

YEAH, I SMOKED IT

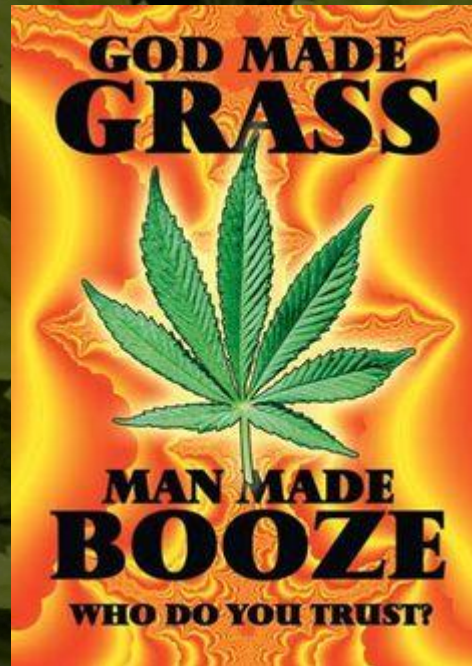
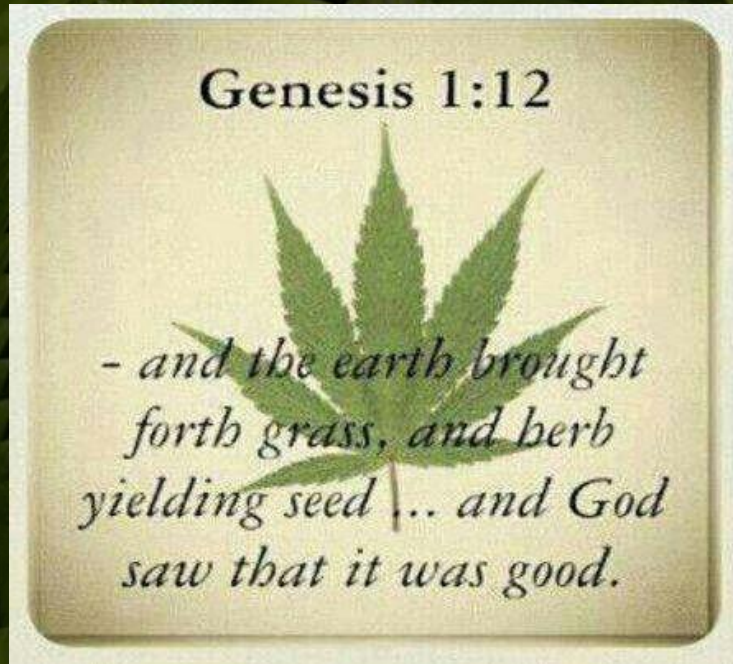


BUT I DIDN'T INHALE

CONFUSED ABOUT CANNABIS?

A Look at the Evidence
for Medical Marijuana
in Pets

CANNABIS: GOD'S GIFT OR DEVIL'S WEED?



CANNABIS IS BAD

Drugs Destroy Lives.
Don't let Your Life Go
Up In Smoke.

pot
IS A
trop

stoppot2016.com

Health Risks

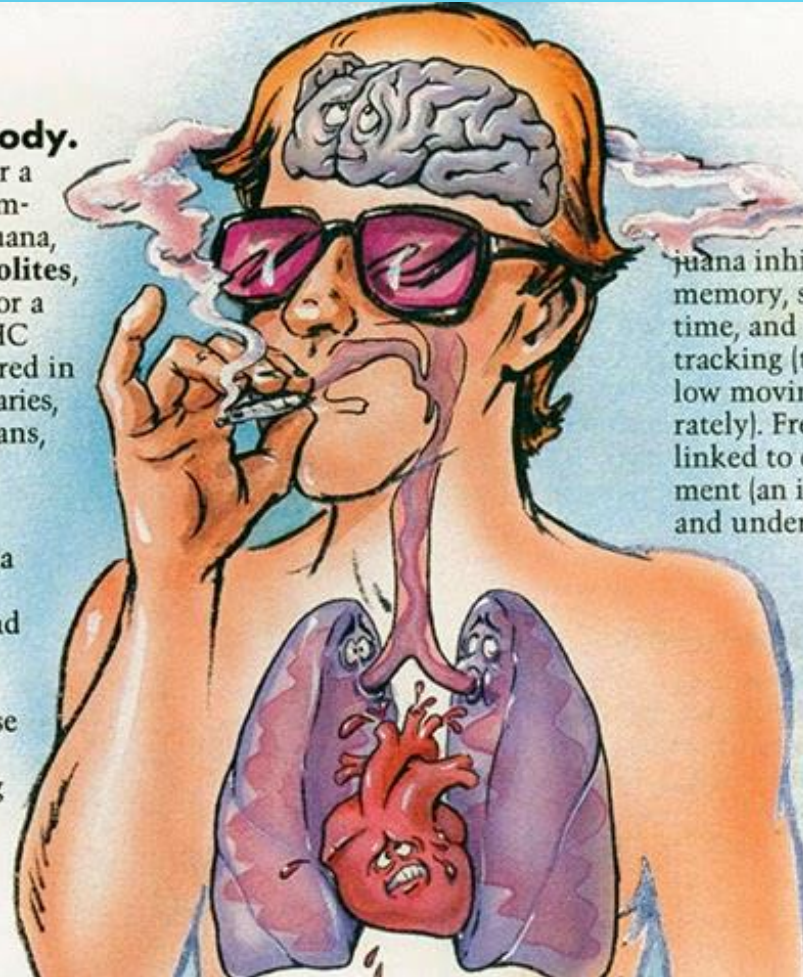
THC in your body.

You're only high for a few hours. But chemical traces of marijuana, called **THC metabolites**, stay in your body for a month or more. THC metabolites are stored in the brain, testes, ovaries, and other fatty organs, and are detectable by urine tests.

Lungs. Marijuana smoke irritates the throat and lungs and has twice as much "tar" as cigarette smoke. Frequent use is linked to an increased risk of lung cancer, bronchitis, and emphysema.

Brain. Marijuana inhibits short-term memory, slows reaction time, and impairs visual tracking (the ability to follow moving objects accurately). Frequent use is also linked to cognitive impairment (an inability to abstract and understand concepts).

Heart. Marijuana speeds a user's heartbeat as much as 50% while high, an increased risk for anyone with heart disease.



CANNABIS IS BAD



Marijuana is probably the most dangerous drug in America today.

— *Ronald Reagan* —

AZ QUOTES

CANNABIS IS GOOD

Marijuana cures cancer
US government has known since 1974

FDA

CANNABIS OIL

#BlackStuff



A DROP A DAY KEEPS THE CANCER AT BAY

...AND DIABETES, AND SEIZURES,
CHRON'S, ASTHMA, PTSD, ADD
ARTHRITIS, CHRONIC PAIN, NEUROPATHY
MULTIPLE SCLEROSIS, GLAUCOMA
AND THE LIST GOES ON AND ON AND ON...

CANNABIS IS GOOD



“ Cannabis is the single most versatile herbal remedy, and the most useful plant on Earth. No other single plant contains as wide a range of medically active herbal constituents. ”



DR. ETHAN RUSSO
CANNABINOID RESEARCH INSTITUTE

CANNABIS IS BAD (FOR PETS)



POT MAKES PETS SICK

Pot ingestion leads to:

- Coordination issues
- Depression
- Seizures
- Vomiting
- Coma

Cost for treatment
(based on Trupanion claims history)

- Lowest: \$89
- Highest: \$1,783
- Average: \$603

Prevention is easy:

- Keep pot (leaves, smoke, or in baked goods) away from pets!


trupanion

CANNABIS IS GOOD (FOR PETS)

Health Benefits of Cannabidiol (CBD)

- Antiepileptic
- Anticancer
- Anti-inflammatory
- Bone stimulant
- Analgesic
- Anti-depressant
- Antibacterial
- Antipsoriatic
- Antidiabetic
- Antimicrobial
- Anti-nausea
- Anti-anxiety
- Intestinal anti-prokinetic
- Antipsychotic
- Neuroprotective
- Vasorelaxant
- Antispasmodic
- Anti-ischemic
- Anti-proliferative
- Antineoplastic
- Immunosuppressive

These statements have not been evaluated by the FDA. Canna-Pet products are not intended to diagnose, treat, cure, or prevent any disease.



Brain
antipsychotic antioxidant
neuroprotective
anti-depressant anti-anxiety

Bones, Joints & Spine
strengthens bones anti-inflammatory analgesic

Eyes
vasorelaxant
anti-inflammatory

Intestines
anti-prokinetic

Heart
anti-ischemic
anti-inflammatory

Stomach
anti-nausea
appetite control

The Original
Canna-Pet™
Capsules

NEW
Maximum CBD
Capsules
&
Canna-Biscuits™
for Dogs

Canna-Pet™

the ONLY pet products with CBD

Canna-Pet.com
designed for pets

made in the USA
from hemp

© Canna-Pet

CANNABIS IS GOOD (FOR PETS)

“Quite a few studies that show many benefits.”

- Anxiety
- Arthritis
- Epilepsy
- Diabetes
- Nausea and Vomiting
- Skin Issues
- Cognitive Dysfunction
- Cancer

Hemp Benefits for Dogs



<https://www.natural-dog-health-remedies.com/hemp-benefits.html>

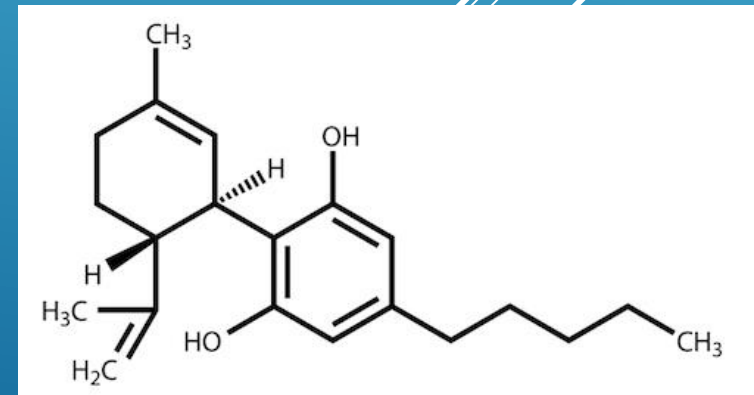
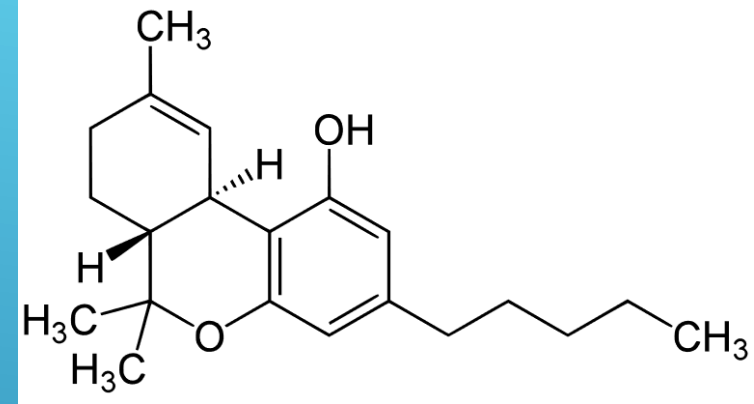


WHAT IS CANNABIS?

- Genus *Cannabis*
 - Possible species or subspecies *C. sativa* and *C. indicus*
- Hundreds of chemical compounds
 - Cannabinoids
 - Terpenoids
 - Flavanoids
 - Others

WHAT IS CANNABIS?

- Key compounds
 - Tetrahydrocannabinol (THC)
 - Cannabidiol (CBD)





WHAT IS CANNABIS?

- Physiologic effects of cannabinoids
 - Endocannabinoid receptors in the brain, also in the GI tract, liver, skeletal muscle
 - Other receptors (serotonergic, vanilloid, adenosine)
 - Antioxidant effects



WHAT IS CANNABIS?

- Physiologic effects of cannabinoids
 - Wide range of effects on mood, appetite, emesis, pain, inflammation, immune function, nerve function



WHAT IS CANNABIS?

- Physiologic effects vary with
 - Strain of *Cannabis* and relative levels of various compounds
 - Route of administration
 - Form (herbal, extracts, resin, medicinal products)

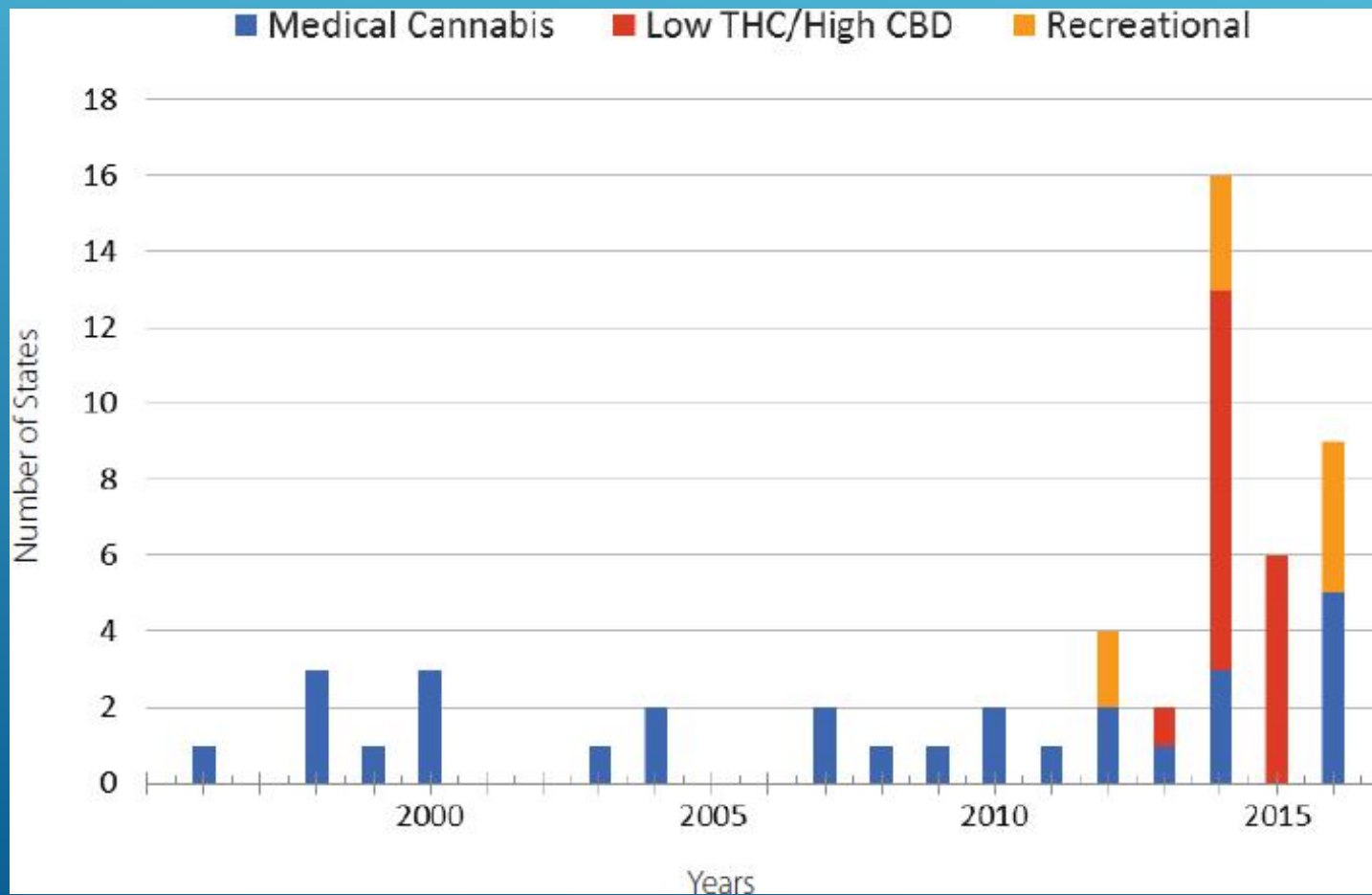
MEDICINAL USE OF CANNABIS

- Long history of medicinal use
- Currently few approved Cannabis-based products
 - dronabinol- synthetic THC (nausea, inappetence)
 - nabilone- synthetic THC analog (nausea, pain)
- In development or approved outside the US
 - Sativex- THC/CBD extract (MS)
 - Epidiolex- CBD extract (epilepsy)



MEDICINAL USE OF CANNABIS

- Variable state laws regarding medical and non-medical use in humans.



MEDICINAL USE OF CANNABIS

- No FDA approved products for veterinary use
- Off-label use of dronabinol and nabilone not specifically prohibited
- Both THC-containing and CBD-containing products are illegal under federal law
- No state laws specifically allow veterinary use of *Cannabis*-derived products
- The FDA specifically excludes products with THC or CBD from looser regulation for dietary supplements



WHAT IS THE EVIDENCE?

- Clinical trials in veterinary patients
- Clinical trials in humans
- Laboratory research in relevant species
- Other laboratory evidence (rats, *in vitro*, etc.)
- Anecdotal experience



WHAT IS THE EVIDENCE?

- Clinical trials in veterinary patients- none (yet)

WHAT IS THE EVIDENCE?

- Clinical trials in veterinary patients- coming soon!
 - Pending studies
 - Upenn, Cornell, CSU, Auburn



WHAT IS THE EVIDENCE?

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
RECOMMENDATIONS FOR RESEARCH

Committee on the Health Effects of Marijuana:
An Evidence Review and Research Agenda

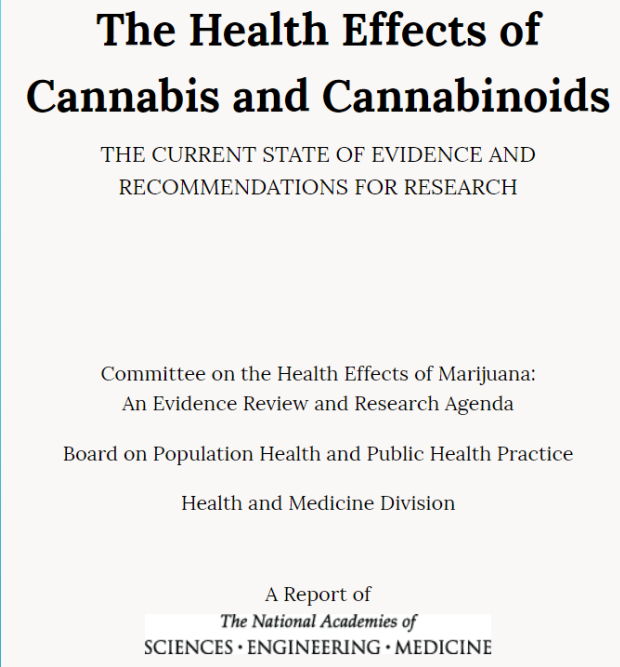
Board on Population Health and Public Health Practice
Health and Medicine Division

A Report of
The National Academies of
SCIENCES • ENGINEERING • MEDICINE

- Clinical trials in humans
 - 2016 review
- Evaluated many therapeutic indications and potential risks
- Graded the strength of evidence
- Identified limitations in evidence and strategies for improvement

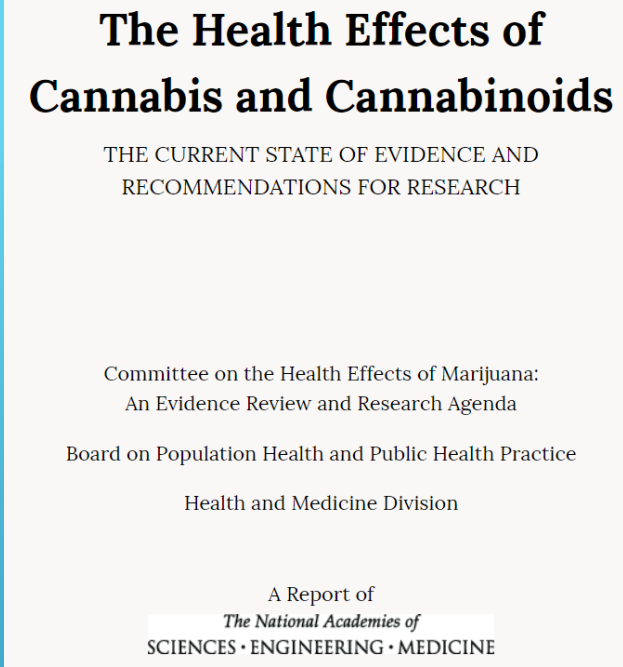
WHAT IS THE EVIDENCE?

- Evidence Levels
 - Conclusive
 - Strong evidence from RCTs
 - Many supportive findings and no credible opposing findings
 - Negligible limitations to evidence
 - Substantial
 - Strong evidence
 - Several supportive findings and minimal opposing findings
 - Minor limitations to evidence



WHAT IS THE EVIDENCE?

- Evidence Levels
 - Moderate Evidence
 - Some good-to-fair quality evidence
 - Very few opposing findings
 - Cannot confidently rule out bias/error
 - Limited Evidence
 - No or Insufficient Evidence



WHAT IS THE EVIDENCE?

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting
- For improving patient-reported multiple sclerosis spasticity symptoms

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
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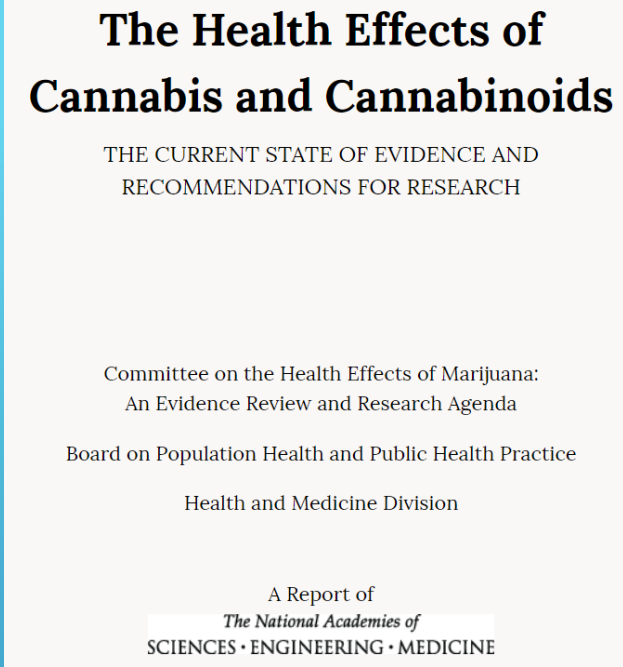
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WHAT IS THE EVIDENCE?

There is moderate evidence that cannabis or cannabinoids are effective:

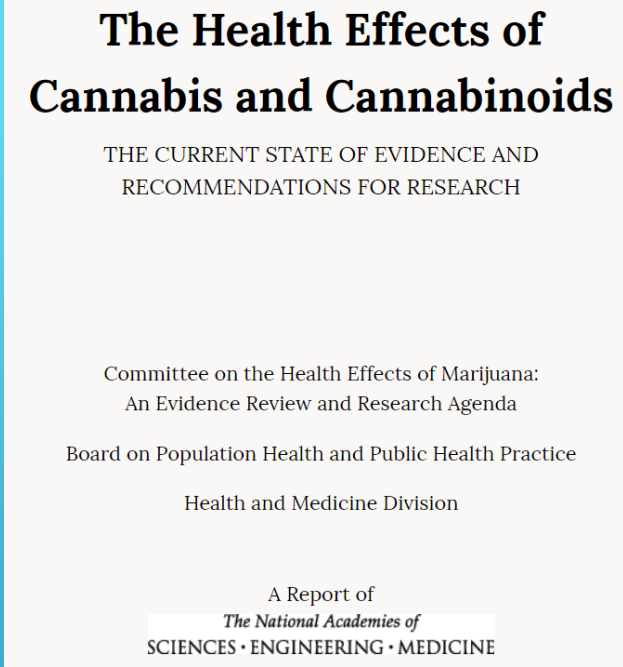
- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis



WHAT IS THE EVIDENCE?

For everything else:

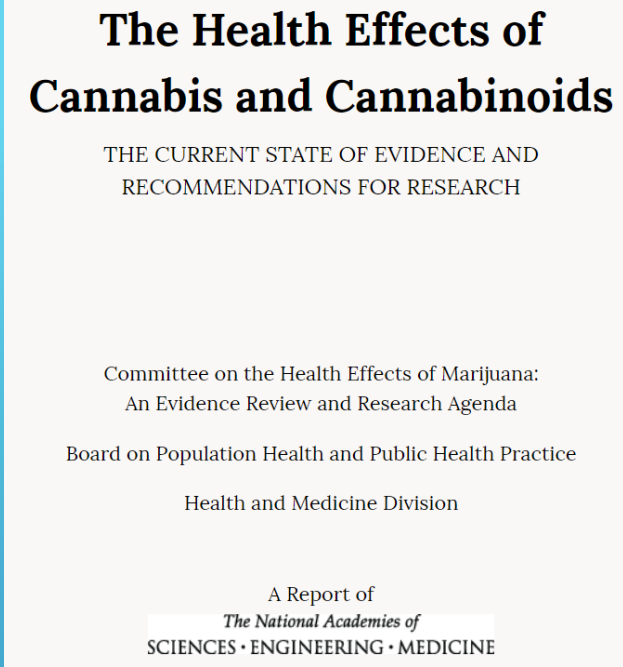
- Limited evidence for or against efficacy
- Insufficient evidence to form a conclusion



WHAT IS THE EVIDENCE?

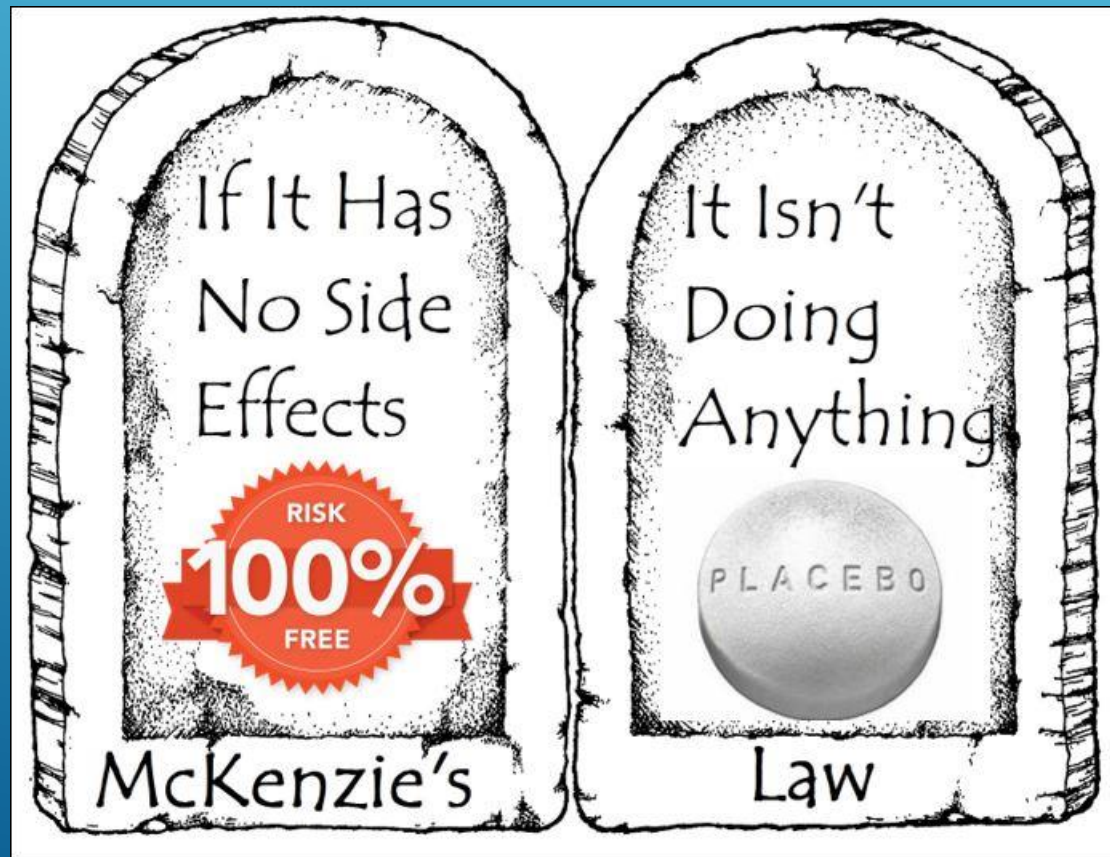
What About...

- Glaucoma
 - Short-term effects in lab and uncontrolled studies
 - No moderate or better evidence
- Epilepsy
 - Few recent studies of CBD (after 2016 review)
 - Reduction in Sz in patients with drug resistant epilepsy
 - Common adverse effects (GI, neuro)



WHAT IS THE EVIDENCE?

What about Risks and Harms?



The Health Effects of Cannabis and Cannabinoids

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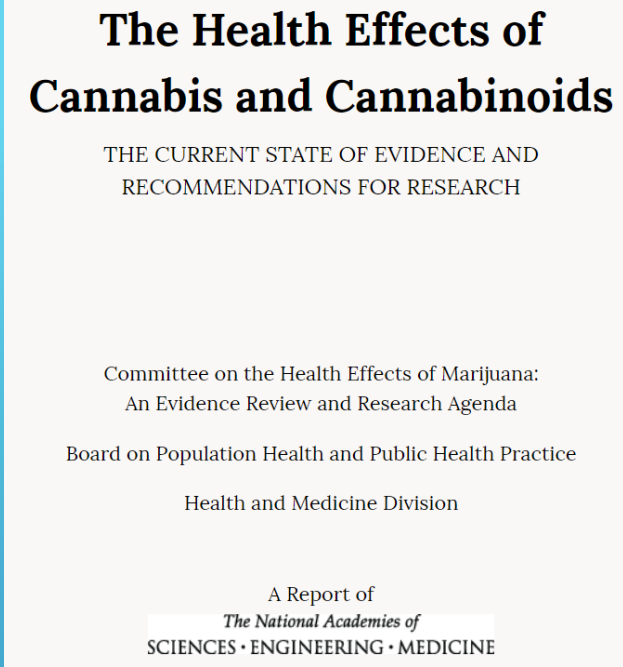
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WHAT IS THE EVIDENCE?

Risks and Harms (moderate or better evidence)

- NOT associated with lung or head and neck cancers
- Worsening of respiratory disease symptoms/bronchitis (smoking)
- Increased risk of motor vehicle accidents



WHAT IS THE EVIDENCE?

Risks and Harms (moderate or better evidence)

- Accidental overdose in children where legalized (and dogs)
- Lower birth weight if used while pregnant
- Dose-dependent increase in development of schizophrenia and psychoses
- Other psychological symptoms (bipolar, depression, suicidal ideation, etc.)

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
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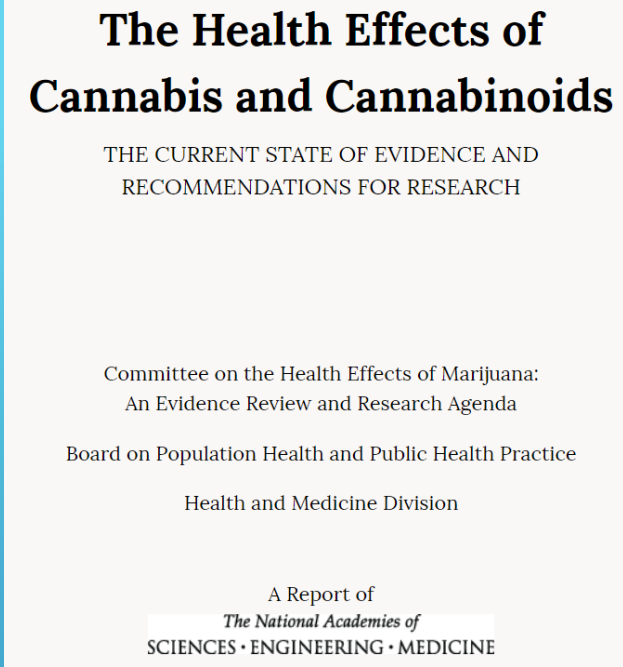
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WHAT IS THE EVIDENCE?

Risks and Harms (moderate or better evidence)

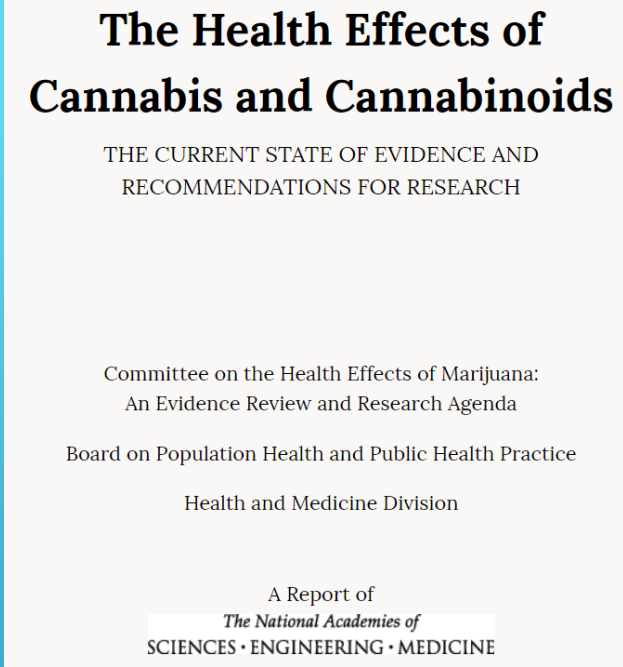
- Development of substance abuse



WHAT IS THE EVIDENCE?

Risks and Harms Seen in RCTs

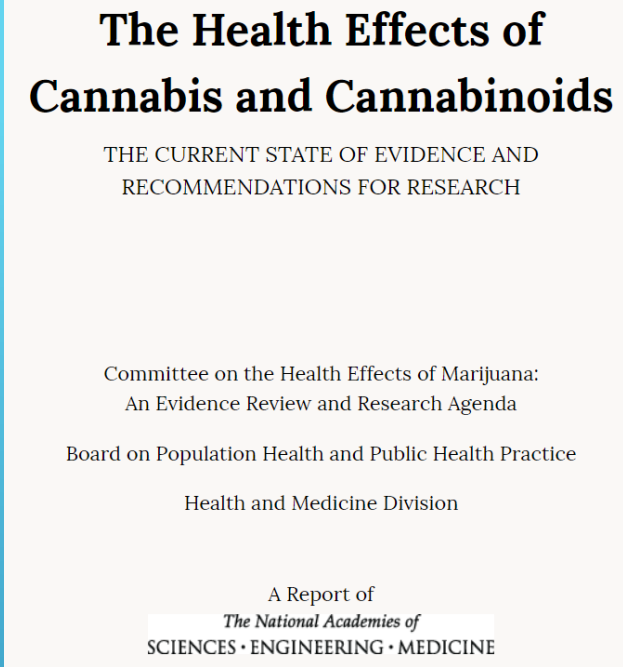
- Vomiting/Diarrhea/Inappetance
- Sedation/Fatigue
- Drug Interactions? (cytochrome enzyme inhibitor)
- Infections?
- Allergies



WHAT IS THE EVIDENCE?

Risks and Benefits Relevant to Veterinary Patients

- Chronic pain
- Nausea and vomiting
- Accidental overdose
- Allergies
- Use in pregnancy?
- Psychological risks?



WHAT IS THE EVIDENCE?

Laboratory Studies in Relevant Species

- Few studies, mostly from 1950s-1970s
- Pharmacokinetic/pharmacologic studies
- Toxicity studies
- IV THC or inhaled marijuana, some oral exposure
- No info directly evaluating therapeutic uses



WHAT IS THE EVIDENCE?

Laboratory Studies in Relevant Species

- Confirm cannabinoid receptors present homologous to other species, dogs have more in the brain than humans
- Evidence of toxicity similar to clinical case reports (neuro, GI, reproductive)



WHAT IS THE EVIDENCE?

Laboratory Studies in Relevant Species

- Variable evidence for bioavailability



Samara E, Bialer M, Mechoulam R. Pharmacokinetics of cannabidiol in dogs. *Drug Metab Dispos.* 1988 May-Jun;16(3):469-72.

In three of the six dogs studied, CBD could not be detected in the plasma after oral administration. In the other three, the oral bioavailability ranged from 13 to 19%. The results of this study show that CBD is barely absorbed after oral administration to dogs. This low bioavailability may be due to a first pass effect.

ASSESSMENT OF SAFETY, TOXICITY, AND PHARMACOKINETICS OF CANNABIDIOL IN HEALTHY DOGS. L. Bartner¹, L. Hyatt², L. Wittenburg³, S. Rao⁴, S. McGrath⁵. ¹Colorado State University, Fort Collins, CO, USA, ²College of Veterinary Medicine, University of Tennessee, Knoxville, TN, USA, ³University of California Davis, Davis, CA, USA, ⁴Adjunct Faculty of Epidemiology, Colorado School of Public Health, University of Colorado, Denver, Fort Collins, CO, USA, ⁵Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Fort Collins, CO, USA

Our purpose was to determine the pharmacokinetics (PK) and tolerability of cannabidiol (CBD) in healthy dogs. We hypothesized oral and transdermal delivery would be well tolerated and provide measurable systemic levels of CBD.

Thirty, healthy Beagle dogs were randomly assigned to receive one of three CBD formulations (capsule, oil, or transdermal cream), twice daily for a total dose of 150 or 300 mg/day (approximately 10 and 20 mg/kg/day), over 6 weeks. Blood was collected for 12 hours following the first dose for CBD PK. At 2-, 4-, and 6-weeks, blood was collected for CBC, chemistry panel, bile acids, and CBD plasma levels. Daily observational notes and weekly physical examinations were also performed.

Pharmacokinetic analysis demonstrated that the oil formulation resulted in higher plasma concentrations and systemic exposure, with less variability. Cannabidiol exposure was dose proportional. Elimination half-life of the oil formulation following a dose of 75 and 150 mg was 199.7 ± 55.9 and 127.5 ± 32.2 minutes, respectively. Twice-daily administration maintained plasma CBD levels until study completion.

There were no significant abnormalities on CBC, urinalysis, or pre- and postprandial bile acids. Mild elevations in serum alkaline phosphatase (ALP) occurred at 4 and 6 weeks, more frequently with capsule and oil formulations at 300 mg/day. All dogs experienced diarrhea; presence, onset, and severity did not correlate with formulation or dose.

Cannabidiol appears to be well tolerated in dogs. Exposure is proportional to dose and oil formulation provides more favorable PK. These results provide a framework for future efficacy studies of CBD in dogs.

WHAT IS THE EVIDENCE?

Potential Toxicity

- Large case series and isolated case reports
 - Ataxia/incoordination
 - Vomiting
 - Can be mixed toxicosis (chocolate, xylitol, etc.)
 - Rarely fatal



WHAT IS THE EVIDENCE?

Laboratory Research in other species

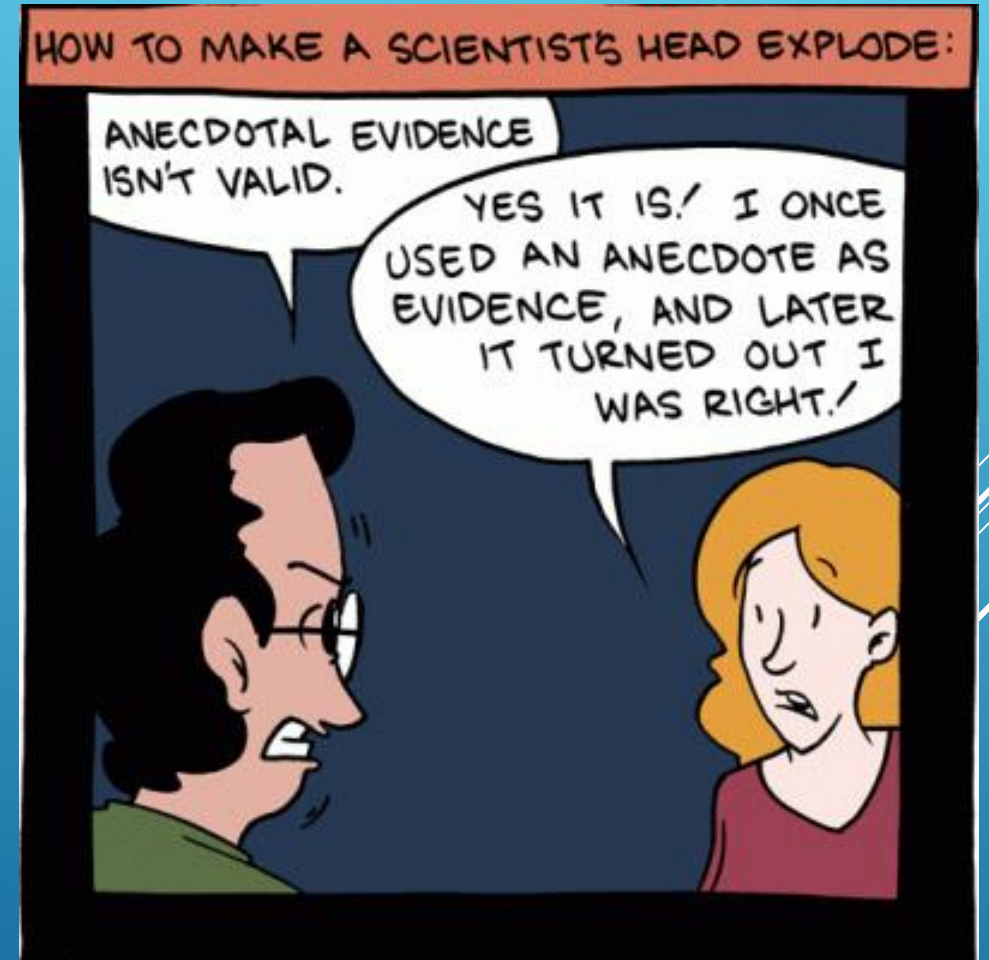
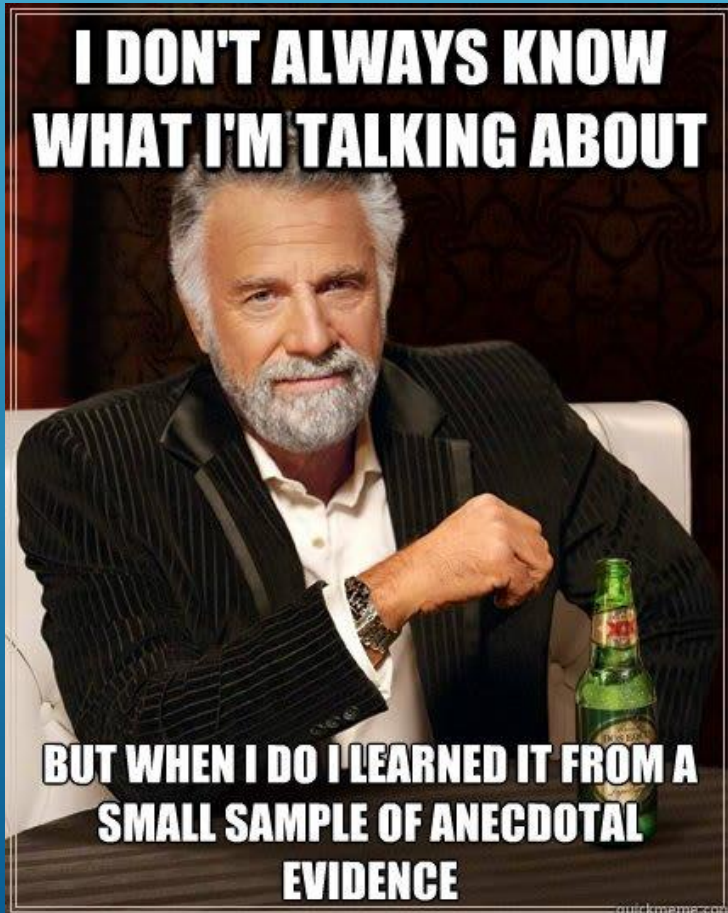
- Analgesic
- Anti-emetic
- Anti-tumor
- Anti-inflammatory & immunomodulatory
- Modulates sleep cycle
- Diabetes
- Cardiovascular function

- Clinical Relevance???



WHAT IS THE EVIDENCE?

Anecdotal Evidence



WHAT IS THE EVIDENCE?

Anecdotal Evidence

- Surveys
 - Selection bias
 - cannabis company web site
 - clients of advocates
 - Dislike conventional Tx
- Usage rates
- Benefits
- Adverse effects
- Medical guidance



Quality Control

- Unregulated products often mislabeled
 - Only 17% accurately labeled
 - 60% had more THC than on label
 - Many had no detectable CBD

Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products

Table 1. Accuracy of Product Labeling

	Accuracy of Labeled Tetrahydrocannabinol (THC) Content		
	Accurately Labeled ^a	Underlabeled ^b	Overlabeled ^c
Overall (3 Cities)			
Products tested, No. (%) (N = 75)	13 (17)	17 (23)	45 (60)
Type of product, No.			
Baked goods	2	7	13
Beverages	3	2	8
Candy or chocolate	8	8	24
Amount of THC, mg			
Label range	15 to 200	20 to 1000	2 to 325
Actual range	15 to 183	34 to 1236	<1 to 267
Deviation in THC content amount, % ^d			
Mean (SD)	-3 (4)	28 (13)	-47 (29)
Maximum	9	55	-99

Ryan Vandrey, PhD¹; Jeffrey C. Raber, PhD²; Mark E. Raber²; Brad Douglass, PhD³; Cameron Miller, MS³; Marcel O. Bonn-Miller, PhD⁴
JAMA. 2015;313(24):2491-2493. doi:10.1001/jama.2015.6613.

Quality Control

- Unregulated products often mislabeled
 - 36% had less than labeled amount CBD
 - 22% had more than labeled amount of CBD
 - Are veterinary products any better?

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			Total (N = 84)
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	
Label accuracy, No. of products (%) [95% CI]				
Accurate ^a	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under ^b	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over ^c	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]

Quality Control

“Over the past several years, FDA has issued several warning letters to firms that market unapproved new drugs that allegedly contain cannabidiol (CBD). As part of these actions, FDA has tested the chemical content of cannabinoid compounds in some of the products, and many were found to not contain the levels of CBD they claimed to contain.”

Firm	Product	State	Purchase Website	Product Size CBD Label Claim	Lab Results (mg/g)			Lab Results %(w/w)		
					CBD	Δ9-THC	Other Cannabinoids	CBD	Δ9-THC	Other Cannabinoids
Canna Companion, LLC	Canna Companion Capsule Size: 4	WA	cannaforpets.com	4 capsules N/A CBD	1	1	CBDA: 9 THCA: 3	0.1%	0.1%	CBDA: 0.9% THCA: 0.3%
Canna-Pet, LLC	CBD Wedges - Canna-Biscuits for Dogs	WA	canna-pet.com	2oz N/A CBD	None detected above 1 mg/g			None detected above 0.1% (w/w)		
Canna-Pet, LLC	Canna-Pet for Cats	WA	canna-pet.com	14 capsules N/A CBD	5	—	—	0.5%	—	—
Canna-Pet, LLC	Canna-Pet MaxCBD Capsules for Dogs	WA	canna-pet.com	10 capsules N/A CBD	26	1	CBC: 1	2.6%	0.1%	CBC: 0.1%



BUREAU OF CANNABIS CONTROL CALIFORNIA

ALL CANNABIS HARVESTED ON OR AFTER 1/1/2018 AND ALL CANNABIS PRODUCTS MANUFACTURED ON OR AFTER 1/1/2018, SHALL BE TESTED ACCORDING TO TITLE 16 OF THE CALIFORNIA CODE OF REGULATIONS, SECTION 5715, AND THE REGULATIONS THAT FOLLOW.

PHASE-IN OF REQUIRED LABORATORY TESTING	INHALABLE CANNABIS	INHALABLE CANNABIS PRODUCTS	OTHER CANNABIS & CANNABIS PRODUCTS
JANUARY 1, 2018			
Cannabinoids Testing	✓	✓	✓
Moisture Content Testing	✓		
Category II Residual Solvents and Processing Chemicals Testing		✓	✓
Category I Residual Pesticides Testing	✓	✓	✓
Microbial Impurities Testing (A. fumigatus, A. flavus, A. niger, A. terreus)	✓	✓	
Microbial Impurities Testing (Escherichia coli and Salmonella spp.)	✓	✓	✓
Homogeneity Testing of Edible Cannabis Products			✓
JULY 1, 2018			
Category I Residual Solvents and Processing Chemicals Testing		✓	✓
Category II Residual Pesticides Testing	✓	✓	✓
Foreign Material Testing	✓	✓	✓
DECEMBER 31, 2018			
Terpenoids Testing	✓	✓	✓
Mycotoxins Testing	✓	✓	✓
Heavy Metals Testing	✓	✓	✓
Water Activity Testing of Solid or Semi-Solid Edibles	✓		✓



Quality Control

- Testing Regulations
 - THC/CBD content
 - Contaminates

POT for PETS: HELPFUL Or HARMFUL?



- Basic Science
- Clinical Experience in Humans
 - Pain, nausea
- Dog/Cat lab studies
 - Basic physiology
 - Bioavailability?
 - Toxicity?

Very Promising

Limited but Promising

Limited, mixed

POT for PETS: HELPFUL Or HARMFUL?

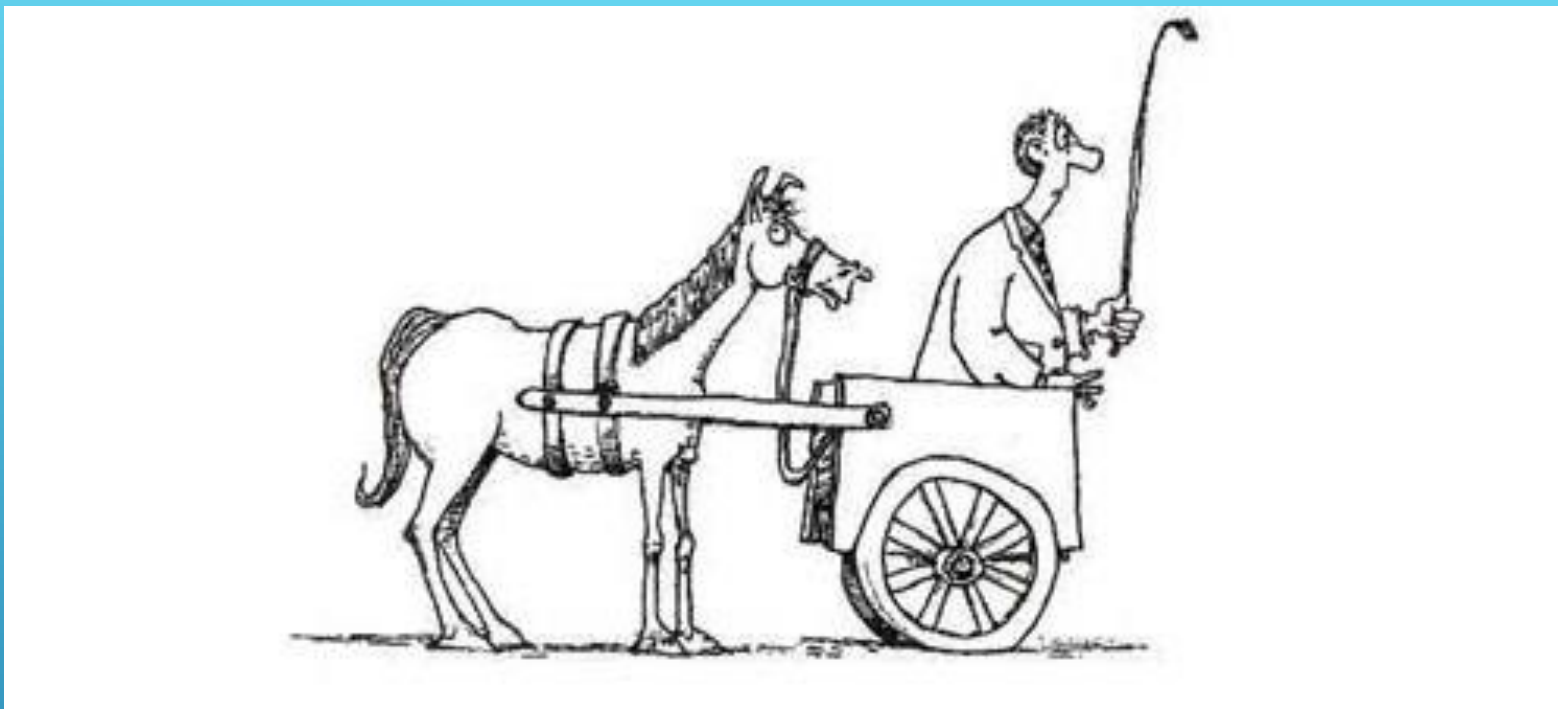


- Veterinary Clinical Studies
- Anecdotes
- Practical Issues
 - Laws
 - Quality Control

None (stay tuned)

Who Cares?

Changing?
???



Idea → → Product → → Widespread Use → → Research Evidence

...learned a lot as a result of the FDA warning letter. We changed our verbiage in the company's marketing materials, informed the FDA and have been left alone since...We are comfortable with the gray zone.

Firm	Product	State	Purchase Website	Product Size CBD Label Claim	Lab Results (mg/g)			Lab Results %(w/w)		
					CBD	Δ9-THC	Other Cannabinoids	CBD	Δ9-THC	Other Cannabinoids
Canna Companion, LLC	Canna Companion Capsule Size: 4	WA	cannaforpets.com	4 capsules N/A CBD	1	1	CBDA: 9 THCA: 3	0.1%	0.1%	CBDA: 0.9% THCA: 0.3%
Canna-Pet, LLC	CBD Wedges - Canna-Biscuits for Dogs	WA	canna-pet.com	2oz N/A CBD	None detected above 1 mg/g			None detected above 0.1% (w/w)		
Canna-Pet, LLC	Canna-Pet for Cats	WA	canna-pet.com	14 capsules N/A CBD	5	—	—	0.5%	—	—
Canna-Pet, LLC	Canna-Pet MaxCBD Capsules for Dogs	WA	canna-pet.com	10 capsules N/A CBD	26	1	CBC: 1	2.6%	0.1%	CBC: 0.1%

Unfortunately, the FDA prohibits us from discussing ***any diseases or medical conditions*** in conjunction with our products. We recommend you try [our] products for one month and observe the results with your own pet....We're so confident you and your pet will benefit...we offer our 100% satisfaction money-back guarantee.

All [our] products are guaranteed safe for any size pet. Canna-Pet products are **NOT** pharmaceuticals. They are organic, plant-based, non-GMO nutritional products that you can feed your pet with total confidence and ease.

CLIENT QUESTIONS

- Evidence is extremely limited
 - Safety?
 - Efficacy?
 - Better evidence coming soon!
- Probably illegal
- No reliable quality control



Don't substitute Cannabis for treatments with better evidence!!