

Cannabis: Evaluating the Evidence

Presenters:

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Disclaimer

- Consultant for Greenwich Biosciences, Inc.

FDA's position on non-pharmaceutical cannabis products



FDA
Food and Drug Administration
Scott Gottlieb
FDA Commissioner until April, 2019

“Research to demonstrate that marijuana or its components could be safe and effective in the treatment of medical disorders should be held to the same standard as other drug compounds. And certainly it should not be held to a lower standard, as some proponents would suggest.”

“Controlled clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA’s drug approval process, is the most appropriate way to bring marijuana-derived treatments to patients.”

“Such a process ensures that any new therapies from marijuana and its constituents are safe, effective and manufactured to a high and consistent quality.”

FDA approval answers critical questions important for all, but especially for vulnerable patients

+

DOES THE DRUG WORK?

- What does it work for?
- What doesn't it work for?
- How well does it work?
- How does it compare to alternatives?
- How long does it take to work?
- Will it stop working?
- How much should I take?
- How long should I take it?
- Should I take it with or without food?

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IS THE DRUG SAFE?

- What are the side effects?
- How closely should I be monitored?
- Do the benefits outweigh the harms?
- Can I take it if I'm pregnant or trying?
- Will it conflict with my other medications?
- How is it manufactured?
- Is each dose the same?
- Is it free of contaminants?

Quality defects in dispensary products place patients at increased risk

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ology team was consulted and recommen
and fosphenytoin for seizure control. The
drowsy in the emergency department but
intubation. While in the hospital, he was r
A broad workup including MRI brain,
and lumbar puncture revealed no obvious cause for his
new symptoms. Urine drug immunoassay was positive for
benzodiazepines and cannabinoids. After two days he
returned to baseline and was ultimately discharged from
the hospital. Analysis of the patient's CBD oil using liquid
chromatography-quadrupole time-of-flight mass spectrometry
(LC-QTOF/MS) confirmed that it contained both CBD and
AB-FUBINACA, a synthetic cannabinoid consistent with the
patient's symptoms [3]. No other xenobiotics were found.

While CBD may be useful in a small subset of patients
with refractory seizures, we are concerned that its off-label
use from non-pharmaceutical sources appears to be increas
ing in frequency. Retail CBD may not have the purity and
testing requirements of Epidiolex. Interestingly, both

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To the Editor,
Cannabidiol (CBD) is approved by the Food

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Epidiolex
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His parents reported discussing the
initiation of CBD treatment with their
neurologist, who had agreed with its use
as a trial.

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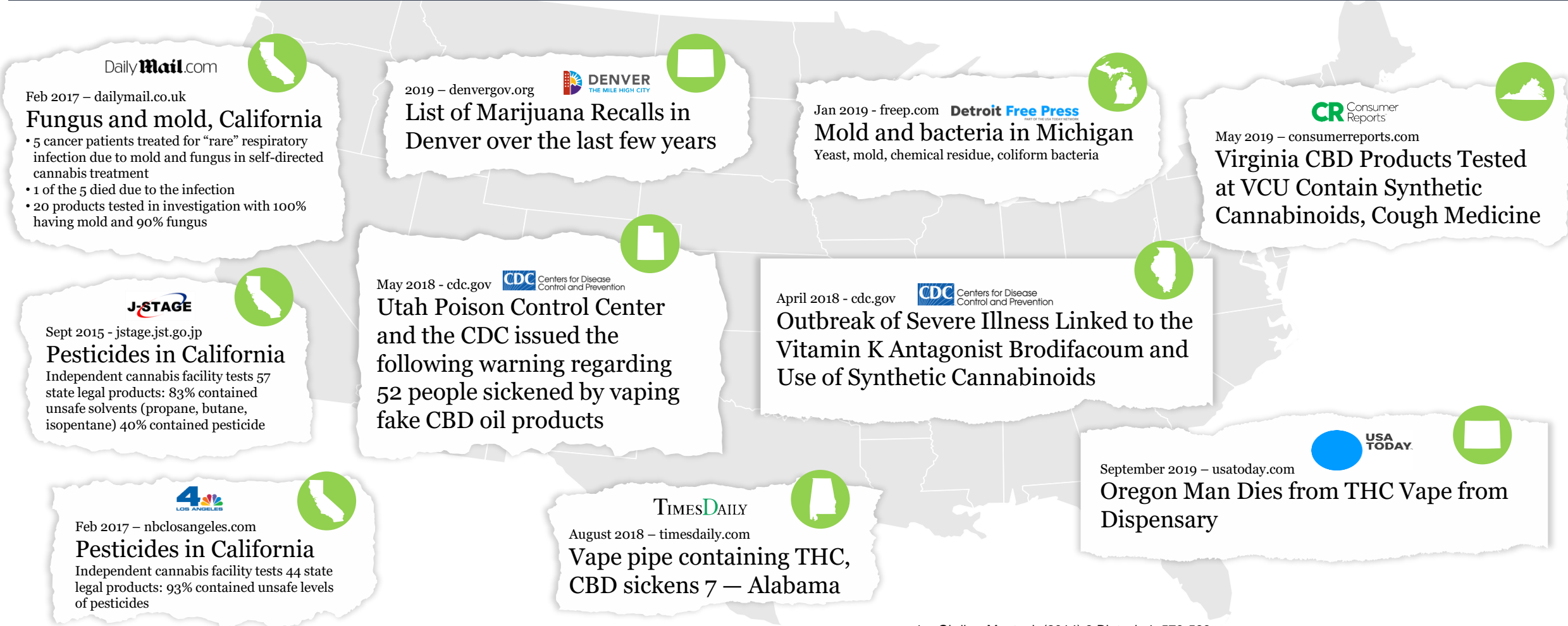
After a 9-day period of seizure-free activity
on the CBD oil, the patient was brought to
the emergency department for evaluation
of a **24-hour period in which he had >14
tonic-clonic episodes**. He was noted to
have intermittent agitation, delirium,
depressed mental status, tachycardia, and
mydriasis.

Analysis confirmed presence of
AB-FUBINACA
a dangerous synthetic cannabinoid
associated with multiple illness
outbreaks and deaths

The boy survived after
treatment in the ICU

Quality defects in dispensary products place patients at increased risk

Cannabis naturally draws toxins from soil, so it can become contaminated with heavy metals, pesticides and various other contaminants



1. Girdhar M, et. al. (2014) 3 Biotech 4: 579-589.
2. Congressional Research Service Potential Use of Industrial Hemp in Cannabidiol Products.

Evidence-Based Medicine



Current EBM movement dates from the 1970s (see Eddy, Virtual Mentor: AMA Journal of Ethics, Vol. 1, pp 55-60, Jan. 2011)



EBM is a shift from subjective judgments from clinical experience and reliance on expert opinion toward an analysis and often grading of the published scientific evidence for a given health intervention



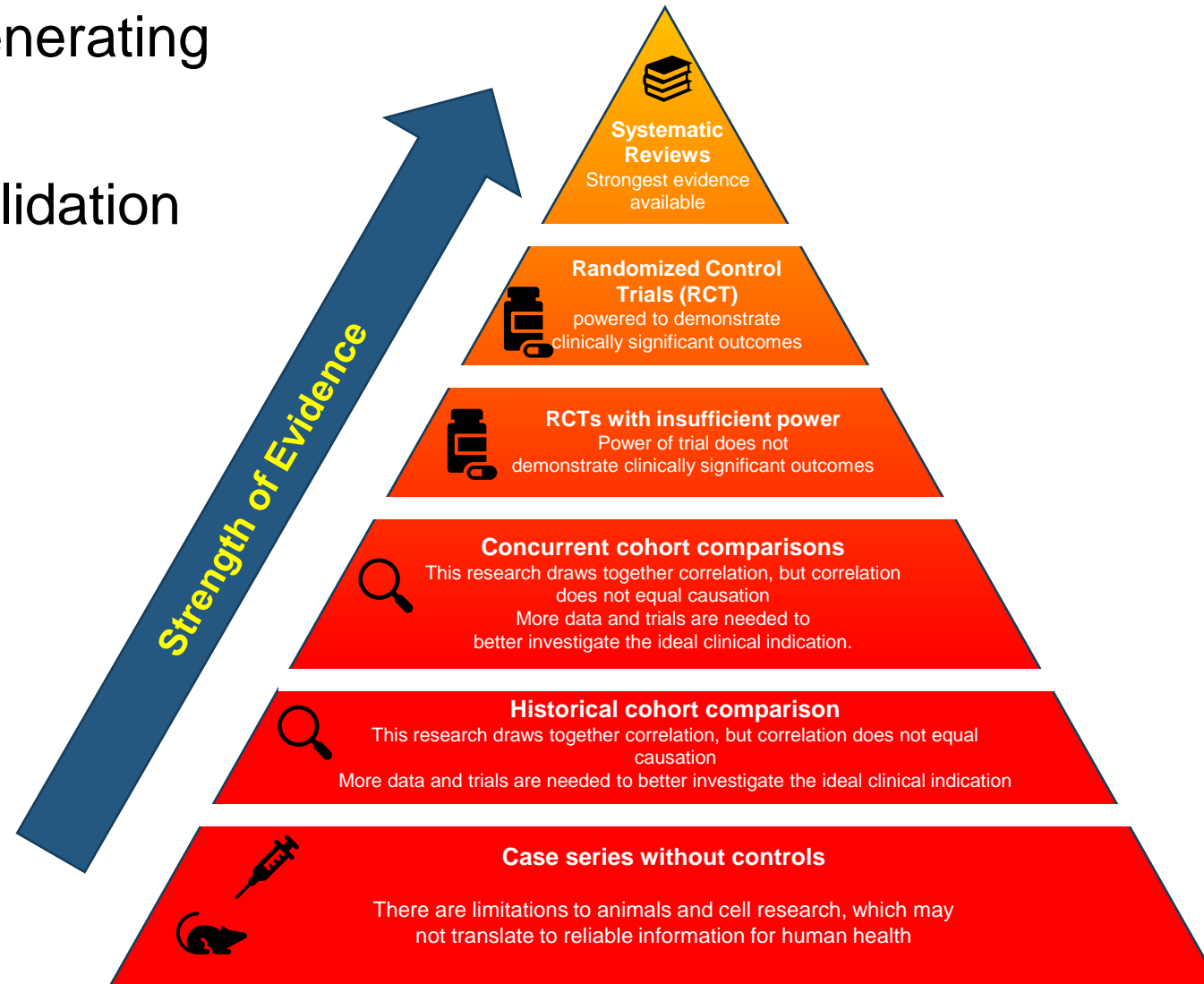
“...Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and patho-physiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.” EBM Working Group, JAMA 1992



EBM reports include technology assessments, systematic reviews, evidence-based practice guidelines, and other formal analyses.

Evaluating the evidence

- Hypothesis generating
vs.
- Hypothesis validation



Low-strength evidence influences decision-making in state medical marijuana programs



2014: ecological study shows association, but no causal connection, between states with MMJ laws and fewer opioid-related deaths




New York State Department of Health Announces Opioid Use to be Added as a Qualifying Condition for Medical Marijuana

“Studies of some states with medical marijuana programs have found notable associations of reductions in opioid deaths and opioid prescribing with the availability of cannabis products. State with medical cannabis programs have been found to have lower rates of opioid overdose deaths than other states, perhaps by as much as 25 percent”

2018: NY adds opioid use as qualifying condition, citing 2014 ecological study



Original Investigation | Substance Use and Addiction

Association of State Policies Allowing Medical Cannabis for Opioid Use Disorder With Dispensary Marketing for This Indication

Chelsea L. Shover, PhD; Noel A. Vest, PhD; Derek Chen; Amanda Stueber, BS; Titilola O. Falasinnu, PhD; Jennifer M. Hah, MD, MS; Jinhee Kim, BA; Ian Mackey, BA; Kenneth A. Weber II, DC, PhD; Maisa Ziadni, PhD; Keith Humphreys, PhD

2020: study shows inclusion of OUD on states' lists of qualifying conditions leads to increased marketing of cannabis for that indication

Low-strength evidence influences decision-making in state medical marijuana programs



Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover^{1*}, Corey S. Davis², Sanford C. Gordon¹, and Keith Humphreys^{1,3}

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*Work by Kenneth M. Warner, University of California, Berkeley, CA, and approved May 18, 2017 (received for review February 21, 2017)

- Caputi TL, Humphreys K. *Medical marijuana users are more likely to use prescription drugs medically and non-medically.* J Addict Med. 2018;12 (4):295-299.
- Mark Olfson, et al., *Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States*, 175 Am. J. Psychiatry 47, (2018).
- Campbell G, et al. *Effect of cannabis use in people with chronic non-cancer pain prescribed opioids.* Lancet Public Health. 2018; 3(7):e341-e350.

Scientific and medical authorities raise concerns over the safety and efficacy of dispensary cannabis products



“~~[T]he use of unapproved cannabis and cannabis-derived products *can have unpredictable and unintended consequences, including serious safety risks.*~~ There has been no FDA review of data from rigorous clinical trials to support that these unapproved products are safe and efficacious for the various therapeutic uses for which they are being used.”

“Scientifically valid and well-controlled clinical trials conducted under federal investigational new drug applications are necessary to assess the safety and effectiveness of all new drugs, including potential cannabis products for medical use.”



“~~[T]he AAN *does not support the use of, nor any assertion of therapeutic benefits of, cannabis products as medicines for neurologic disorders...*~~ [T]he evidence is lacking to draw conclusions regarding the effectiveness of cannabis for... neurologic conditions.”

“~~[T]here is *no current scientific evidence*~~ that cannabis is in any way beneficial for the treatment of any psychiatric disorder. Current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders.”

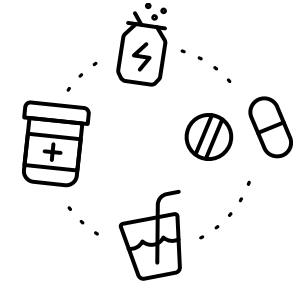
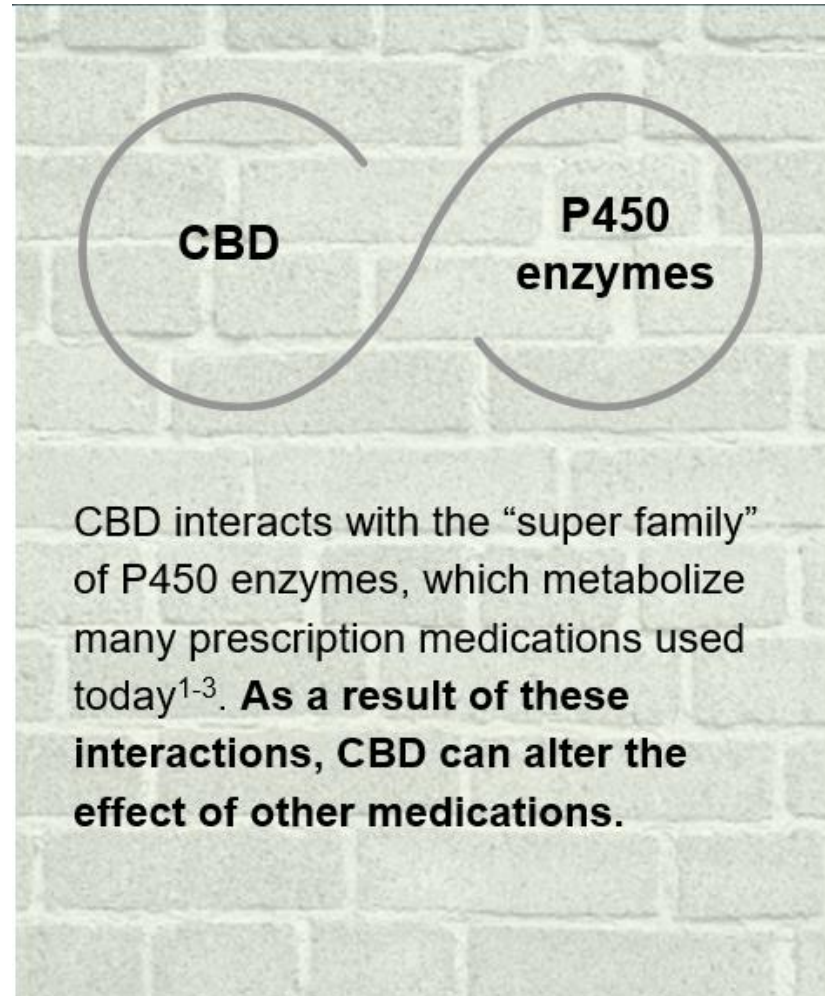


Evidence derived from clinical trials is essential to managing the prescribing and utilization of medicines



Lack of healthcare professional oversight poses a serious concern in patients who take multiple drugs because—

- CBD can alter the effect of other medications
- CBD could decrease or increase the potency of the other drugs the patient is taking

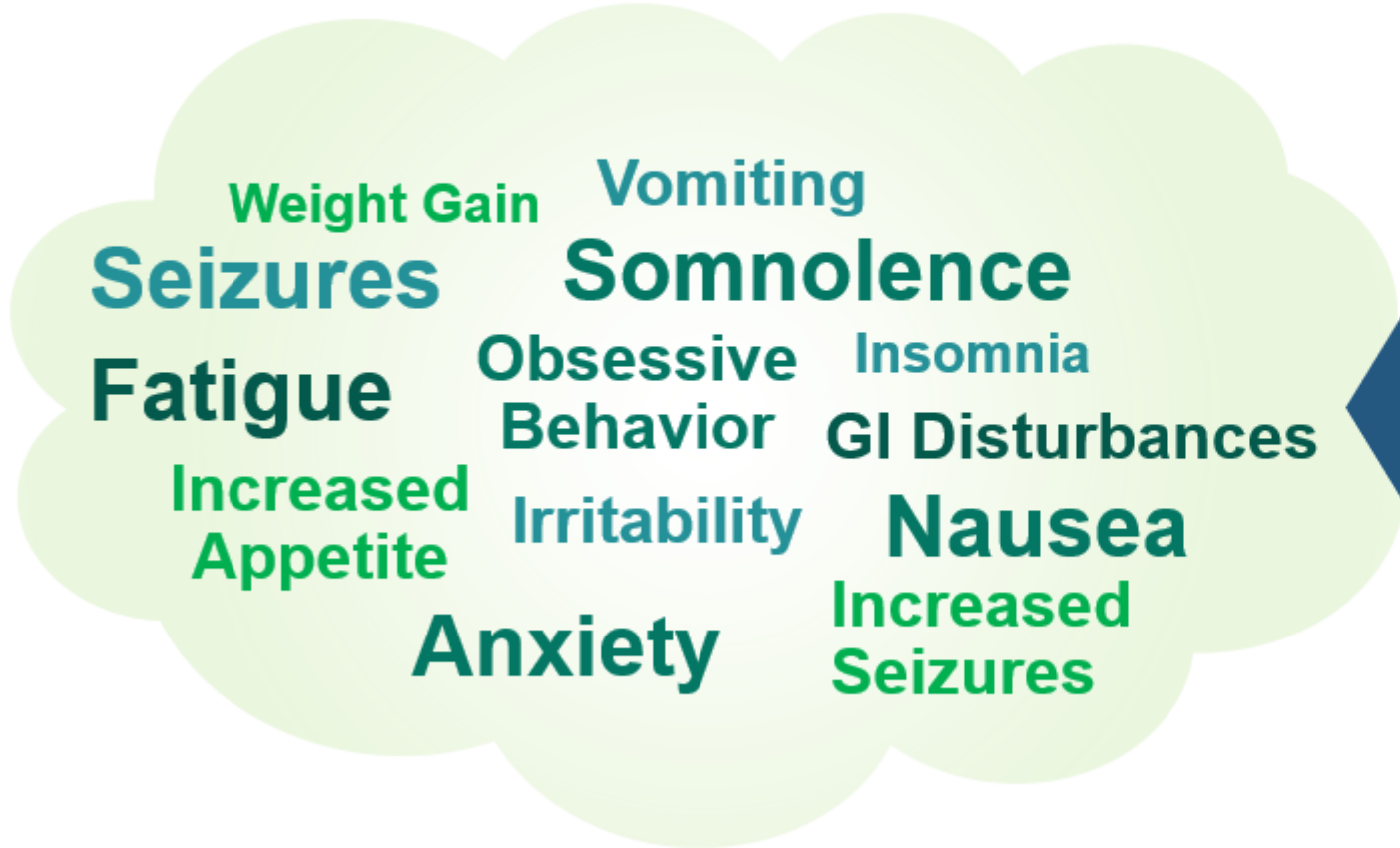


Some commonly prescribed drug classes metabolized by P450 enzymes⁴:

- Antiseizure drug
- Proton pump inhibitors
- Antidepressants/Prozac
- Anti-virals
- Anti-bacterials
- Oral contraceptives

Evidence derived from clinical trials is essential to managing the prescribing and utilization of medicines

Self-reported side effects of CBD products and oral cannabis extracts* (>10% of patents)¹⁻³



Controlled studies with regular monitoring

Liver toxicity
was found in 10% of participating patients in Epidiolex trials

*Liver transaminases were not monitored

1. Hussain et al. (2015) Ep & Beh. 47: 138-141; 2. Press & Knupp. (2015) Epi & Beh. 45:49-52; 3. Treat et al. (2017) Epilepsia; 58(1): 123-127.

Many potential formulations—each with potentially unique safety/efficacy profile

MEETING NEWS

American Academy of Neurology Annual Meeting

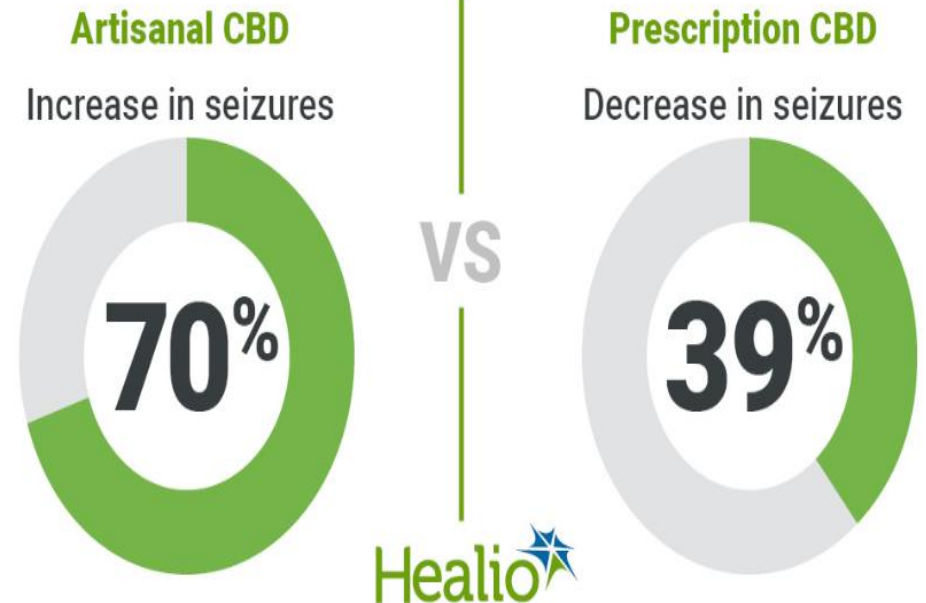
Seizure control greater with prescription vs. artisanal CBD in pediatric epilepsy

February 27, 2020

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Pediatric patients with epilepsy [treated with pharmaceutical CBD](#) had better seizure control than those treated with artisanal CBD, according to findings from a retrospective chart review that will be presented at the American Academy of Neurology annual meeting this spring.

Among 31 children with some form of epilepsy:



FDA-approved vs. non-FDA approved cannabinoid products

Food & Drug Administration (FDA)-Approved Cannabinoid Products^{1,2} *Plant-Based and Synthetic Medicines*

Non-FDA Approved Cannabinoid Products³ *Hemp-Derived Dispensary Products and Medical Marijuana*

Study Evidence & Requirements

✓ Studied in placebo-controlled, clinical trials

Large-scale randomized clinical studies that meet FDA standards have not been conducted. Public disclosure of smaller, informal studies not required

Manufacturing

✓ Produced and federally inspected to ensure good manufacturing practices (cGMP) while adhering to strict specifications that ensure batch consistency and stable shelf life

Testing standards vary from state to state, and some states require no testing. There are no federal standards; FDA does not inspect the manufacturing sites for adherence to cGMP

Quality Standards

✓ Meets FDA standards for quality, stability, consistency

Non-prescription, non-FDA approved cannabinoid products are subject to inconsistent regulation at the state level. There are no federal standards for testing to ensure accuracy and consistency⁴

Legality

✓ Federally legal as prescribed; similar to other DEA-controlled prescription medicines

Restrictions to access vary by state.⁵ Healthcare providers can “recommend” but not prescribe hemp-derived dispensary products or marijuana, as they are illegal at the federal level. Interstate transportation of these products is federally illegal

Coverage

✓ Can be eligible for insurance coverage

Insurance coverage is non-existent

1. <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm>. Accessed October 31, 2017.
 2. <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>. Accessed October 30, 2017.
 3. https://oacu.oir.nih.gov/sites/default/files/uploads/arac-guidelines/pharmaceutical_compounds.pdf. Accessed October 30, 2017.
 4. <https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm>. Accessed January 23, 2018.
 5. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>. Accessed October 31, 2017.



THANK YOU

Establishing regulatory “swim lanes” for cannabis-based products

