A Guide to Medical Marijuana

Thousands of Marijuana Medicines
Why Can Doctors *Prescribe* Only Two?

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National Families in Action has been educating the public about the science of addictive drugs and working to prevent their industries from targeting children since it was founded in Atlanta, Georgia, in 1977.

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Introduction: What doctors can and cannot prescribe

Marijuana (cannabis) is a plant that contains more than 400 individual chemicals. Some 70 of these are cannabinoids, so called because they are unique to the cannabis plant. One, delta-9-tetrahydrocannabinol (THC), is principally responsible for the "high" associated with marijuana use and with some of its identified clinical effects. It is available in pharmaceutical form, and scientists are investigating a number of other cannabinoids that show potential for treating symptoms, and perhaps one day causes, of various illnesses.[1]

The issue of medical marijuana in the United States ultimately comes down to intent. On the one hand, some genuinely wish to learn if marijuana, or more likely some of its components, can be useful medicines. These are mostly researchers who look for answers in their laboratories and clinics. They understand the new drug development process that is guided by well-accepted Food and Drug Administration (FDA) protocols designed to identify safe, effective drugs. Responsible state regulations recognize the FDA standards as essential to protecting their citizens.

On the other hand, well-financed political advocates have used medical marijuana as a stalking horse to legalize the drug for recreational use. They have cynically exploited the public's lack of understanding about how basic and clinical scientists develop new drugs and the complex business of bringing them to market. They have played on the public's compassion for seriously ill people to side-step FDA's drug development process and persuaded states to "legalize" marijuana as "medicine." To them, the profits legalization will bring trump patient protections.

The result? Today, there is a complicated and confusing mix of 1) synthetic cannabinoids, 2) cannabinoids purified from marijuana, and 3) marijuana plant materials that are called "medicines." What's the difference? Which ones can doctors prescribe?

1. **Doctors can prescribe only medicines approved by FDA.** Synthetic cannabinoids are created in chemistry laboratories from pure chemicals. To date, only two medicines based on marijuana—both synthetic cannabinoids—have been approved by FDA as safe and effective for distribution to the public, after the same rigorous testing every prescription medicine available at a pharmacy must have.

2. **Doctors can administer cannabinoids to patients taking part in clinical trials.** Natural cannabinoids like THC and cannabidiol (CBD) can be purified from the marijuana plant just like morphine can be purified from the opiate poppy. Currently, two purified cannabinoids are being tested under FDA

protocols. Depending on outcomes, they may be approved by FDA.

3. **Doctors cannot prescribe any "marijuana medicines" states have legalized.** Marijuana products, which many call "marijuana medicines," are being made by growers, processed by entrepreneurs, and sold in dispensaries in medical marijuana states by people who are neither trained nor certified to develop new drugs. None have subjected their "medicines" to the testing process required by FDA. This guide explains the difference between FDA-approved synthetic cannabinoids, purified cannabinoids under study, and so-called "marijuana medicines" produced and sold without FDA approval in the medical marijuana states.

How the FDA approval process protects patients

When sick people require medications as part of their treatment, they take for granted that those medicines are safe and effective. Ensuring that they are is just what the drug development process is all about. Producers of new medicines must satisfy several FDA requirements to protect patients even before testing in humans can begin:

1. They must submit preclinical data showing that:
    - the drug has been tested in animals and is safe to administer to humans
    - the drug has the intended effect in animals
2. They must submit evidence about:
    - the composition of the drug (that it is pure and contains no contaminants that could make the patient sicker)
    - the drug's stability (that it can deliver a consistent dose over time)
    - controls used to produce the drug (such as consistency batch-to-batch and clean environments in which the drug is produced)
3. They must submit their proposed plans for at least four layers of clinical trials to ensure that:
    - patients will not be subjected to unnecessary risks
    - the researchers are qualified to conduct the trials
    - an institutional review board has approved the plans
4. They must certify their commitment to provide informed consent to patients. This means:
    a. each patient is informed about the purpose of the study
    b. what benefits, if any, the patient might accrue, and
    c. what risks they will encounter, that is, all the known side-effects the drug can produce in humans.

d. Patients can then choose to give researchers written permission to administer the experimental drug or to withdraw from the trial.

Investigational New Drug (IND) Once such evidence can be presented to FDA, the producer submits an Investigational New Drug (IND) application to begin testing the drug in humans. Testing occurs under a number of strict conditions designed to protect sick patients. The goal of the IND is to identify possible additional side effects not found in preclinical testing and to ensure that the drug is effective in humans, that is, that it does what its producer claims it will do. Testing begins with only a few people and moves step-wise to larger and larger groups.

Research using a controlled substance If the producer is seeking approval for a drug that is a federally controlled substance, two more steps are required. Each physician who conducts a clinical trial for the producer must:

- obtain a license from the U.S. Drug Enforcement Administration to dispense the controlled substance, and
- obtain a permit to do so from the state substance abuse agency.

Double blind studies Generally, the best way to determine whether a drug is effective is through a double blind study. The experimental drug is compared with a standard medication or a placebo. Patients are randomly assigned to an experimental group or a control group. Someone outside the study codes the two drugs which are formulated to look exactly alike so that neither the patients nor the researchers know who is receiving which drug. Throughout the trial patients are monitored for potential side effects and for information about the effectiveness of the drug they are taking. At the end of the trial, the code is broken. Then, and only then, can researchers see if the experimental drug lived up to its promise.

New Drug Application (NDA) If enough evidence is collected to show the experimental drug is both safe and effective, the producer can submit a New Drug Application (NDA) to FDA to present its data. If approved, the drug can be marketed throughout the United States.[2] The testing and approval processes can take several years and several million dollars to complete.

How does marijuana fit into this picture?

In addition to all the patient protections listed above, clinical trials involving either whole marijuana or one or more of its cannabinoids require two additional steps.

Research-grade marijuana Researchers studying cannabinoids and whole marijuana only use research-grade marijuana in their work. In the U.S., the National Institute on Drug Abuse contracts with the University of Mississippi to grow pure marijuana free of contaminants. It is carefully grown and tested to ensure it is pure, is safe for human use, and can provide a consistent dose from batch to batch.

Extracted, purified cannabinoids Pure chemicals are used in clean environments to extract THC and other cannabinoids from research-grade marijuana, again to guarantee safety for patients participating in clinical research. Any commercial company wishing to develop and seek FDA approval for a pharmaceutical drug involving whole marijuana or any of its cannabinoids must adhere to these same steps.

Patients seeking "marijuana medicines" in states that have legalized the drug for medical use should understand that the "medicines" they buy in these states are neither safe nor effective. They have not been approved by FDA, and they may in fact be harmful. "Medicines" patients buy at dispensaries are completely different from prescription drugs they buy at pharmacies. Unfortunately, few people buying "medicines" in medical marijuana states understand the risks to which they expose themselves and their families.

Three kinds of marijuana medicines

1. Synthetic cannabinoids

To date, two synthetic cannabinoids based on THC have been developed, tested, and approved by FDA for doctors to prescribe. Available since the 1980s, they are dronabinol (trade name Marinol®, AbbVie Pharmaceuticals) and nabilone (trade name Cesamet®, Meda Pharmaceuticals).[3, 4] Both treat cancer chemotherapy-induced nausea and AIDS wasting in patients who do not respond to traditional medicines. Both were synthesized in the laboratory, meaning pure chemicals were used to create them, thus guaranteeing the absence of contaminants.

Equally important, synthesis and proper formulation allow manufacturers to produce a more stable and defined drug. When a doctor prescribes 2.5 mg twice a day, for example, these medicines will actually deliver 2.5 mg with each dose rather than fewer milligrams per dose as the drug deteriorates over time, which is the case with marijuana plant material.

2. Purified cannabinoids

Researchers are studying a number of marijuana components in laboratories and preclinical or clinical trials. In addition, GW Pharmaceuticals is the first pharmaceutical company in the world to develop cannabis-based extracts as pharmaceutical products. GW received permission from the British government in 1998 to grow research-grade marijuana, extract cannabinoids from it, purify those cannabinoids, and develop them into useful medicines. Two of their products are described here.

Sativex® Nabiximois (trade name Sativex®) combines extracted THC and CBD into a mouth spray for the treatment of pain from advanced cancer and the spasticity and nerve pain from multiple sclerosis.[5] Sativex® has been approved in 24 countries including Canada and is in FDA Phase III clinical trials here. If approved, U.S. doctors will be able to prescribe a third medicine derived from marijuana.

Epidiolex® In October 2013, FDA approved seven expanded-access programs giving families whose children suffer severe seizures from rare forms of epilepsy access to this Investigational New Drug. These expanded-access applications were submitted to FDA by individual physicians to give Epidiolex®, also manufactured by GW Pharmaceuticals, to such children.[6] The children are not being placed in experimental groups or control groups, but will take the drug continuously while clinical trials are underway. The purpose of these expanded access programs is two-fold:

1. to treat severely ill children who do not respond to standard medications with a drug that has met FDA requirements for safety in preclinical research while clinical trials take place, and
2. to gather preliminary information for phased trials that will determine whether Epidiolex® can reduce epileptic seizures more effectively than standard medications.

Similar expanded-access applications from more physicians await FDA approval. Each may enroll 25 children, or possibly more, in these programs. As a result, hundreds of children likely will have access to such programs throughout the U.S. soon.[7] Epidiolex® is purified CBD that

contains no THC, which can *cause* seizures. GW's safety and efficacy data from preclinical research and its manufacturing protocols enabled U.S. pediatric epilepsy neurologists to access Epidiolex® for their patients. Should FDA approve Epidiolex® in the future, doctors will be able to prescribe a fourth medicine derived from marijuana.

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3. Marijuana plant materials ("marijuana medicines")

In contrast to the careful, monitored, step-wise process used by medical scientists, twenty states have legalized marijuana for medical use, but no "marijuana medicines" sold in these states offer FDA protections to patients. Few have been tested to ensure they are free of contaminants. Those that have may or may not be up to standards set by the National Institute on Drug Abuse for research grade-marijuana. Growers, processors, and sellers have created an endless array of "marijuana medicines," including a large number of marijuana strains to smoke, marijuana edibles to eat, CBD oils for children with rare forms of epilepsy, and marijuana oils to vaporize and inhale or take by mouth.

Marijuana strains

Growers constantly invent new strains of marijuana and tell patients one strain is good for this problem; another strain is good for that one, with no scientific evidence to support such claims. None of the growers and sellers has conducted clinical trials of any of their "medicines" to demonstrate they are safe or effective for any medical use.[8] None of these "medicines" has been approved by FDA. For all of these reasons, doctors cannot prescribe "marijuana medicines," only recommend them.

Marijuana edibles Medical marijuana industries in these 20 states also have developed "medicines" in the form of food products that are infused with the drug. Pictured are just two of hundreds of marijuana edibles. Again, there is little or no testing to guarantee that the marijuana infused into these food products is pure. FDA has not approved any of these "marijuana medicines," and doctors cannot prescribe these either.

CBD oils This year families with children who suffer seizures from severe forms of epilepsy have lobbied state legislatures throughout the nation to legalize a CBD oil made in Colorado, which legalized medical marijuana in 2000. The problem with this marijuana "medicine" is the same: it has not been approved as safe of effective by FDA and doctors cannot prescribe it. Worse, state regulations requiring marijuana products to be tested for contaminants will not go into effect until later this year. New Haven University is developing testing methods which have commonly found in marijuana plant material such contaminants as pesticides, mold, fungi, E. Coli, and other toxins. Finally, nearly all the CBD oils also contain THC, which can *cause* seizures.

Marijuana concentrates The latest innovation in "marijuana medicine" is Butane Hash Oil, also called budder, wax, and shatter. BHO is made by placing marijuana plant material in a container, adding butane or other solvents to strip the cannabinoids from marijuana, and cooking the mixture to evaporate the solvents. Using butane, a highly flammable solvent, can result in powerful explosions and fires. It has killed not only people trying to make BHO, but innocent bystanders as well.

What remains after cooking is a waxy or glassy substance that is heated so that its vapors can be inhaled. Marijuana entrepreneurs have developed E-Joints, which are like E-Cigarettes but contain a capsule of BHO instead of nicotine. YouTube offers many videos showing how to make marijuana oils, such as this one[9] in which a man teaches browsers how to make "Simpson oil for cancer patients." FDA has not approved any of these forms of "marijuana medicines." After watching how Simpson Oil is made, readers can begin to appreciate why the safety data FDA requires is so important.

How can states make marijuana-based medicines available to patients without putting them at risk?

A state can work with FDA to set up a statewide IND for physicians to investigate purified cannabinoids and/or marijuana for potential medical use. States that do this, however, must provide a supply of research-grade marijuana and extracted cannabinoids that are pure, free of contaminants, and that have been tested in animals to demonstrate safety for human use. This can be accomplished by purchasing purified cannabinoids extracted from research-grade marijuana from the National Institute on Drug Abuse via the University of Mississippi or from pharmaceutical companies that are producing pharmaceutical grade cannabinoids and testing them in clinical trials to determine efficacy for FDA approval. Commercial "marijuana medicines" sold in medical marijuana states that ignore FDA regulations offer no such protections.

For people with illnesses that anecdotal reports suggest certain cannabinoids might help, a state can establish a statewide expanded-access IND program to provide the drug to them while clinical trials are underway.

References

[1] To see information about studies exploring marijuana's potential use in medicine, go here: http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient

[2] An overview of the FDA process of approving new drugs for distribution to the public can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

[3] To learn more about Marinol®, go here: http://www.marinol.com/

[4] To learn more about Cesamet®, go here: http://www.cesamet.com/patient-home.asp

[5] Information about Sativex can be found here: http://www.gwpharm.com/Sativex.aspx

[6] "Comes Now Epidiolex (FDA Approves IND Studies of CBD)," Fred Gardner, O'Shaughnessy's online, October 22, 2013. http://www.gwpharm.com/uploads/oshaughnessysarticle-comesnowepidiolex.pdf

[7] Learn more about Epidiolex here: http://www.gwpharm.com/GW%20Pharmaceuticals%20Provides%20Update%20on%20Orphan%20Program%20in%20Childhood%20Epilepsy%20for%20Epidiolex.aspx

[8] A list of all clinical trials involving marijuana or its components underway in the U.S. can be found here: http://clinicaltrials.gov/ct2/results?term=cannabinoids&Search=Search

[9] Making Simpson oil for cancer patients. http://www.youtube.com/watch?v=nhA5XkAfPiI

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