prescription medication and surgical treatments available. Ophthalmologists also caution that marijuana has side effects which could further endanger the user's eye health.*

The American Academy of Family Physicians calls for further studies:

*The AAFP recognizes that there is support for the medical use of marijuana but advocates that usage be based on high quality, patient-centered, evidence-based research and advocates for further studies into the use of medical marijuana and related*

*compounds. The AAFP requests that the Food and Drug Administration change marijuana's classification for the purpose of facilitating clinical research. This process should also ensure that funding be available for such research.*

*The AAFP also recognizes that some states have passed laws approving the medical use of marijuana; the AAFP does not endorse such laws. The AAFP encourages its members to be knowledgeable of the laws of their states and consult with their state medical boards for guidance regarding the use of medical marijuana.*

The American Cancer Society has also weighed in (updated August 26, 2014), calling for further research:

*The American Cancer Society supports the need for more scientific research on cannabinoids for cancer patients, and on better and more effective therapies that can overcome the often debilitating side effects of cancer and its treatment. The Society also believes that the classification of marijuana as a Schedule I controlled substance by the U.S. Drug Enforcement Administration imposes numerous conditions on researchers and deters scientific study of cannabinoids. Federal officials should examine options consistent with federal law for enabling more scientific study on marijuana.*

*Ultimately, medical decisions about pain and symptom management should be made between the patient and his or her doctor, balancing evidence of benefit and harm to the patient, the patient's preferences and values, and applicable laws and regulations.*

## **Conclusion**

The Pennsylvania Medical Society believes a compelling case exists for a serious scientific examination of the potential medical use of marijuana. That is why five years ago PAMED joined the AMA in urging that marijuana's status as a federal Schedule I controlled substance be reviewed, with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines.

Despite existing federal hurdles, serious research is well under way into the use of CBD to treat epileptic seizure disorders in children, some of it here in Pennsylvania. The results of that research will be forthcoming soon, and should provide badly needed data on the safety and efficacy of CBD-based medications.

“Gold standard,” large randomized, double-blinded placebo-control (RDBPC) studies are also needed to determine whether cannabinoid-based medicines may have value in other diseases and conditions where anecdotal evidence and more limited studies have demonstrated possible efficacy.

However, policymakers should take a cautious approach to medical marijuana until the results of solid scientific research are available, due to the well-known health risks associated with marijuana use. Diversion, including the obtaining of marijuana edibles by youth, has been noted in states that have legalized medical marijuana, as has an increase in recreational use, abuse and dependence.

Of great concern to physicians is that except for Marinol and Cesamet, marijuana is not a medicine, in the sense that there is no standardized, scientifically tested and FDA-approved cannabis drug to prescribe to patients. It is telling that Senate Bill 3 and similar legislation in other states authorizes physicians to “recommend,” rather than “prescribe” marijuana concoctions to their patients.

Given the uncertainties attendant to a non-approved “medication,” physicians who are considering recommending marijuana to their patients will find themselves unable to answer these important questions:

- What is the ideal combination of THC and CBD for each disease or condition?
- How important are the trace compounds (there are many) in marijuana?
- Do I even know what trace compounds are in the medication I’m recommending?
- What is the appropriate strength and dosage, and how frequently should it be administered?
- What is the best route of administration – oil, tincture, edible, smoked or vaped?
- What are the possible side effects?
- What are the long-term effects?
- What are the contraindications (don’t take it with, or if...)?

At this point the risks associated with marijuana are well known, and the possible medical benefits are uncertain. Accordingly, PAMED believes legislation legalizing medical marijuana in Pennsylvania would be premature at this time.

