

Everything You Need to Know About CBD

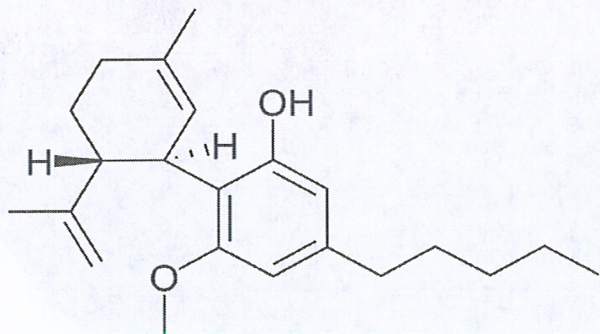
Facts and Talking Points



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TOP TALKING POINTS

- Components of marijuana have medical value, but that does not mean we should smoke or vaporize non-standardized products to get that value.
- Recently, due to CNN and other media outlets, there has been a flood of interest in CBD – a component contained in marijuana.
- CBD does not get you high, and as such, it has been generally bred out of modern, smoked marijuana. But it can be grown under special conditions.
- There is some limited anecdotal and other evidence showing CBD effectiveness for epilepsy, especially in children.
- We should find a way to get CBD to patients who need it, but we owe those who suffer a product with safety assurances. Many products on the current “medical” marijuana market have no such assurances, are never tested in FDA-registered labs, and have no guarantees of quality and content or information on dosing or side effects.
- For those who might benefit from CBD, a company in Britain has developed a standardized CBD product which will soon be in clinical trials in the U.S. and which may also be available from physicians through special FDA-approved channels.



- Many groups are trying to sell or give away CBD in different states without going through any FDA or NIH process. However these products have no such safety assurances.
- SAM is working on a long-term solution to expand and accelerate the current research so that every patient who might benefit from CBD can obtain it.

What is CBD?

CBD and THC are the two primary cannabinoids produced by the cannabis (marijuana) plant. CBD does not have THC-like psychoactivity. CBD was essentially bred out of high-potency modern recreational cannabis, but there has been recent interest in its therapeutic potential. As a result, a number of breeders claim to have “high CBD” strains and numerous purveyors are selling products that they claim are high in CBD. However, many of these products also contain significant levels of THC.

How does CBD work?

CBD works through a number of complex mechanisms. Preclinical studies indicate that CBD has analgesic (pain-relieving), anti-convulsant, anti-psychotic and neuroprotective effects. Unlike THC, it does not bind to the CB1 or CB2 cannabinoids receptors, which is why it does not produce THC-like psychoactivity.

What is the legal status of CBD?

Because CBD is a component of the cannabis/marijuana plant, it is a Schedule I substance under the federal Controlled Substances Act (CSA). The FDA has recently confirmed that CBD is, indeed, a Schedule I substance. Lisa Kubaska, PharmD, who works for the FDA's Center for Drug Evaluation and Research stated in an email to an inquiry from a journalist: "CBD meets the definition of Schedule 1 under the Controlled Substance Act."

Are these CBD products safe?

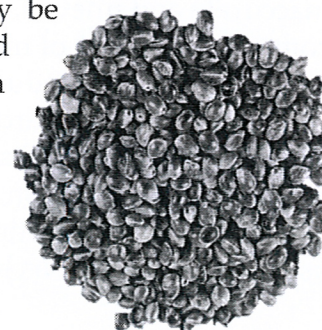


"High CBD" plant material usually also contains varying levels of THC, sometimes significant amounts. Most simple extraction processes cannot reliably extract CBD solely or primarily. Indeed, extremely complex and expensive equipment is required to remove the THC from a "high CBD" extract. The situation is made more hazardous by the fact that existing research demonstrates that, in many cases, large doses of CBD are needed to achieve a specific therapeutic effect. Accordingly, a child taking a therapeutic dose of CBD (100-1000 milligrams per day) would potentially also be exposed to a large amount of THC. For example, using a 10:1 preparation, a child who ingested 300 mg of CBD per day would also be ingesting 30mg of THC. That is the equivalent of three of the highest dose (10mg) Marinol capsules, which would make most adult patients intoxicated. A 2:1 or 1:1 plant ratio product would contain even higher levels of THC.

For example, some companies advertise the following as "high CBD" strains: Harlequin at 11.6%/6.9% CBD: THC; Canna Tonic at 8.11%/6.9% CBD: THC; Sour Tsunami at 7.24%/4.32% CBD: THC (see <http://www.synergymmj.com/products.html>). It is also unclear whether their advertised ratios are accurate, i.e., whether the testing results are valid.

Recent internet comments by parents complain that batches of "artisanal" CBD products do not have a consistent or anticipated effect and/or they are horrified that their children become "high". This is a problem because medicines should be standardized and consistent among batches.

Finally, in many cases, the "high CBD" products may be contaminated by pesticides, synthetic fertilizers, and dangerous microbes. Pesticides are neurotoxic, which could be quite dangerous to children with epilepsy. A number of physicians are reporting instances of bacterial infections, allegedly resulting from the use of these products.



Don't you need some THC to synergize with CBD?

There is absolutely no reliable scientific evidence that THC is necessary to synergize the effects of CBD. Instead, there is evidence from preclinical research that THC may be pro-convulsant in sensitive brains; other research indicates that chronic use of THC can impair IQ in adolescents. Physicians are beginning to report instances of THC toxicity in children taking "high CBD" preparations, e.g., high anxiety, increased seizures, insomnia, etc. Until more is known, the most conservative course of action would be to remove THC entirely from a CBD product.

Why is there so much interest in CBD now?

A number of years ago, Project CBD in California, inspired by research being conducted by GW Pharmaceuticals in the U.K. (see below), began to educate interested patients and others about the therapeutic potential of CBD, which was virtually absent in high-THC marijuana in the U.S. Indeed, before GW embarked on its cannabinoid research and development program, many individuals in the U.S. believed that CBD was an inert compound. There were also anecdotal reports of some adults with epilepsy who discovered that inhaled marijuana seemed to prevent or reduce their seizures. As more and more scientific research demonstrated that CBD had a variety of therapeutic effects, interest in the use of CBD in epilepsy grew.



The CNN program hosted by Dr. Sanjay Gupta in August 2013 portrayed the case of a little girl with horrible, life-threatening intractable epilepsy. According to Dr. Gupta, her condition was greatly improved by a CBD-rich preparation produced by a company in Colorado. Understandably, this program resulted in enormous interest in CBD from families of children with epilepsy.

As desperate parents sought "high CBD" products wherever they could purchase them, a number of dispensaries and other opportunistic vendors began to sell these products. However, the labeled potency and composition are often inaccurate and uneven, depending on the marijuana strain from which they come, the methods of manufacture used to prepare them, and the quality of the testing facility/procedures. At many places in the cultivation and manufacturing process, lack of standardization can result in higher levels of THC and lower levels of CBD - as well as the varying levels of dangerous microbes or pesticides - in the final preparation, e.g. growing from seed rather than clones; differences in the cultivation, harvesting, and drying conditions; uneven decarboxylation; and use of toxic extraction chemicals, such as butane or non-pharmaceutical ethanol.

Should the law be changed to allow high CBD, low THC products?

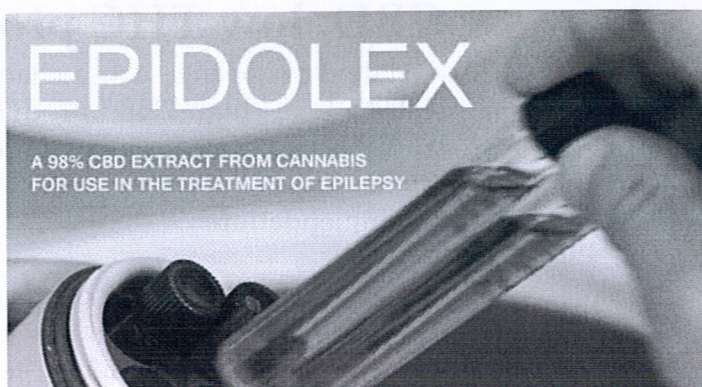
A state considering such a change in law should look to the example of other states where “high-CBD” products are legal for medical use, such as California. In California, various preparations are available, and children can readily be given these products with 1) parental consent and 2) a physician’s recommendation.

Nevertheless, for the reasons stated above, the “legality” of these products has not made properly tested and standardized CBD products available to parents. Products vary in consistency; testing laboratories do not provide reproducible and reliable results; testing each batch is expensive; most testing CBD laboratories do not test for pesticides or microbes; parents do not know how to prepare extracts from plant materials; the products themselves can be expensive; no dosing information is available; and more.

Legislation is a blunt instrument, and any change in state law will, necessarily, be quite broad (e.g. “high CBD, low THC”) to permit various opportunistic growers and vendors to enter the state and prey upon vulnerable parents. Unless an elaborate testing system is established and enforced by the state, this will not ensure the safe, tested, and standardized products that parents seek for their children. Even certain more popular products are of uncertain composition, quality and efficacy. Companies selling these products have not made public the composition/ratio of an adequate number of batches, nor have they provided full battery anonymized case studies showing how many patients benefit and to what extent, how many patients get little or no benefit, what side effects they experience, and what they charge for the product. At most, 11 “selected” case studies have been presented, all of which show benefit. However, these are anecdotal cases reported by parents, and it is unlikely that current CBD preparations work for all seizure conditions.

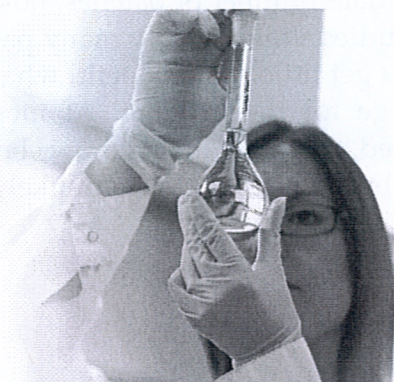
What is Epidiolex®?

Epidiolex® is produced by GW Pharmaceuticals in the U.K. It is an oral liquid formulation of a highly purified extract of a high-CBD strain of the cannabis/marijuana plant. The extract is passed through several complex purification steps to remove the THC. Epidiolex® contains more than 98% pure CBD and infinitesimal amounts of THC. While GW generally believes in the beneficial effects of cannabinoid synergy (indeed, it was GW that brought the concept of cannabinoid synergy to public awareness), GW is concerned that the presence of THC may be harmful to children with brains already stressed by epilepsy.



GW's CBD has been tested in a wide range of rodent models of epilepsy and has a substantial body of safety data. All steps in the Epidiolex® manufacturing process are conducted under Good Manufacturing Processes (GMP). The formulation is produced in two defined CBD concentrations (either 25 mg/ml or 100 mg/ml).

Is Epidiolex® available in the U.S.?



Epidiolex® has not yet been approved by the FDA for marketing as a prescription medication. Therefore, it is considered an investigational drug. Investigational drugs are only available through Investigational New Drug (IND) programs. Currently, there are seven physician-sponsored Investigational New Drug (IND) programs that the FDA has approved under its "expanded access" regulations (2 individual INDs and 5 intermediate size INDs). INDs allow the drug to be used legally, Children are being treated with Epidiolex® under two of those INDs, and the others are in the final stages of DEA registration and state controlled

substance licensing. They are expected to be underway sometime early in 2014. In addition, a number of other physician-INDs will be subsequently opened. GW is providing Epidiolex® free of charge to patients in these INDs until the product is approved by the FDA for prescribing.

GW has also announced that, following receipt of their orphan designation for the use of CBD in Dravet's Syndrome, the company anticipates holding a pre-IND meeting with the FDA in the near future to discuss a clinical trial development plan for Epidiolex®. They are actively designing that program, and the first clinical trials are expected to be underway in 2014. Patients who enter into a clinical trial will receive either Epidiolex® or a placebo (on top of their existing anti-epileptic medications) for 2-3 months and then will be offered the opportunity to enter into a long term extension study.

Statement by Dr. Stuart Gitlow

President, American Society of Addiction Medicine
Chair-Elect, American Medical Association Committee
on Science and Health
Board Member, Project SAM (Smart Approaches to
Marijuana)

Written Testimony Submitted to the New York
State Legislature
Hearing on Medical Marijuana
December 18, 2013

Members of the Committee, thank you for allowing my statement to be entered into the record. I am the President of the American Society of Addiction Medicine, Chair-Elect of the American Medical Association Committee on Science and Health, and a Board Member of Project SAM – Smart Approaches to Marijuana – a nonpartisan group of professionals dedicated to sensible marijuana policy grounded in science.

The issue of medical marijuana is an emotional one. On the one hand, advocates, many of whom advocate for the legalization of marijuana for any purpose, claim that marijuana is a miracle drug that can cure cancer, help alleviate pain, and ease the suffering of millions. On the other hand, there are people who claim marijuana has no medicinal properties whatsoever.

The scientific fact is that while there are medical components contained in marijuana, crude herbal marijuana – smoked, vaporized, eaten, etc. – is not medicine. It has not undergone the FDA process for demonstrating safety and efficacy, and no major medical association supports its use. I realize there are some people who claim they cannot wait for the FDA to approve marijuana-based medications, and that is why I support the Federal IND program currently allowing doctors of parents whose children have intractable epilepsy to obtain a pure, properly-tested and standardized CBD product (CBD is an element within marijuana that is nonintoxicating). One organization I am a part of, Smart Approaches to Marijuana, supports such efforts.

Science has also synthesized the marijuana plant's primary psychoactive ingredient – THC – into a pill form. This pill, dronabinol (or Marinol®, its trade name) is sometimes prescribed for nausea and appetite stimulation. Another drug, Cesamet, resembles chemical structures that naturally occur in the plant.

But when most people think of medical marijuana these days, they don't think of a pill

rather the entire smoked, vaporized, or edible version of the *whole marijuana plant*. Rather than isolate active ingredients in the plant – like we do with the opium plant when we create morphine, for example – many legalization proponents advocate vehemently for smoked marijuana to be used as a medicine. But the science on smoking any drug is clear: smoking especially highly-potent whole marijuana, is not a proper delivery method, nor do other delivery methods (vaporization, “medibles”) ensure a reliable dose. And while parts of the marijuana plant have medical value, the Institute of Medicine said in its landmark 1999 report: “Scientific data indicate the potential therapeutic value of cannabinoid drugs...smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances...and should not be generally recommended...”¹

It is not so unimaginable to think about other marijuana-based medications that might come to the market very soon. Sativex®, an oral mouth spray developed from a blend of two marijuana extracts (one strain is high in THC and the other in CBD, which counteracts THC's psychoactive effect), has already been approved in 23 countries and is in late stages of approval in the U.S. It is clear to anyone following this story that it is possible to develop marijuana-based medications in accordance with modern scientific standards, and many more such legitimate medications are just around the corner.

Who uses medical marijuana in states now?

It is important that New York State learns from the example of other states that have passed medical marijuana either by referenda or legislative action. A study published in the *Harm Reduction Journal*, found that the average user of medical marijuana was a 32-year-old white male who had used cocaine and methamphetamine in their lifetime.² According to a 2011 study in the *Journal of Drug Policy Analysis* that examined 1,655 applicants in California who sought a physician's

recommendation for medical marijuana, very few of those who sought a recommendation had cancer, HIV/AIDS, glaucoma, or multiple sclerosis.³ In fact, in Colorado, according to the Department of Health, only 2% of users reported cancer, and less than 1% reported HIV/AIDS as their reason for marijuana. The vast majority (94%) reported "severe pain."⁴ In Oregon, there are reports that only 10 physicians made the majority all recommendations for "medical" marijuana⁵, and agitation, seizures, cancer, HIV/AIDS, cachexia, and glaucoma were the last six reasons people utilized marijuana for "medical" purposes.⁶

Effects on use among youth

A major study in *Drug and Alcohol Dependence* by researchers at Columbia University looked at two separate datasets and found that residents of states with "medical" marijuana had marijuana abuse/dependence rates almost twice as high than states without such laws.⁷ A study in the September 2011 issue of *Annals of Epidemiology* found that, among youths age 12 to 17, marijuana usage rates were higher in states with medical marijuana laws (8.6%) compared with those without such laws (6.9%).⁸

A more recent study, by Rosalie Pacula of RAND and Dr. Eric Sevigny found that states with two main characteristics - legal home cultivation and medical marijuana "dispensaries" - were positively associated with increased youth marijuana use even when controlling for other factors.

Most of the medical groups I am part of have reiterated several times that marijuana should be subject to the same standards that are applicable to other prescription medications and that these products should not be distributed or otherwise provided to patients unless and until such products or devices have received marketing approval from the Food and Drug Administration. ASAM, the AMA, and other groups reject smoking as a means of drug delivery since it is not safe. We also reject

a process whereby State and local ballot initiatives approve medicines because individuals not qualified to make such decisions are deciding these initiatives. I have included a compendium below of medical organizations' positions on this matter.

New York State has a choice: It can listen to advocates or to scientists. As a scientist, I strongly recommend New York State does not go down the path of creating a state-based system for administering medical marijuana and that parents and others who need relief today enroll in the NIH programs available to them.

Thank you.

Notes:

¹ *Marijuana and Medicine: Assessing the Science Base*, Institute of Medicine

1999. http://books.nap.edu/catalog.php?record_id=6376

² O'Connell, T and Bou-Matar, C.B. (2007). Long term marijuana users seeking medical cannabis in California (2001-2007):

demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. *Harm Reduction Journal*, Retrieved from:

<http://www.harmreductionjournal.com/content/4/1/16>

³ Nunberg, Helen; Kilmer, Beau; Pacula, Rosalie Liccardo; and Burgdorf, James R. (2011) "An

Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California,"

Journal of Drug Policy Analysis: Vol. 4: Iss. 1, Article 1. Retrieved from: <http://www.bepress.com/jdpa/vol4/iss1/art1>

⁴ See Colorado Department of Public Health,

<http://www.cdph.state.co.us/hs/medicalmarijuana/statistics.html>

⁵ See for example, Danko, D. (2005). Oregon Medical Marijuana Cards Abound, *The Oregonian*, January 23, 2005. Also see Oregon Medical Marijuana, Protect the Patients & Treat it Like Medicine,

http://www.oregon.gov/Pharmacy/Imports/Marijuana/Public/ORStatePolice_OMMALegPP.pdf?ga=t

⁶ Oregon Medical Marijuana Program Statistics, <http://public.health.oregon.gov/DISEASES/CONDITIONS/CHRONICDISEASE/MEDICALMARIJUANAPROGRAM/Pages/data.aspx>

⁷ Cerda, M. et al. (in press). Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence*. Found at

<http://www.columbia.edu/~dsh2/pdf/MedicalMarijuana.pdf>

⁸ Wall, M. et al (2011). Adolescent Marijuana Use from 2002 to 2008: Higher in States with Medical Marijuana Laws, Cause Still Unclear, *Annals of epidemiology*, Vol 21 issue 9 Pages 714-716.

MEDICAL ASSOCIATION POSITIONS ON MARIJUANA

American Society of Addiction Medicine:

"ASAM asserts that cannabis, cannabis-based products, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications and medical devices and that these products should not be distributed or otherwise provided to patients unless and until such products or devices have received marketing approval from the Food and Drug Administration. ASAM rejects smoking as a means of drug delivery since it is not safe. ASAM rejects a process whereby State and local ballot initiatives approve medicines because these initiatives are being decided by individuals not qualified to make such decisions."

American Cancer Society:

"The ACS is supportive of more research into the benefits of cannabinoids. Better and more effective treatments are needed to overcome the side effects of cancer and its treatment. The ACS does not advocate the use of inhaled marijuana or the legalization of marijuana."

American Glaucoma Foundation:

"Marijuana, or its components administered systemically, cannot be recommended without a long term trial which evaluates the health of the optic nerve," said the editorial. "Although marijuana can lower 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."

National Multiple Sclerosis Society:

"Although it is clear that cannabinoids have potential both for the management of MS symptoms such as pain and spasticity, as well as for neuroprotection, the Society cannot at this time recommend that medical marijuana be made widely available to people with MS for symptom management. This decision was not only based on existing legal barriers to its use but, even more importantly, because studies to date do not demonstrate a clear benefit compared to existing symptomatic therapies and because issues of side effects, systemic effects, and long-term effects are not yet clear."

(Recommendations Regarding the Use of Cannabis in Multiple Sclerosis: Executive Summary. National Clinical

The American Academy of Pediatrics (AAP) believes that "[a]ny change in the legal status of marijuana, even if limited to adults, could affect the prevalence of use among adolescents." While it supports scientific research on the possible medical use of cannabinoids as opposed to smoked marijuana, it opposes the legalization of marijuana. - Committee on Substance Abuse and Committee on Adolescence. "Legalization of Marijuana: Potential Impact on Youth." (*Pediatrics* Vol. 113, No. 6 (June 6, 2004): 1825-1826. See also, Joffe, Alain, MD, MPH, and Yancy, Samuel, MD. "Legalization of Marijuana: Potential Impact on Youth." *Pediatrics* Vol. 113, No. 6 (June 6, 2004): e632-e638h.)

The American Medical Association (AMA) has called for more research on the subject, with the caveat 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." Furthermore, AMA believes (1) cannabis is a dangerous drug and as such is a public health concern; (2) sale of cannabis should not be legalized.

John Knight, director of the Center for Adolescent Substance Abuse Research at Children's Hospital Boston, recently wrote: "Marijuana has gotten a free ride of sorts among the general public, who view it as non-addictive and less impairing than other drugs. However, medical science tells a different story."

The American Psychiatric Association (APA) states:

(1) There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. Current evidence supports...a strong association of cannabis use with the onset of psychiatric disorders. (2) 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...must be simultaneously studied. (3) No medication approved by the FDA is smoked.