



Weeding Out the Stigma of CBD

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Why do We Care About CBD?

- "There is a critical need for increased owner education and awareness regarding the composition, consistency, and safety of various CBD pet treats."
 - 93% of pet owners felt that CBD performed equally or better than standards of care
- "Given the positive feelings expressed by veterinarians in this study, it is suggested that all those affected by both the potential benefits as well as the risks, work together for legislative change that would allow for the expansion of knowledge needed to best capitalize on this potential medical tool for companion animals"
 - Most veterinarians (61.5%) felt comfortable discussing the use of CBD with their colleagues, but only 45.5% felt comfortable discussing this topic with clients.
- The US Pet CBD market expanded by more than 10 times its 2018 size in 2019, producing \$321 million in sales. In 2020 it is projected to reach \$563 million in sales.



What is Cannabis?

- *Cannabis sativa* L.
- Member of the Cannabaceae family
 - Shares many of the same terpenes and terpenoids as Hops (*Humulus lupulus*)
- Contains more than 421 individual compounds
 - Cannabinoids
 - Terpenes, Terpenoids
 - Flavonoids



What is Cannabis?

- Two main cultivars
 - Hemp
 - Legally contains < 0.3% THC
 - Typically contains high concentrations CBD
 - Often lacks robust terpenoid and cannabinoid spectrum
 - Historically grown for fiber and seed oil
 - Marijuana
 - Any cannabis plant containing > 0.3% THC
 - Typically contains high concentrations THC
 - Contains full range of cannabinoids



What is Cannabis?

- What about Sativa vs. Indica? Are they different plants?
 - Not really - broad categories of strains that produce differing amounts of the many different phytoconstituents of cannabis
- Sativa
 - Energizing high
 - Can be anxiety inducing
- Indica
 - Relaxing high
 - Couch lock
- Hybrids are common

Is all Cannabis Psychoactive?



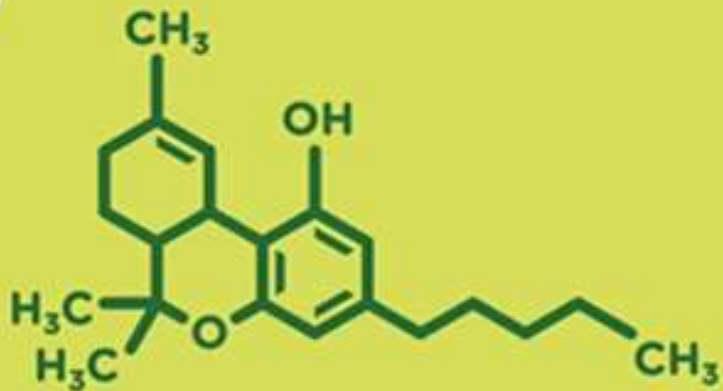
CBD vs. THC

- Phytocannabinoids produced on trichomes of *Cannabis sativa* that interact on endocannabinoid receptors throughout the body
- The Endocannabinoid System and the Entourage Effect
 - Our body produces endocannabinoids (anandamide, 2-AG) that act on cannabinoid receptors and help to regulate bodily systems; released due to stress or pain
 - Cannabis is a combination of biologically active phytochemicals working synergistically
 - Its complicated and there's still a lot that isn't understood



THC

TETRAHYDROCANNABINOL

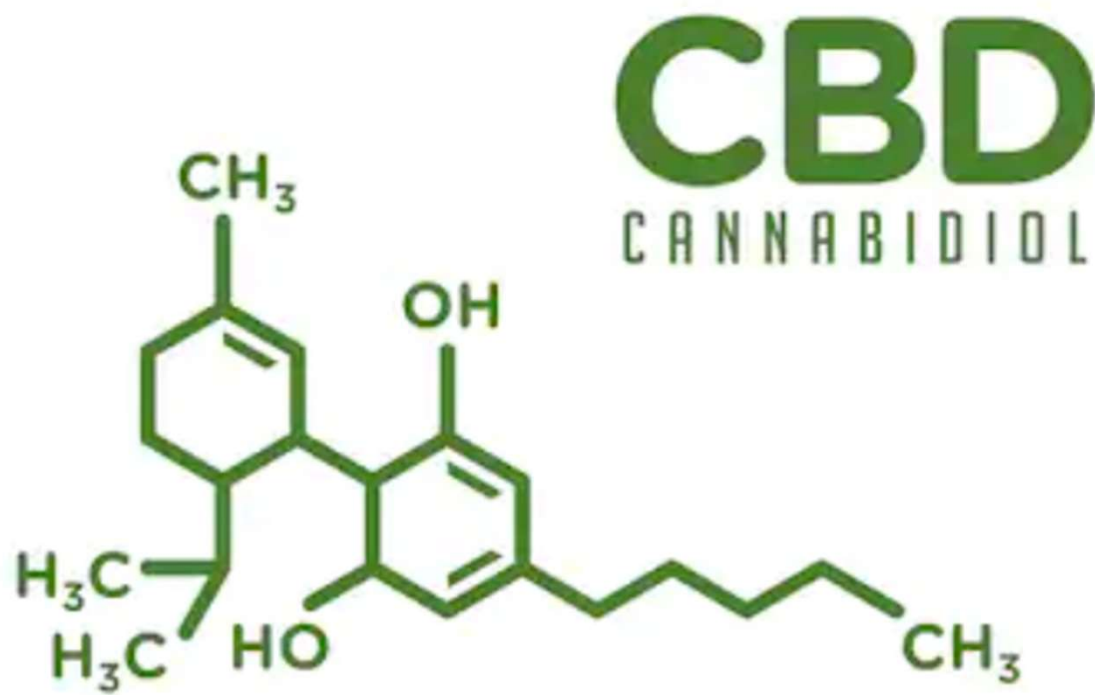


THC Tetrahydrocannabinol

- Psychoactive – but only after it is decarboxylated
- Binds to CB1 – CNS; inhibits neurotransmitter release, increases dopamine
- Binds to CB2 – immune system, GI tract, body tissues; anti-inflammatory effects
- Agonist for 5-HT_{1A} receptor (serotonin)
 - Also inhibits serotonin reuptake

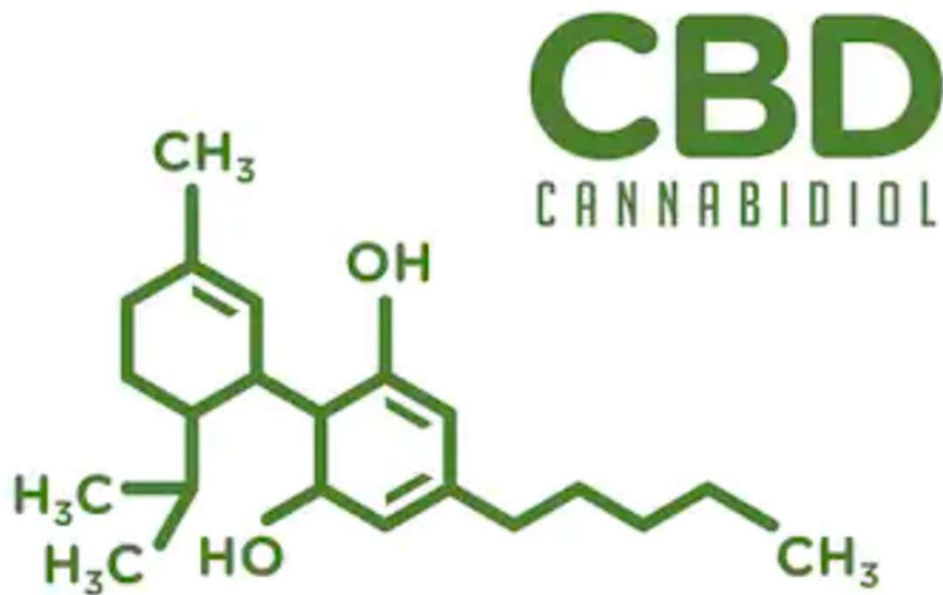
Rimonabant – blocked CB1 receptors; released Europe 2006 but withdrawn 2 years later due to depression & suicidal thoughts

CBD - Cannabidiol



- Non-psychoactive
- Binds to CB2
 - Inhibits CB1?
- Antagonizes agonists of CB1 and CB2 - modulation
- Agonist for 5-HT_{1A} receptor (serotonin)
- Inhibits cytochrome P450 enzymes
 - May modulate effects of anticonvulsants (clonazepam, phenobarbital?)
 - May decrease the metabolism of warfarin

CBD - Cannabidiol



- LD₅₀ 980mg/kg CBD in rats PO
- LD₅₀ 254mg/kg CBD in dogs IV
- LD₅₀ of crude marijuana extract >3000mg/kg in dogs
- log P 6.5 – VERY lipophilic
- Controls pain through multiple methods:
 - anti-inflammatory (inhibits COX2, reduces effects of pro-inflammatory cytokines)
 - allosteric modulation of opioid receptors

Hemp vs CBD vs THC in Food & Beverage



	HEMP		MARIJUANA	
	Seeds (Hearts)	Cannabidiol (CBD)	Flowers and Trim	Cannabidiol (CBD)
HOW CONSUMED	Whole or processed (hemp seed oil is common) in a variety of beverages and foods like granola, baked goods, burgers/hot dogs, and more. Topical products, too.	Chemical compound extracted from leaves and flowers and then eaten/drunk in oils, pills, edibles, etc. Topical products, too.	Whole, ground, or turned into a hash or concentrate, and then smoked, vaped, or eaten/drunk in pills, edibles, etc. Topical products, too.	Chemical compound found on the leaves and flowers. Can be consumed from smoking flower and trim whole, or extracted and infused into oils, medications, edibles, and topical products.
PHYSICAL EFFECTS	None, it is not psycho-active, but many consider it a health food because it is high in fiber, protein, and other vitamins and minerals.	None, it is not psycho-active. Some say there are medicinal and calming qualities. CBD from hemp is high in omegas, potassium, and magnesium and is often considered a health supplement.	Flowers and trim contain tetrahydrocannabinol (THC), the chemical compound that produces a euphoric buzz. Some say there are medicinal and calming qualities, too.	CBD on its own does not make you high (though some say there are medicinal and calming qualities). However, CBD from marijuana often contains THC (the compound that makes you high) because it comes from the same part of the plant.
LEGAL STATUS	Legal in all of the USA as long as there is less than .3% THC present.	CBD from hemp is legal to possess but not legal to add to food or topicals (as of January 2019).	Federally, marijuana is a schedule 1 drug. However, it is legal for medicinal use in 33 states and for recreational use in 10 states (as of January 2019).	In the states where marijuana and/or medical marijuana is legal, CBD products can be purchased pursuant to that state's laws.

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Types of Cannabis Products

Flower

- Raw plant material
 - Most often the bud of a female cannabis plant
- What you smoke
 - joint, blunt, roach, spliff, bud, nug, herb, weed
- Can also be consumed using a bong or pipe or a vaporizer (not a vape pen)
- Silly strain names
 - Headband, Purple Urkle, Zombie Killer OG



Types of Cannabis Products

Flower

- THC and CBD concentrations vary
 - Typically 10-20% THC but can be up to 30%
 - Balanced strains tend to have CBD and THC levels of roughly 6-12%
- THC content of marijuana in the 70s was <4%
- Flower is rarely used for CBD consumption



Types of Cannabis Products

Concentrates

- Concentrated extracts – kief, hashish, budder, wax, dabs, shatter, crumble, sauce, vaping
- Typically need to be heated
- Most contain THC, some contain CBD (e.g. vape pens), some both
 - Often contain 50-80% THC, sometime up to 90%
- Vape pens
 - Labeled with total mg strength of CBD or THC in the entire pen or cartridge (100, 250, 500 or 1000mg)
 - Set to deliver a specified dose per puff (often 5-20mg)

THC Vape Pens



Types of Cannabis Products Edibles



- Things you can ingest - gummies, cookies, soft drinks, chocolate, mints...just about anything you can eat/drink
 - Onset of effects delayed and often last longer (4-6 hours)
 - Liver converts delta-9-THC into 11-hydroxy-THC, which is more potent, has a longer half-life in the body, and can convey sedative effects
- Contain varying amounts of THC and CBD
 - Some come in individual-sized servings (5mg-25mg each piece) but have total mg strength listed
 - Some come in product meant to be split – chocolate bars, cookies, large candies
- Don't forget about xylitol, especially for mints
- Calming soft chews for pets
 - Many products contain hemp seed oil, no THC or CBD



ASPCA | Animal Poison Control Center

Types of Cannabis Products Topicals



- Often contain other ingredients
 - Essential oils
 - Arnica
 - Menthol
 - Xylitol?
- Typically non-intoxicating when applied topically, even if it contains THC
 - Could see THC effects if ingested



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Types of Cannabis Products

Capsules



- Can contain any form of cannabis
 - Distillate (oil)
 - Crystalline (powder)
 - Ground decarboxylated flower
- Can contain a single cannabinoid or mixed percentages of THC or CBD
 - Full spectrum = contains all cannabis compounds
- Time-released capsules available
- More accurate dosing, if you trust the manufacturer



Types of Cannabis Products Tinctures/Oil



- Made by dissolving cannabis in alcohol
- Administered sublingually or mixed into food/drinks
- Fast acting sublingually
- Commonly used in pets for “medicinal” purposes





Does the Product Contain THC or CBD?

- Think THC:
 - Sativa, Indica, flower, dab, shatter, wax, resin, shake, pot, weed
 - RSO (Rick Simpson Oil), Phoenix Tears – highly concentrated THC oil
- Think CBD:
 - Hemp, CBD oil, full-spectrum (+/- THC), whole plant (if Hemp)
- There are many products that contain both CBD and THC so its important to read labels
- If you aren't sure, search for the product online
 - Dispensary websites will often have that information

Why are Labels Important?



- No federal regulation of the industry so:
 - No required quality assurance testing
 - No confidence you are getting what you pay for
 - Risk for contaminants
 - No FDA approved CBD products (except Epidiolex)
- The best advice we can give clients until there is guidance is to find companies who are having their products tested by outside labs and providing transparency through detailed and accurate labeling
- There is still no guarantee that you are getting what you are paying for
- NASC and US Hemp Authority – set standards, perform audits



SCAN FOR FULL
PRODUCT DETAILS



Blue Dream

STRAIN: Hybrid

TYPE: Flower

DATE TESTED: 7/7/2014

REG NO:

Client Name

Client Email

Client Website

Client Phone

THC

13.2%

CBD

1.2%

CBN

<0.1%

THC : CBD

11 : 1



PATIENT: _____ QTY: _____

This product has not been analyzed or approved by the FDA. There is limited information on the side effects of using this product, and there may be associated health risks. Do not drive or operate machinery when under the influence of this product. KEEP AWAY FROM CHILDREN.

mcr
LABS

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(508) 872 - 6666

Should have at the very least...

- Ratio of CBD:THC
- Total amt (mg) in product
- Concentration (mg/mL if oil)
- Manufacturing date and batch number

Aphria Colour Indicator

- THC Dominant
- CBD Dominant
- Balanced THC & CBD

Potency Scale

- Low
- Medium
- High

Product Type: DRIED MARIJUANA / MARIJUANA SÈCHÉE | 5g

Aphria Strain Name: BIENVILLE

Common Name: (JEAN GUI)

Dominant Active Compound: THC

POTENTIAL POTENTIEL	THC + THCA ¹	22% W/WIP/P	CBD + CBDA ¹	<0.05% W/WIP/P
ACTUAL ACTUEL	THC ¹	<0.05% W/WIP/P	CBD ²	<0.05% W/WIP/P

Potential Values
Potential values represent the total amount of THC and CBD present once activated (decarboxylated).

Actual Values
Actual values represent the amount of THC and CBD before decarboxylation (i.e. if you were to consume a dried cannabis bud without heating it).

Strain Variety



Why is Independent Testing Important?

- Potential contaminants:
 - Microbes – fungal, bacterial, viral
 - Heavy metals – cadmium, lead, mercury
 - Pesticides – insecticides, fungicides
 - Others – plant growth regulators, polycyclic aromatic hydrocarbons (CBD oils)
- “Edible cannabis products from 3 major metropolitan areas, though unregulated, failed to meet basic label accuracy standards for pharmaceuticals. Greater than 50% of products evaluated had significantly less cannabinoid content than labeled, with some products containing negligible amounts of THC.”
 - Only 7% of the products were accurately labeled for the cannabinoid content

Certificate of Analysis (COA)

Should contain the following:

- Name of the lab doing the testing
 - Should be state certified
- Batch number, product name, identifying information
- Cannabinoid profile
 - With concentrations for each cannabinoid
- Presence of contaminants
 - Heavy metals
 - Pesticides
 - Microbes
 - Mycotoxins
- Terpene profile



Certificate of Analysis

QA SAMPLE - INFORMATIONAL ONLY

1 of 3

ICAL ID: 20190731-018
 Sample: 1907ICA3726.10967
 1000mg BSO Peppermint
 Strain: 1000mg BSO Peppermint
 Category: Ingestible

KW Distribution, LLC
 Lic. #
 13653 Central Ave
 Chino, CA 91710

Lic. #

Batch#: _____
 Primary Size: _____
 Total/Batch Size: _____
 Collected: 08/02/2019; Received: 08/02/2019
 Completed: 08/02/2019

Moisture	Δ9-THC	CBD	Total Cannabinoids	Total Terpenes
NT	ND	1,200.19 mg/unit	1,240.79 mg/unit	NT
Water Activity				
NT				

Summary	SOP Used	Date Tested	
Batch			Pass
Cannabinoids	SOP:003Tincture	07/31/2019	Complete
Residual Solvents	SOP:NON-Inhalable	07/31/2019	Pass
Microbials	SOP:qpcrone	08/01/2019	Pass
Mycotoxins	SOP:MYCO ED	07/31/2019	Pass
Pesticides	PEST.002 Edible	07/31/2019	Pass



Scan to see results

Cannabinoid Profile

1 Unit = Bottle, 29.79 g. 1 mL = 0.97 g.

Analyte	LOQ	LOD	%	mg/g	mg/ml	mg/unit	Analyte	LOQ	LOD	%	mg/g	mg/ml	mg/unit
THCa	0.76	0.46	ND	ND	ND	ND	CBDV	0.76	0.46	0.021	0.21	0.21	6.38
Δ9-THC	0.76	0.46	ND	ND	ND	ND	CBN	0.76	0.46	0.036	0.36	0.35	10.61
Δ8-THC	0.76	0.46	ND	ND	ND	ND	CBGa	0.76	0.46	ND	ND	ND	ND
THCV	0.76	0.46	ND	ND	ND	ND	CBG	0.76	0.46	0.016	0.16	0.16	4.86
CBDa	0.76	0.46	ND	ND	ND	ND	CBC	0.76	0.46	0.063	0.63	0.61	18.76
CBD	0.76	0.46	4.029	40.29	39.08	1200.19	Total			4.165	41.65	40.40	1240.79

Certificate of Analysis (COA)

Red flags for CBD products

- Too much THC (<0.3% for hemp)
- Not enough CBD
- Missing cannabinoids
 - If labeled as full-spectrum
- Tested in house instead of by an outside lab

“There are analytical companies that excel in what you want (there are also companies that say they excel but do not). You can find a bunch of them simply by googling cannabinoid analysis. If interested in finding a lab, look for one (ask the question) that carries federal (FDA, EPA, USDA, DEA) and state licenses and accreditations, follows peer reviewed validated methods published by authoritative institutions such as USP (United States Pharmacopeia) and AOAC (Association of Analytical Communities) International, and follows guidelines based on GLP (Good Laboratory Practice) protocols. Such labs should have additional accreditations by independent outside groups (e.g., ISO and A2LA), participate in method validation programs, and undergo regular proficiency testing evaluations to further demonstrate their analytical capabilities.”

-Dawn Boothe, DVM, MS, PhD

State Requirements Vary Greatly

- California, Colorado, Hawaii, DC, Arkansas – all cannabis must be tested for cannabinoids, terpene content, mycotoxins and heavy metals in addition to moisture content, residual solvents, pesticides and microbial impurities
- Connecticut – self-policed testing for contaminants and labeling requirements
- Oregon – no testing requirements for heavy metals or microbiological contaminants
- Vermont and Florida – no testing requirements
- Delaware – testing required for pesticides only
- Illinois – no testing for heavy metals required
- Washington – no testing for heavy metals or pesticides required
- Indiana and Utah – require CBD products sold in retail stores to have website or scannable QR code linking to product's COA



Legal Status of CBD for Pets

- 2018 US Farm Bill - legalized hemp
 - Removed hemp-derived products from Schedule I status BUT CBD is still a Schedule I substance
 - Any cannabinoid derived from hemp will be legal only if it is produced in a manner consistent with the Farm Bill, associated state and federal regulations, and by a licensed grower
 - Most of the CBD products available are still illegal under FDA regulations; there is only one FDA approved cannabis-derived drug (Epidiolex)

CALIFORNIA



Legal Status of CBD for Pets

- California (AB 2215)
 - Prevents the medical board from suspending, denying or revoking the license of a veterinarian solely for discussing the use of cannabis in an animal for medical purposes
 - Also prohibits veterinarians from prescribing, dispensing, or administering any cannabis-based products

Is CBD Safe?

“Other than the approved human prescription drug, we know little about the potential effects of sustained or cumulative long-term use of CBD,” Gnatt continued. “We don’t know about coadministration with other medicines or risks to vulnerable human and animal populations. This doesn’t mean that we know CBD is categorically unsafe under all circumstances but given the gaps in our current knowledge and the known risks that have been identified, we’re not at a point where we can conclude that CBD products are safe for use.”

-Randall Gnatt, senior regulatory counsel in the Office of Surveillance and Compliance in the FDA’s Center for Veterinary Medicine

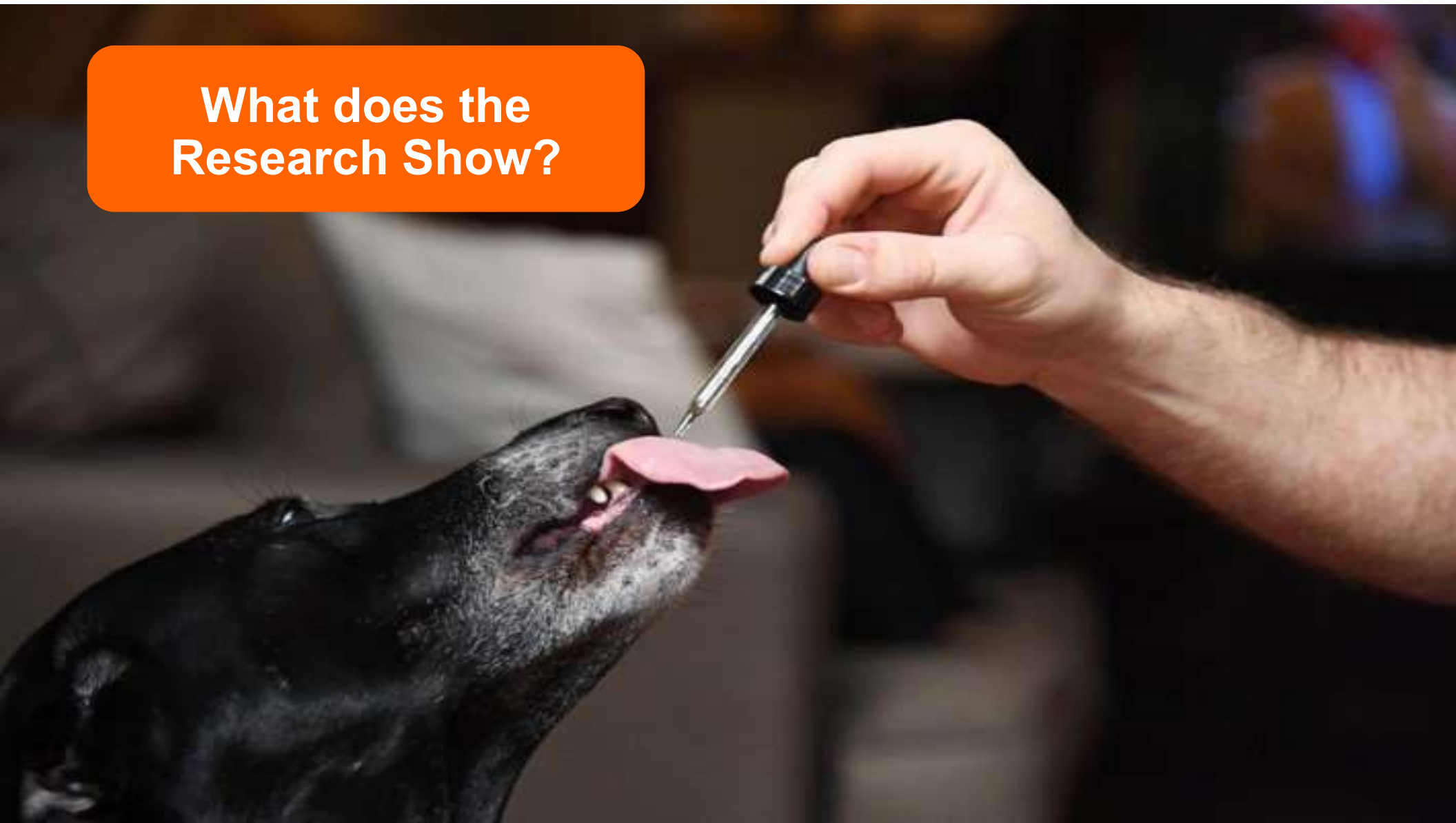
What are We Seeing at APCC?

- Highest dose = 102mg/kg – asymptomatic, no follow-up
- Cases involving oil/tincture
 - Vomiting most common sign
 - Lethargy, head bobbing, ataxia, inappetence
- Cases involving chews/treats
 - Lethargy and polydipsia most common signs
 - Vomiting, diarrhea
- Most cases with CNS signs are from products that contain THC as well as CBD
 - Mild CNS signs can occur with large ingestions
- There are a large number of pets out there that are being administered CBD products by their owners with no apparent side effects

What do State Boards have to Say?

- The AAVSB surveyed state veterinary licensing boards about whether it is legal for a veterinarian to discuss cannabis with a client.
 - 6 states said veterinarians could lose their license if they even talk about cannabis
 - 4 said veterinarians need to adhere to federal law
 - 7 said state boards can't even provide legal advice
 - 7 said they have no formal opinion on the matter
 - 2 said veterinarians could talk about cannabis but only if the client starts the conversation
 - 18 responded that veterinarians could discuss cannabis but could not prescribe or dispense it
 - 4 said veterinarians could discuss the topic
- The position of the AAVSB is that veterinarians should be able to discuss CBD with a client to ensure animal and public protection. "That just makes sense," Penrod said. "If a client comes in and says, 'I'm going to use CBD on an animal,' you should be able to talk to them about it, to warn them about some of the side effects, to watch out for those, to make sure that they're purchasing a product that's been analyzed and it doesn't contain things like pesticides."

**What does the
Research Show?**



Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs

- 30 male research beagles
- Part 1
 - 10mg/kg/day or 20mg/kg/day CBD administered via oil, transdermal cream or microencapsulated oil beads
 - Pharmacokinetics monitored for 12hrs
- Part 2
 - Dosing continued BID and dogs monitored for 6 weeks

Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs

Part 1 Findings

- Large variation between the labeled CBD dose and actual CBD concentration for microencapsulated oil beads
- Higher CBD C_{max} achieved with oil; smallest amount of variability in plasma CBD concentrations
- Shorter $T_{1/2}$ than previous studies – 2.1hr for 20mg/kg and 3.3hr for 10mg/kg

A Report of Adverse Effects Associated With the Administration of Cannabidiol in Healthy Dogs

Those same 30 beagles

Part 2 Findings

- All dogs had diarrhea
- Erythematous pinnae from the transdermal cream
- Ocular discharge, nasal discharge, salivary staining of feet
- Salivation during administration
 - Dose dependent elevations in ALP at 4 and 6 weeks
- BAs remained normal
 - No CNS signs noted

CSU Pilot Epilepsy Study 2019

Promising results, larger study ongoing

- 16 dogs
- 8/9 had fewer seizures during the 12wk study period vs 3/7 in control
- The higher the plasma CBD, the greater the reduction in seizures
- Elevations noted in ALP

Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs

- 16 dogs
- Randomized placebo-controlled, veterinarian and owner blinded, cross-over study
- Allowed to take NSAIDs, fish oil, glucosamine/chondroitin
- 4 weeks of CBD oil at 2mg/kg BID or 8mg/kg BID
- 4 weeks of placebo oil BID
- 2 week washout between CBD and placebo

Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs

Findings:

- $T_{1/2}$ 4.2hr for both dosages
- No psychoactive properties observed
- Significant decrease in pain and increase in activity at weeks 2 and 4
- Decrease in pain scores
- No changes observed in weight bearing capacity, lameness score
- Significant increase in ALP (9/16 dogs)

Epidiolex

Safety Study Data

- Dose-related elevations in ALT and AST noted
 - Dose adjustments recommended for patients with hepatic impairment
 - Monitoring of liver enzymes and Tbili recommended at 1 month, 3 months and 6 months after starting treatment
- Sedation was reported in 32% of people
 - Rate was higher in patients taking clobazam
- Weight loss, decrease in HCT, increase in Creatinine
- Clobazam concentration increased 3-fold when give with Epidiolex (CYP2C19)
 - This did not occur with Midazolam
- Coadministration with a high fat meal increased C_{max} by 5-fold



Epidiolex

- Approved for use in humans to treat seizures associated with Lennox-Gastaut syndrome or Dravet syndrome
- Starting dose 2.5mg/kg BID, then increase to 5mg/kg in 1 week
- Can increase up to 10mg/kg BID
- Significant reduction in seizure frequency noted within 4 weeks



Key Points

- Monitor liver values and Tbili for dogs on long-term CBD
- Learn how to read labels and COAs and be able to explain their importance to clients
 - THC and CBD are very different – make sure clients know this!
 - Learn about products – weedmaps.com, visit a dispensary
- CNS signs are rare as a side effect of CBD, possible with large doses but generally not seen at therapeutic dose
 - Start low and titrate up slowly to avoid side effects
 - GI upset is common, likely from oil base

Key Points

- Legal status makes discussions with clients difficult
- Can often be accomplished by discussing safety concerns and current published studies without actually recommending CBD
- Contact your state board for guidance since there is a lot of variance
- CBD may affect the metabolism of various drugs due to cytochrome P450 inhibition
- May need to adjust the doses and check serum levels of other anticonvulsants if pet is taking CBD