CBD 101: An Introduction to Cannabidiol in Clinical Practice

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Tonight's Topics

- What are "Cannabinoids"
  - CBD (Cannabidiol)
- The Endocannabinoid System
  - The "basics" for the clinician
- The Legal Questions
- CBD Pharmacokinetics
- Clinical Indications for CBD
- Key Dosing and Patient management considerations

Veterinarni Medicina, 67, 2022 (09): 455–462 *Review*

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Cannabidiol and the possibilities of its use in veterinary medicine of dogs and horses: A brief review

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Abstract: In connection with the use of cannabinoids for therapeutic purposes in human medicine, there is increased attention for their use in veterinary medicine, particularly by the owners of companion animals and horses. Therefore, veterinarians are expected to face this interest and have the corresponding knowledge on these substances. Presently, it is not possible to use medical marijuana (in terms of the dried cannabis flowers) for veterinary purposes in many countries, but there is increasing evidence that isolated cannabinoids also have beneficial effects (namely cannabidiol – CBD). Thus, this review summarises the possible therapeutic implications of CBD within the scope of evidence-based medicine, particularly in dogs and horses in association with the treatment of pain, epilepsy and anxiety in order to provide veterinarians with a concise overview of scientific findings in this field.

Keywords: cannabidiol; cannabinoids; dogs; horses; pain treatment

Who am I?

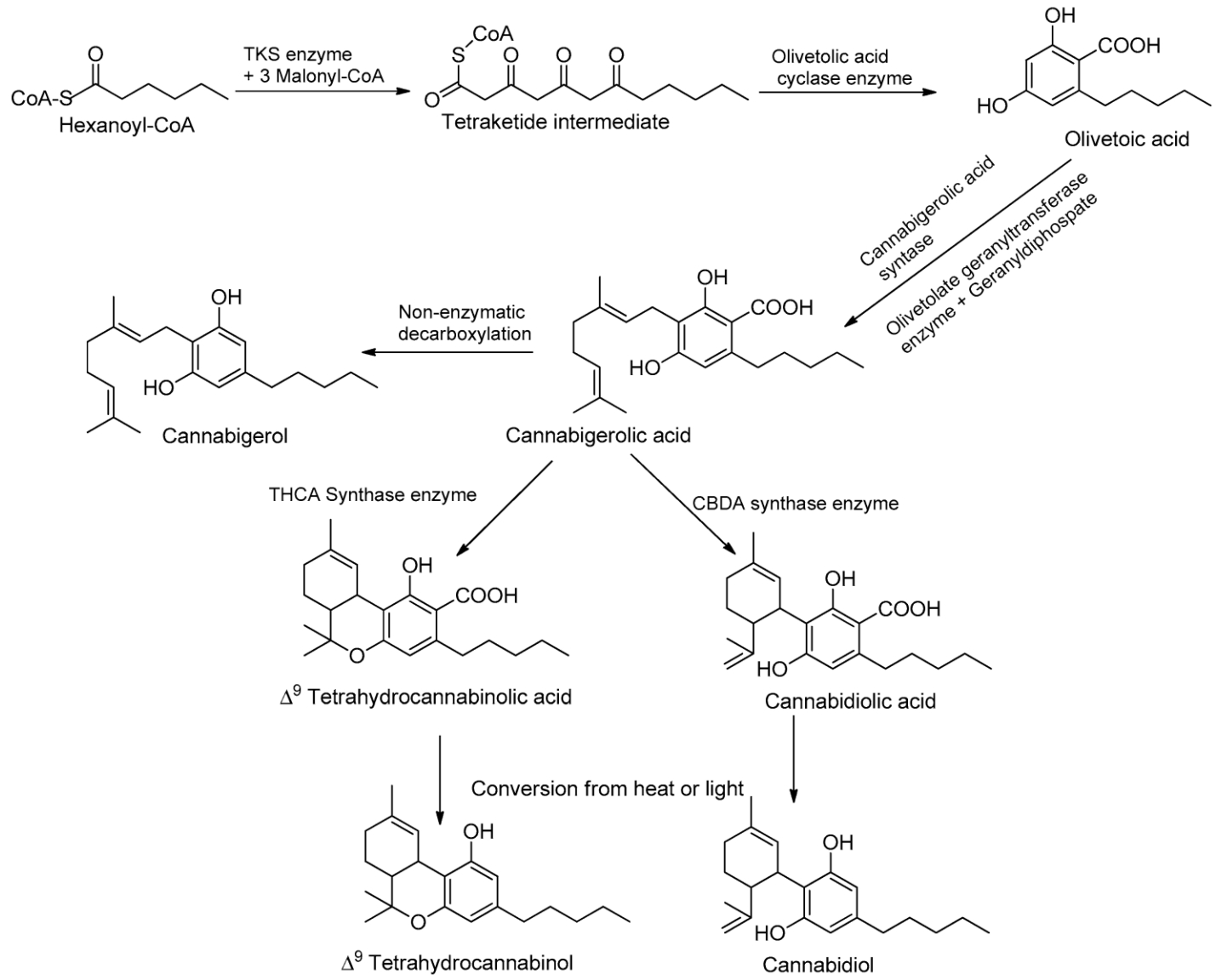
- Graduate of Oregon State University CVM in 2000
- Internship at AMC in NYC
- Owner of North Scottsdale Animal Hospital and Desert View Animal Hospital
- Prior owner of urbanbiscuit.com and consultant for Mission Pharmacal
- And I am still a practicing small animal vet!

Conflict of Interest Disclosure

- I am a founder and the CMO of Companion CBD.
- This session is limited to a discussion of the clinical use of CBD and the ECS.
- We will NOT discuss or field questions about any product or company in the CBD space.

"What conflict of interest?!
I work here in my spare time."

Phytocannabinoids vs. Endocannabinoids



The Endocannabinoid System (ECS): A New Paradigm

- First discovered in 1988
- Highly conserved across most vertebrate and invertebrate species
- Plays a major role in multiple physiologic functions throughout the body
- Anxiety, feeding behavior/appetite, emotional behavior/depression, neurogenesis, neuroprotection, cognition/learning/memory, pain sensation, fertility, pregnancy, prenatal development

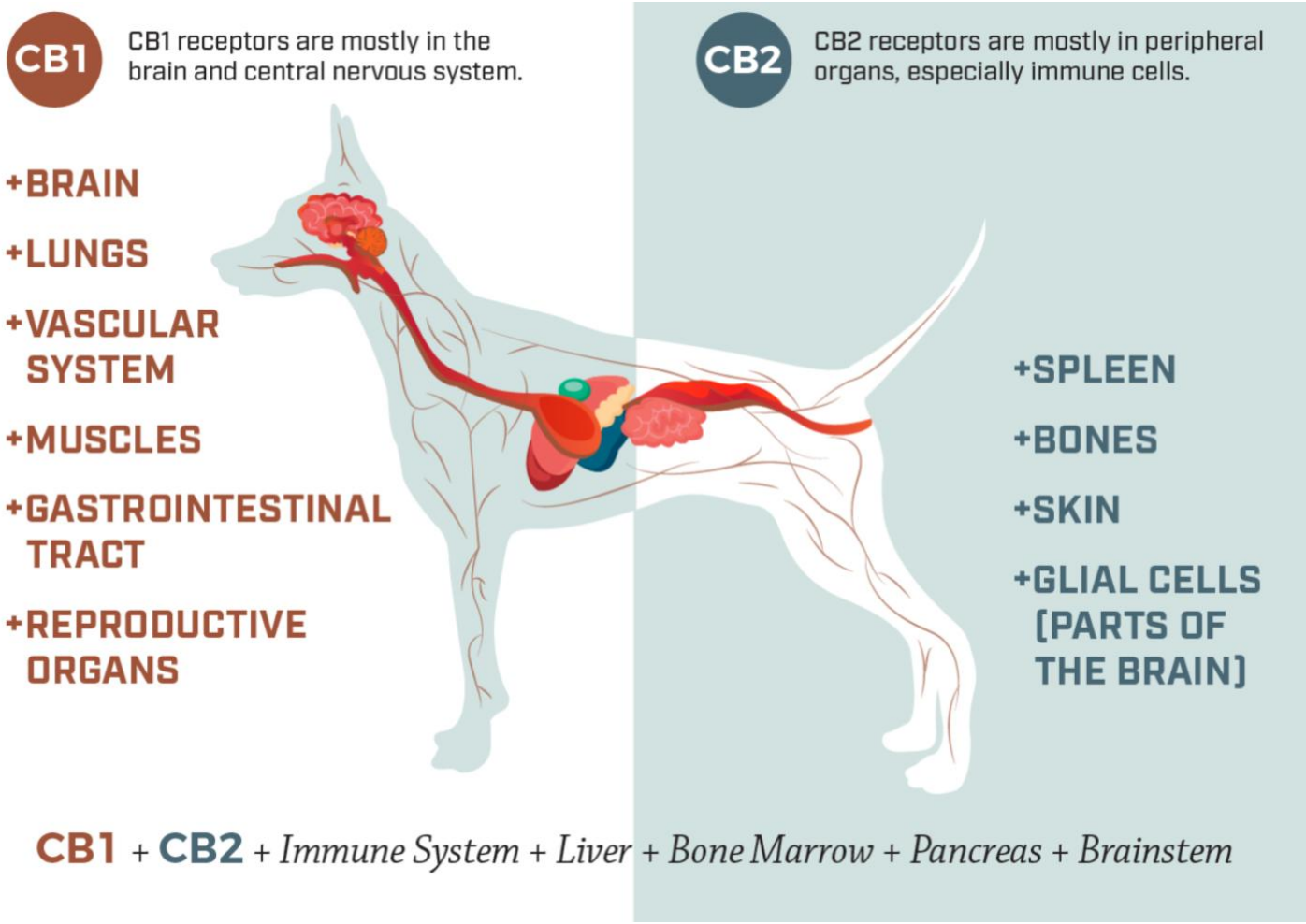
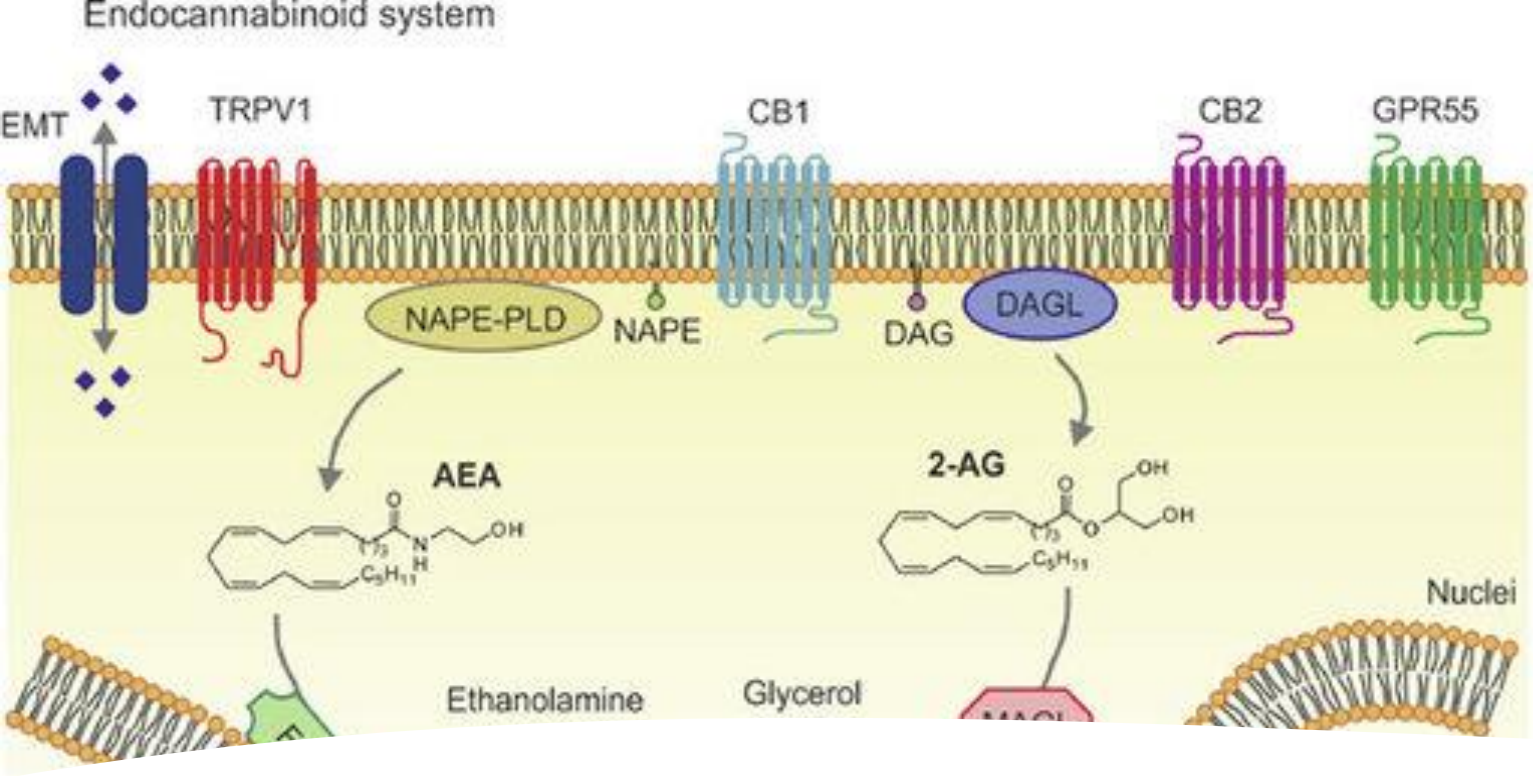
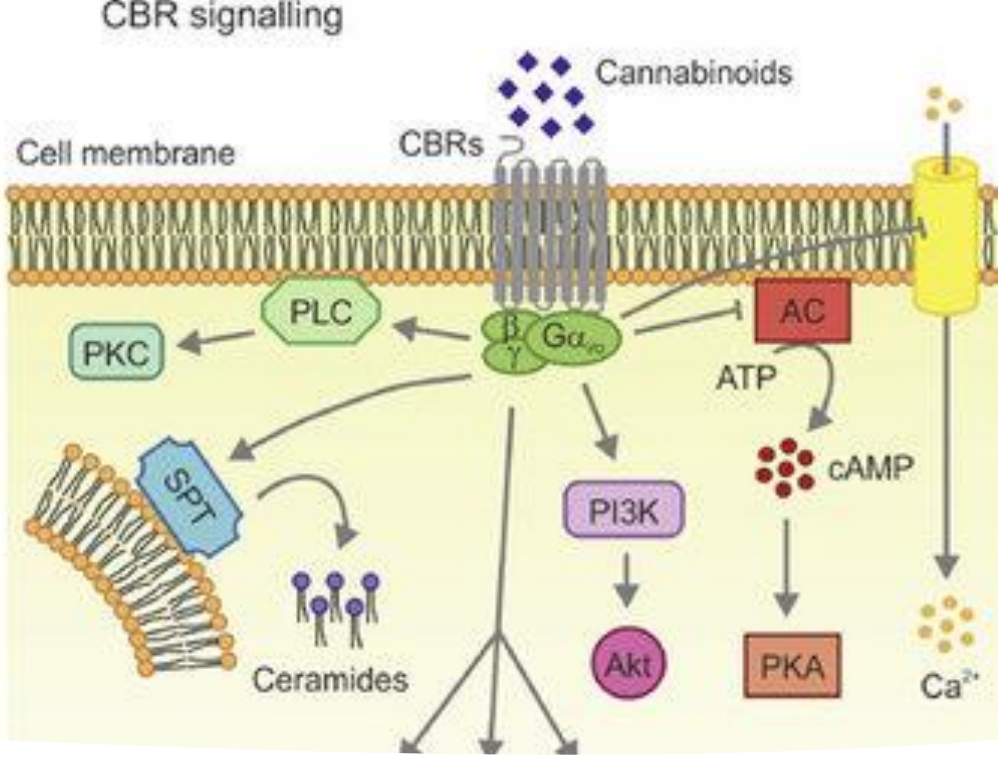


Table 1. Summary of the Endocannabinoid System in the Invertebrates.

	Species	Function of Endocannabinoid System	Location and Endocannabinoid(s) Orthologs/Enzymes Isolated		Presence of CB1/CB2-Like Receptors	Other Putative Endo-cannabi-noid Receptors	References
Porifera	*Dasychalina* sp.	Unknown	Unknown	Desulfohaplosamate (steroid eCB ligand)	Unidentified		Chianese et al. (2011)
Cnidarians	*Hydra vulgaris*	Role in feeding: presence of exogenous AEA exhibited maximal mouth closure; selective CB1 antagonist SR 141716A reversed effect	Polyps	AEA, NAPE, 2-AG, FAAH-like activity detected	Unidentified		De Petrocellis et al. (1999)
Arthropoda	*Drosophila melanogaster*	Putative involvement of dDAGL in axonal growth and guidance, particularly during muscle innervation	Neural tissues	2-AG, *N*-PEA, 2-LG, non-FAAH amidase, dDAGL	Unidentified		McPartland et al. (2001), Tortoriello et al. (2020)
	Apis mellifera	Unknown	Neural tissues	2-AG, *N*-PEA	Unidentified		McPartland et al. (2001)
	Amblyomma americanum	Putative role in host defense reactions	Salivary glands	2-AG, *N*-PEA	Unidentified		Fezza et al. (2003)
Platyhelminthes	*Dugesia dorotocephala*	Putative role in regeneration	Central nervous system	AEA, 2-AG, *N*-PEA, SEA, LEA, OEA	Unidentified		Mustonen (2010), Clarke (2020)
	Schmidtea mediterranea	Unknown	Genome (*in silica* analysis)	FAAH, MAGL	GPCR025 (26% homology with *Danio rerio* CB1-like receptor); GPCR484 (23% homology with NPR-32 of *C. elegans*)	TRPA1 channels, TRPV-type channels, TRPM-type channels	Mustonen (2010), Clarke (2020)
Mollusca	*Aplysia*	Unknown	Unspecified	AEA, 2-AG, NAPE	Unidentified		Lemak et al. (2007)
	Mytilus galloprovincialis	Role in injury response	Unspecified	AEA, *N*-PEA, NAPE, FAAH ortholog	Unidentified		Sepe et al. (1998)
	Tapes decussatus	Unknown	Unspecified	AEA, *N*-PEA	Unidentified		Sepe et al. (1998)
	Crassostrea sp.	Unknown	Unspecified	AEA, *N*-PEA	Unidentified		Sepe et al. (1998)



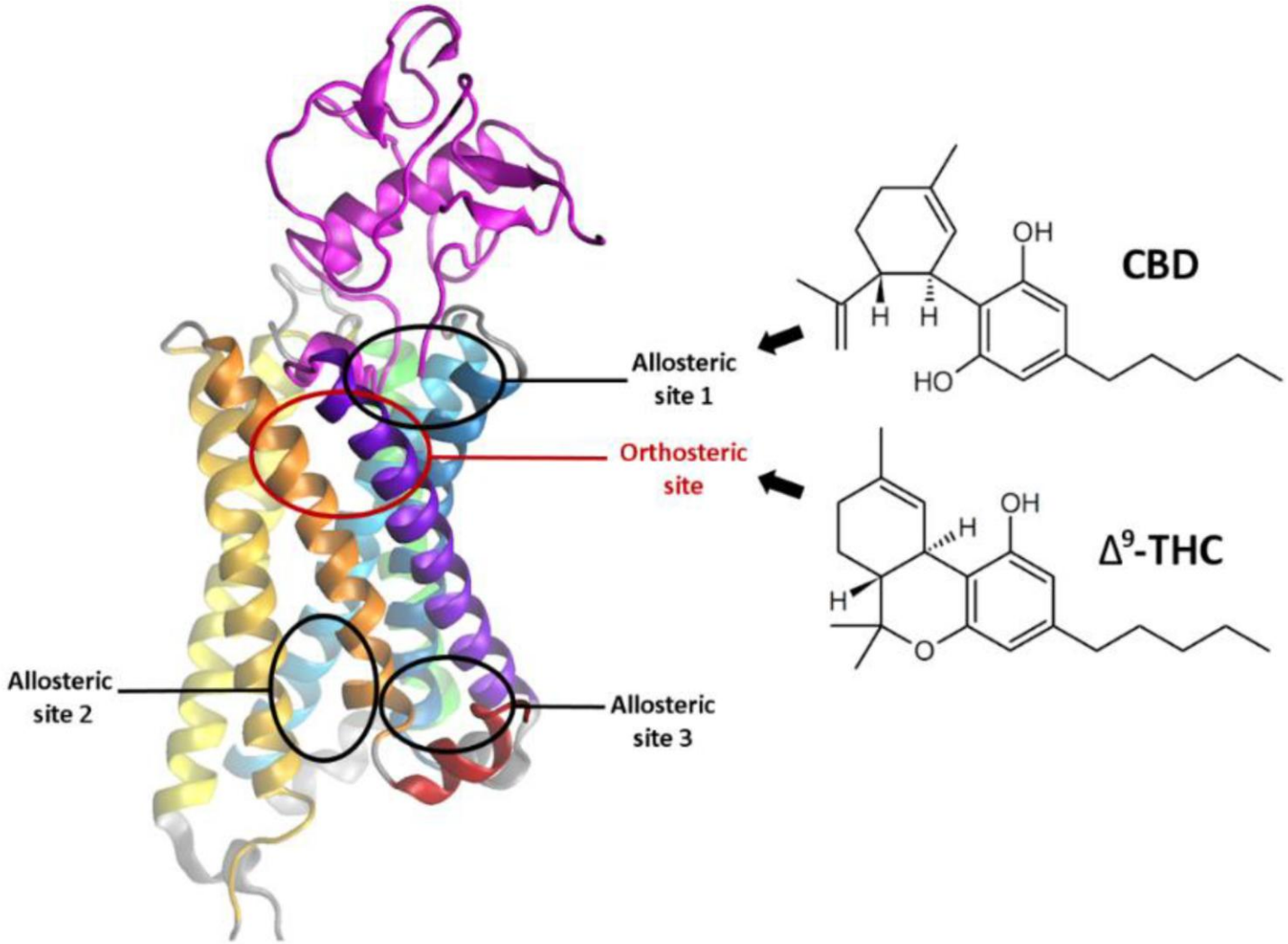


What are the constituent parts of the ECS?

- ECS consists of:
  - Cellular receptors
  - Signaling molecules
  - Enzymes for synthesis/degradation

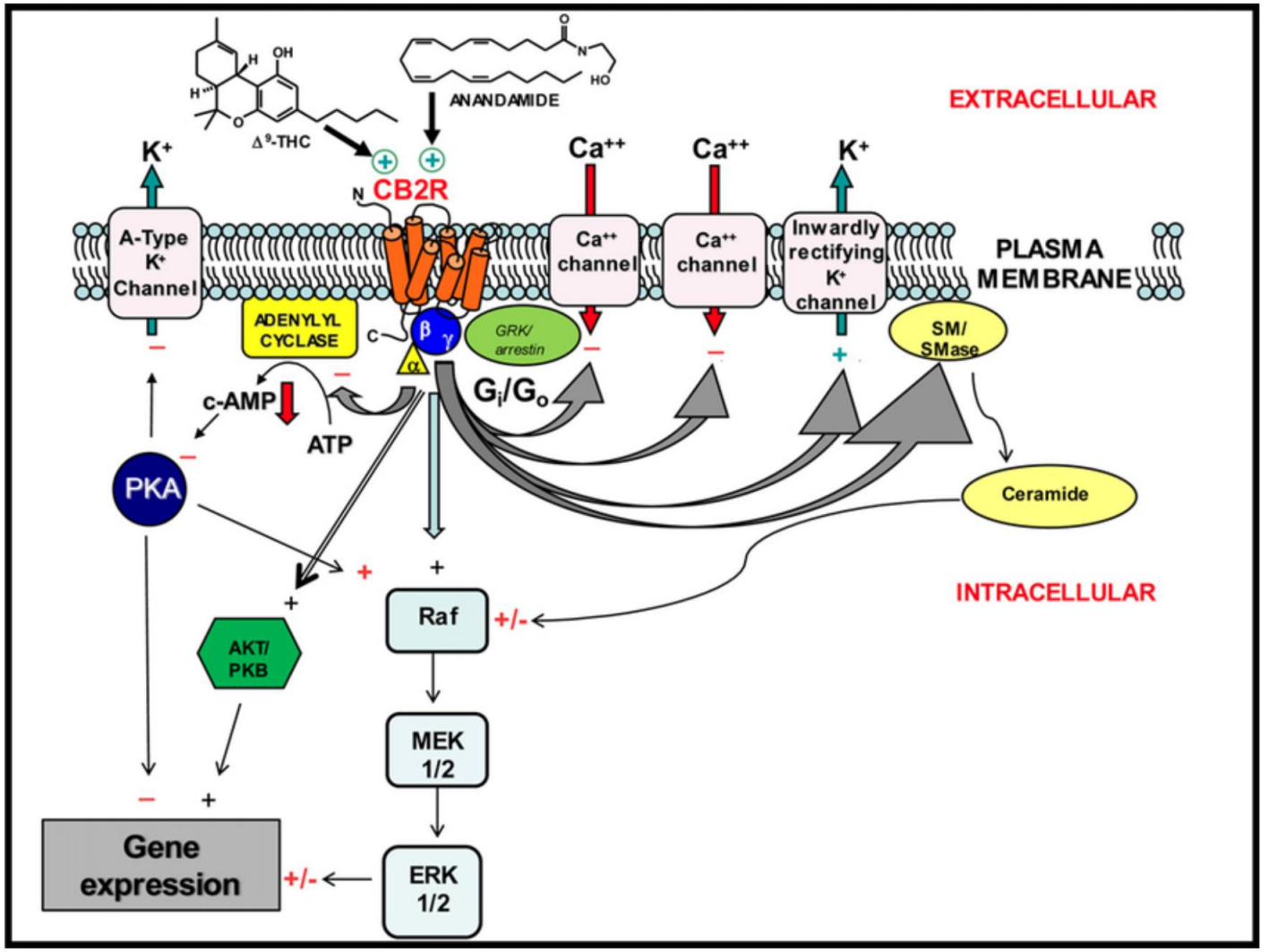
What are the constituent parts of the ECS (continued)

- Receptors
  - CB 1
    - Predominates in the brain and skeletal muscle
    - Also, the liver, heart, pancreatic islet cells
    - Pain pathways (brain and spinal cord)
    - Activation causes retrograde suppression of NT release



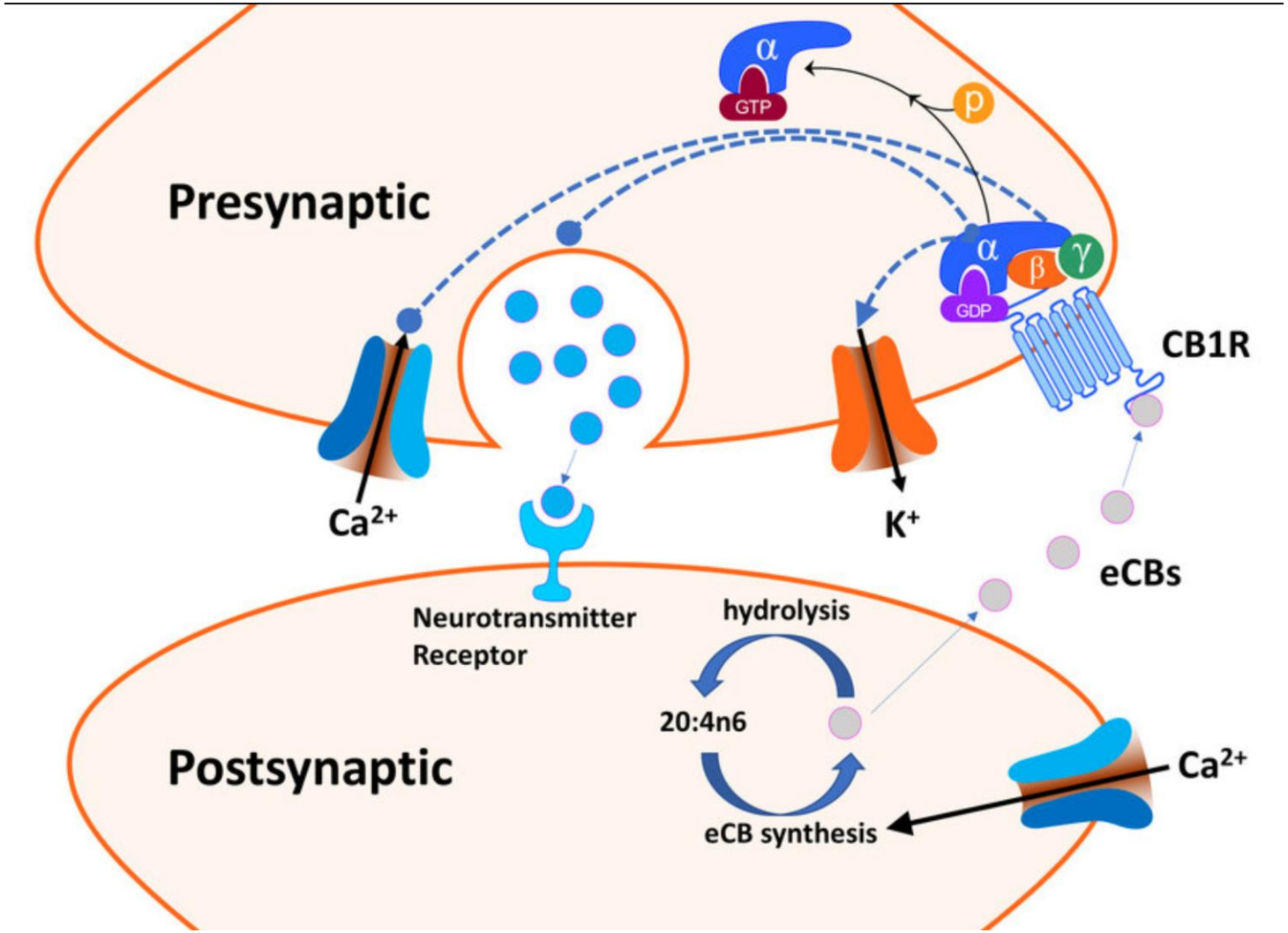
What are the constituent parts of the ECS (continued)

- CB 2
  - Primarily distributed in peripheral tissues – immune system, repro tissues, skin, brain
  - Role in neurodegeneration and neuroinflammation
- Pain and Inflammation mediated by multiple receptors from different families – CB1/CB2, GPR 55/18,5HT, TRPV1, PPAR



What are the constituent parts of the ECS (continued)

- Signaling Molecules (primary):
  - AEA: Anandamide
  - 2-AG: 2-arachidonoylglycerol
- Synthesized from membrane-derived phospholipids in post-synaptic neurons



What are the constituent parts of the ECS (continued)

- The ECS is ultimately involved in the function of multiple drugs classes key to managing pain.

Pharmaceuticals (Basel). 2010 Apr 29;3(5):1335–1347. doi: 10.3390/ph3051335

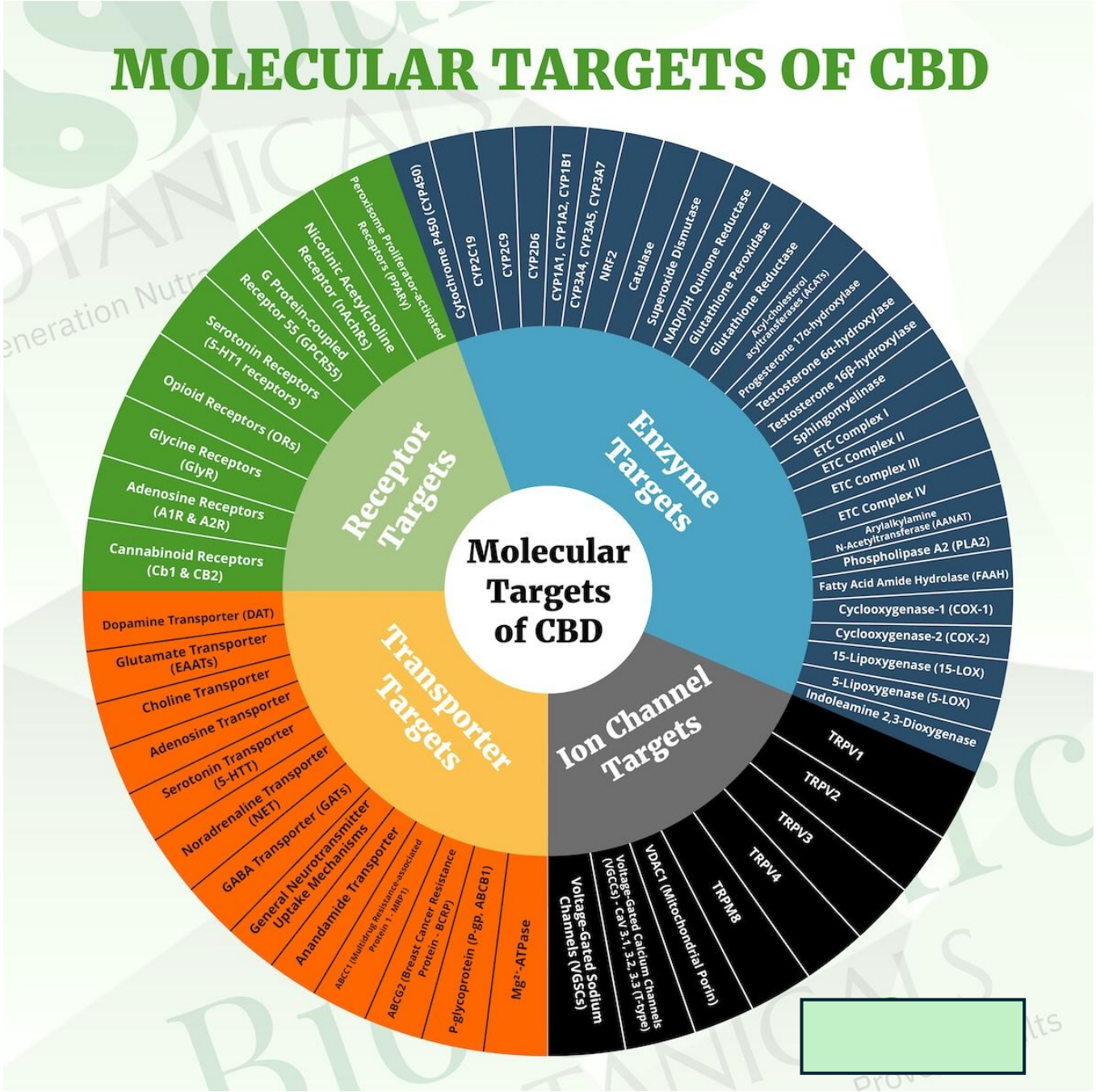
NSAIDs, Opioids, Cannabinoids and the Control of Pain by the Central Nervous System

Horacio Vanegas [1,*], Enrique Vazquez [1], Victor Tortorici [1]

Experimental evidence shows that this is due to an interaction of NSAIDs with endogenous opioids along the descending pain control system. Analgesia by NSAIDs along the descending pain control system also requires an activation of the CB1 endocannabinoid receptor. Several experimental approaches suggest that opioids, NSAIDs and cannabinoids in PAG and RVM cooperate to decrease GABAergic inhibition and thus enhance the descending flow of impulses that inhibit pain.

Take home message about the ECS…

- The variability in receptor distribution throughout the tissues in the body, along with the multiple modes of action of the endogenous cannabinoids, make the application of phytocannabinoids in a clinical environment a process of “discovery”; two patients with the same condition and of the same weight may require different therapeutic approaches in order to reach the same desired therapeutic endpoint.
- One size does not fit all!



The Legal Question: Is it, or isn't it?

- "Laws related to medicinal and recreational use of marijuana and hemp in humans do not apply to veterinary species, and few states have specific laws regarding cannabis in animals."
- "In California, a bill (AB 2215) passed in 2018 provided protection for veterinarians who discuss cannabis; another bill (AB 1885) passed in 2022 prohibited the veterinary board from disciplining a veterinarian for recommending cannabis use in a patient.[1] Nevada has a law (AB 101) protecting veterinarians who recommend hemp-derived products for therapeutic purposes."

Use of Cannabis-Derived Products, Including Cannabidiol, in Veterinary Practice; Request for Information

A Notice by the Food and Drug Administration on 01/16/2025

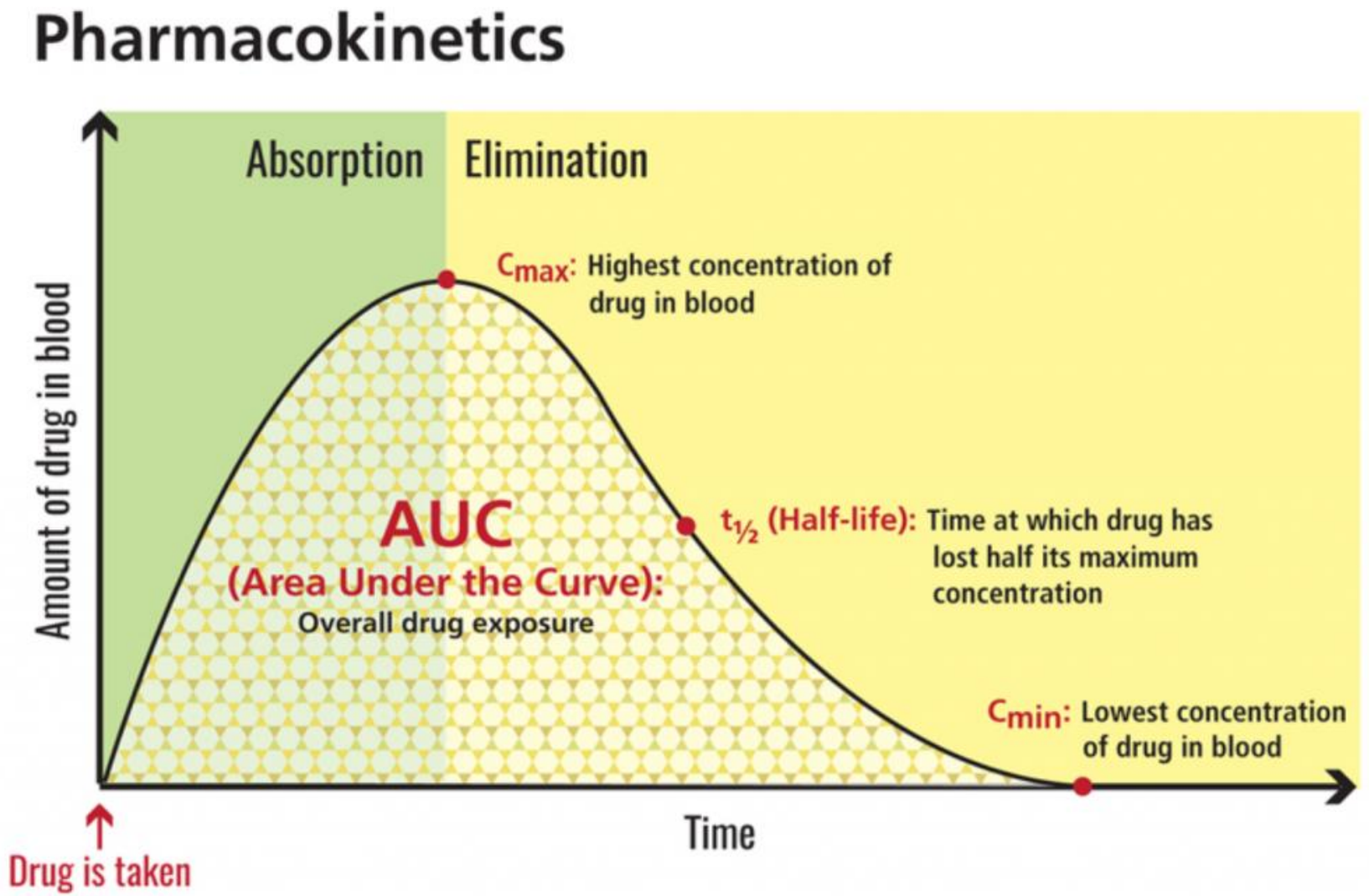
This document has a comment period that ends in 52 days. (04/16/2025) SUBMIT A PUBLIC COMMENT

45 comments received. View posted comments

SUMMARY:

The Food and Drug Administration (FDA, the Agency, or we) is soliciting comments from the public, particularly veterinarians, related to the use of cannabis-derived products (CDPs) in animals, with an emphasis on cannabidiol (CBD) products and general trends associated with those products, including information about: usage trends (*e.g.*, product selection, indications, etc.), quality standards, benefits of use, potential drug interactions, adverse events and safety problems, and toxicological concerns. This information will enhance the Center for Veterinary Medicine's (CVM's) knowledge of potential safety signals associated with these products, in addition to aiding our understanding of veterinarians' experiences related to the use of CDPs for their animal patients.

CBD Pharmacokinetics



CBD Pharmacokinetics

CBD/CBDA -predominant hemp oil[1] (1 mg/kg CBD + 1 mg/kg CBDA)	Oral	4.73 (1.41)
CBD/CBDA -predominant hemp oil[1] (4 mg/kg CBD + 4 mg/kg CBDA)	Oral	4.22 (0.42)
CBD-infused oil (75 mg/dog equal to ~5 mg/kg of CBD)	Oral	3.33§ (0.93)*
CBD-infused oil (150 mg/dog equal to ~10 mg/kg of CBD)	Oral	2.12§ (0.54)*
Microencapsulated CBD oil beads (75 mg/dog equal to ~5 mg/kg of CBD)	Oral	1.59§ (0.49)*
Microencapsulated CBD oil beads (150 mg/dog equal to ~10 mg/kg of CBD)	Oral	1.93§ (1.48)*
CBD enriched Cannabis extract[2] (2 mg/kg)	Oral	2.5# (0.5)
CBD enriched Cannabis extract[2] (5 mg/kg)	Oral	2.6# (0.4)
CBD enriched Cannabis extract[2] (10 mg/kg)	Oral	2.3# (0.2)
CBD enriched soft chews (1 mg/kg CBD + 1 mg/kg CBDA)	Oral	1.0 (0.5)
CBD pure in MCT oil (1 mg/kg)	Oral	2.67§ (0.53)*
CBD pure in MCT oil (5 mg/kg)	Oral	13.4 (4.4)
CBD pure in MCT oil. (5 mg/kg)	Oral	19.3 (7.7)
CBD pure in MCT oil (10 mg/kg)	Oral	6.5 (2.2)
CBD pure in MCT oil (10 mg/kg)	Oral	7.5 (3.5)

- Key Characteristics of CBD:
  - Lipophilic
  - Poor bioavailability/absorption
  - Variability to study product design and size of studies
  - Form factor makes a difference.
    - CBD in a “food-like” matrix likely has better/more predictable absorption then oil-based products.
    - Plasma accumulation may occur, contributing to an increase in half-life

- BID administration is likely sufficient for most dogs
- Time till effect likely to be 2-3 hours
- Tmax doesn’t seem to be affected by dose

CBD Pharmacokinetics and Side Effects in our FELINE friends

- Tmax determined to be between 2 and 4 hrs.
- No significant changes in serum biochemistry profiles noted
- No clinically significant changes in CBC parameters were noted
- Observed adverse events were generally considered to be mild
    - Licking, head shaking, chomping/chewing. Gagging, vomiting. Hypersalivation, drooling, foaming at the mouth

TABLE 2.

Pharmacokinetic parameters of CBD across all doses.

Parameter	Dose (mg/kg)					
	2.5	5	10	20	40	80
C_{max} (ng/ml)	17.8 (3.2–45.3)	61.1 (19.9–148.5)	132.6 (43.2–258.4)	281.0 (14.5–467.4)	251.7 (47.4–467.0)	963.9 (744.6–1126.8)
T_{max} (h)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	2.0 (2.0–24.0)	2.0 (2.0–4.0)	2.0 (2.0)	3.0 (2.0–6.0)
Half-Life (h)	13.2[a] (12.8–13.5)	8.2 (6.0–11.0)	7.5[b] (6.2–8.5)	9.0 (5.7–14.9)	9.6 (6.3–17.7)	6.7[a] (6.6–6.7)
$AUC_{0\text{-}24}$ (ng/ml × h)	83.5 (8.1–165.9)	437.1 (180.0–1139.2)	1000.4 (460.8–1714.1)	1481.0 (92.9–2372.9)	1945.8 (313.1–4150.1)	8738.1 (4269.6–10690.0)
CL/F (L/h/kg)	12.6[a] (12.3–13.0)	17.4 (3.7–23.1)	11.1[b] (5.3–20.2)	45.2 (8.5–84.6)	37.3 (7.7–71.8)	7.13[a] (6.8–7.5)
MRT (h)	4.5 (2.2–8.5)	7.0 (5.9–8.1)	9.0 (7.0–13.9)	6.3 (7.2–8.1)	7.5 (8.1–15.1)	8.4 (7.6–9.4)
Vd/F (L/kg)	239.7[a] (239.6–239.8)	196.9 (50.2–344.7)	110.1[b] (65.1–179.1)	886.6 (73.1–3246.3)	702.0 (89.0–2152.5)	68.3[a] (65.8–70.9)

Drug Interactions

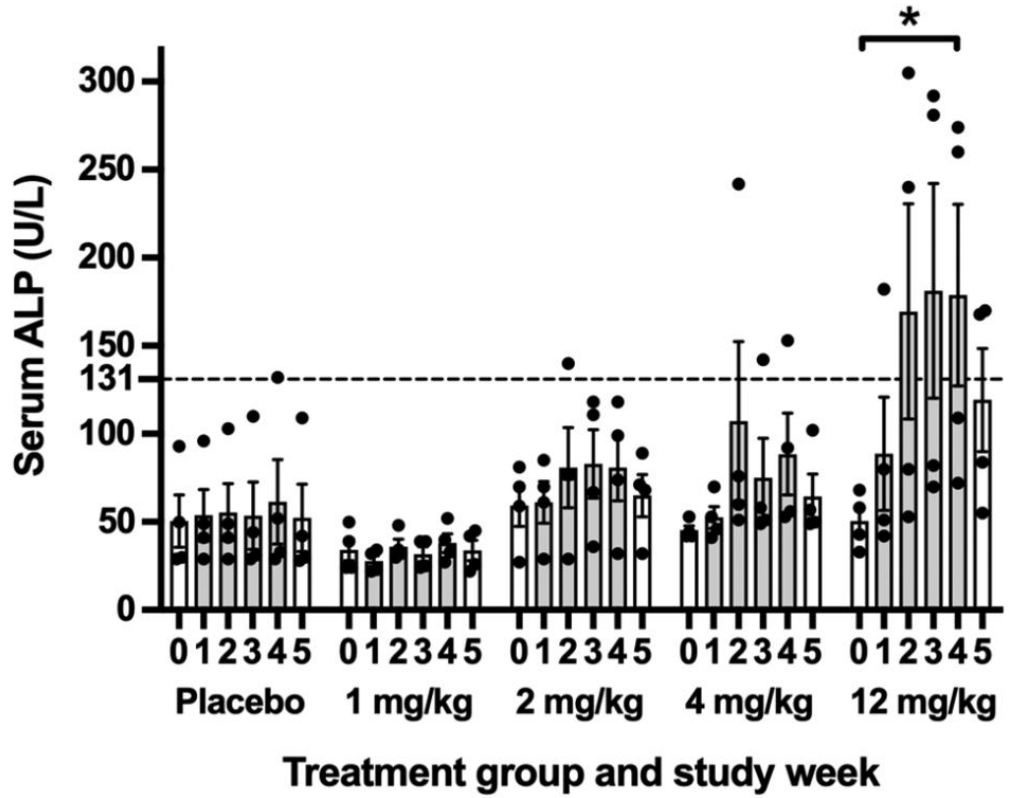
- Potential Drug Interactions
  - CBD is metabolized by the liver, and subject to extensive first pass metabolism (p450 system)
  - Common drug classes used in VetMed – NSAID's, Opioids, Anti-convulsant, thyroid meds, steroids, cancer drugs
- Cytochrome P450 3A4 (CYP3A4) substrates
  - Alprazolam
  - Cyclosporine
  - Erythromycin
  - Ketoconazole/itraconazole

Table 2.

Metabolic drug–drug interactions between cannabidiol and enzyme substrates, inhibitors, or inducers.

Enzyme	Medication Examples	Effect/Recommendation
CYP3A4 substrates	Immunosuppressants, chemotherapeutics, antidepressants, antipsychotics, opioids, benzodiazepines, z-hypnotics, statins, calcium channel blockers, others	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
CYP3A4 inhibitors	Strong: Protease inhibitors, ketoconazole, loperamide, nefazodone Moderate: Amiodarone, verapamil, cimetidine, aprepitant, imatinib	Increased CBD bioavailability, possible increase in risk of adverse effects. Reduce CBD dose.
CYP3A4 inducers	Strong: Enzalutamide, phenytoin Moderate: Carbamazepine, topiramate, phenobarbital, rifampicin, efavirenz, pioglitazone	Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C19 substrates	Antidepressants, antiepileptics, proton pump inhibitors, clopidogrel, propranolol, carisoprodol, cyclophosphamide, warfarin	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
CYP2C19 inhibitors	Strong: Fluvoxamine, fluoxetine Other: Proton pump inhibitors, cimetidine, ketoconazole, clopidogrel, fluconazole, efavirenz	Increased CBD bioavailability, possible increase in risk of adverse effects. Reduce CBD dose.
CYP2C19 inducers	Rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort	Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C8/9 substrates	Rosiglitazone, burprenorphine, montelukast, celecoxib, sulfonylureas, losartan, naproxen, phenobarbital, phenytoin, rosuvastatin, valsartan, warfarin	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.

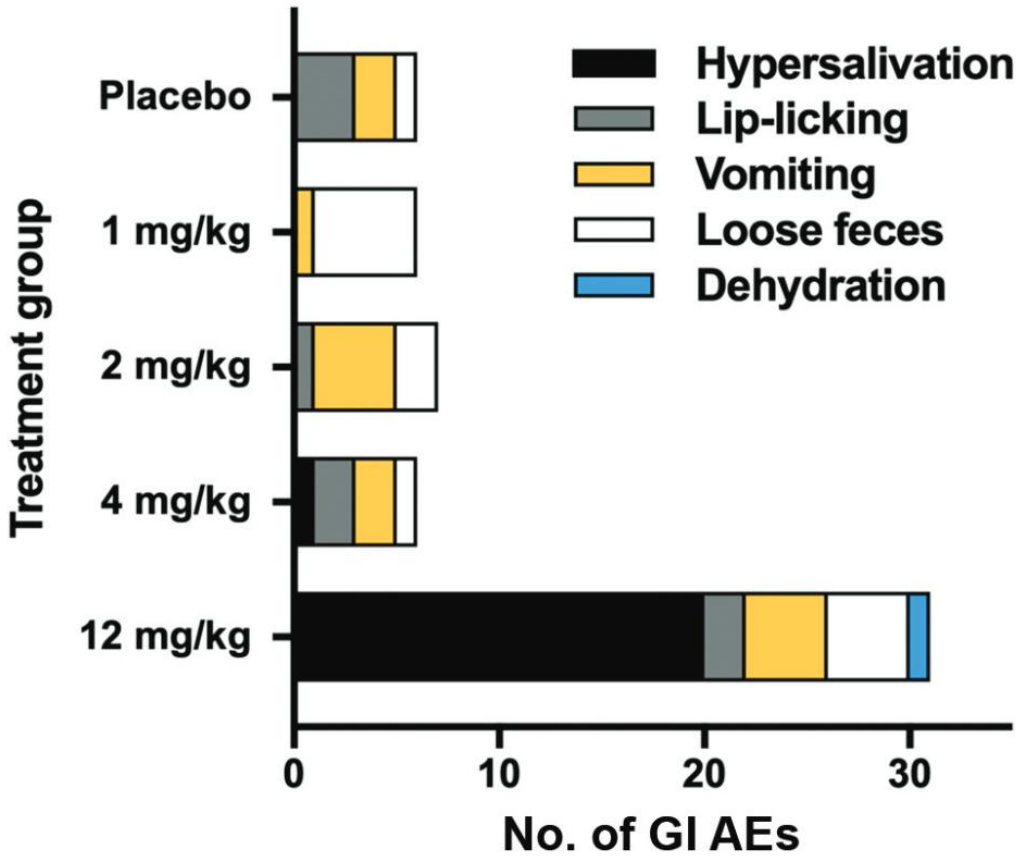
Biochemical Abnormalities associated with CBD administration



- Transient elevations in ALP
- No clinically significant abnormalities detected on CBC's or fasting/post-prandial bile acids
- No significant abnormalities noted in UA's

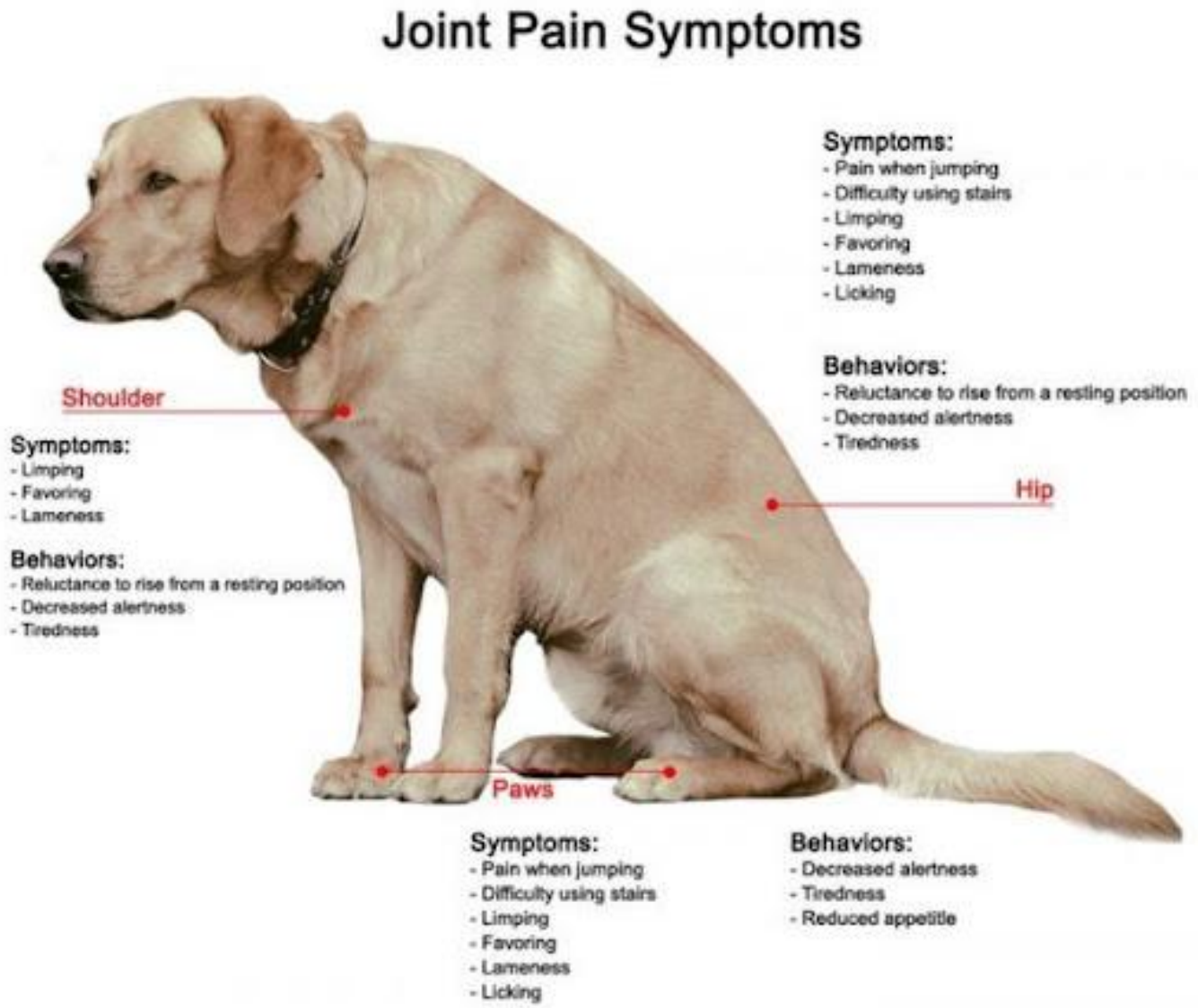
Side Effects/Adverse Reactions to CBD

- Mild and self-limiting
- Not typically does-related
- Abnormalities not typically present on PE
- Anecdotal clinical experience, palatability can be an issue, particularly with broad spectrum products



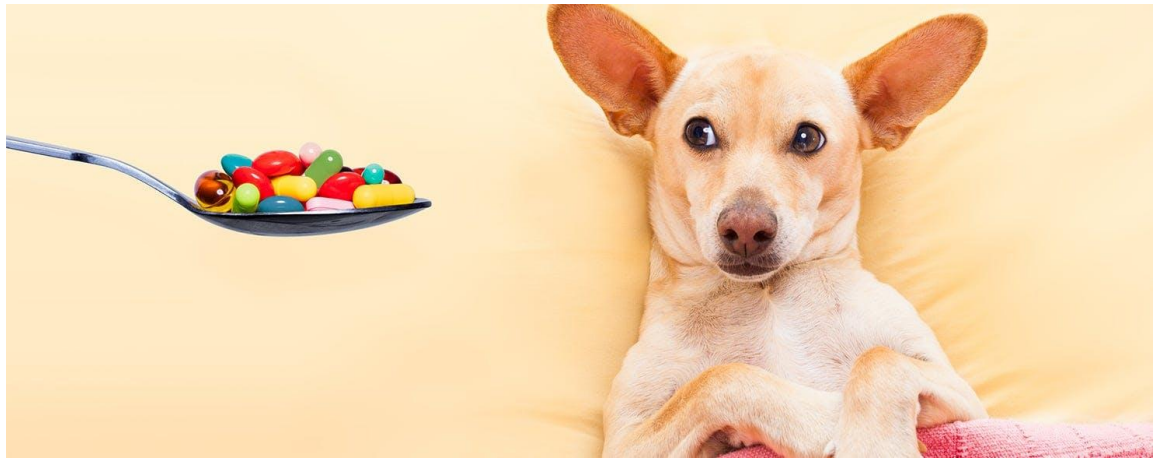
Clinical Indications for CBD Use

- DJD
- Anxiety
- Seizures
- Pain Management
- Tx of Neoplasia
- Atopy?
- GI Disease?
- CNS Neoplasia



CBD Dosing Guidelines to Canine Patients

- The suggested dosing is a starting point and will likely require refinement to more completely address the therapeutic targets in our patients.
- Recognition that there has been an explosion of interest and marketing associated with CBD-based products
- A discussion of CBD is something I have with clients who have pets that are early in the course of their disease and are just beginning to explore treatment options (OA/NP), and as a useful adjunct once more traditional meds are no longer producing the desired effect
- One thing I make clear to owners is that dosing of CBD can be individualized, therefore they need to expect dose adjustments to reach the desired therapeutic potential
- My preference is to use a chew-based product because of its ease of administration and better absorption kinetics



CBD Dosing Guidelines to Canine Patients (continued)

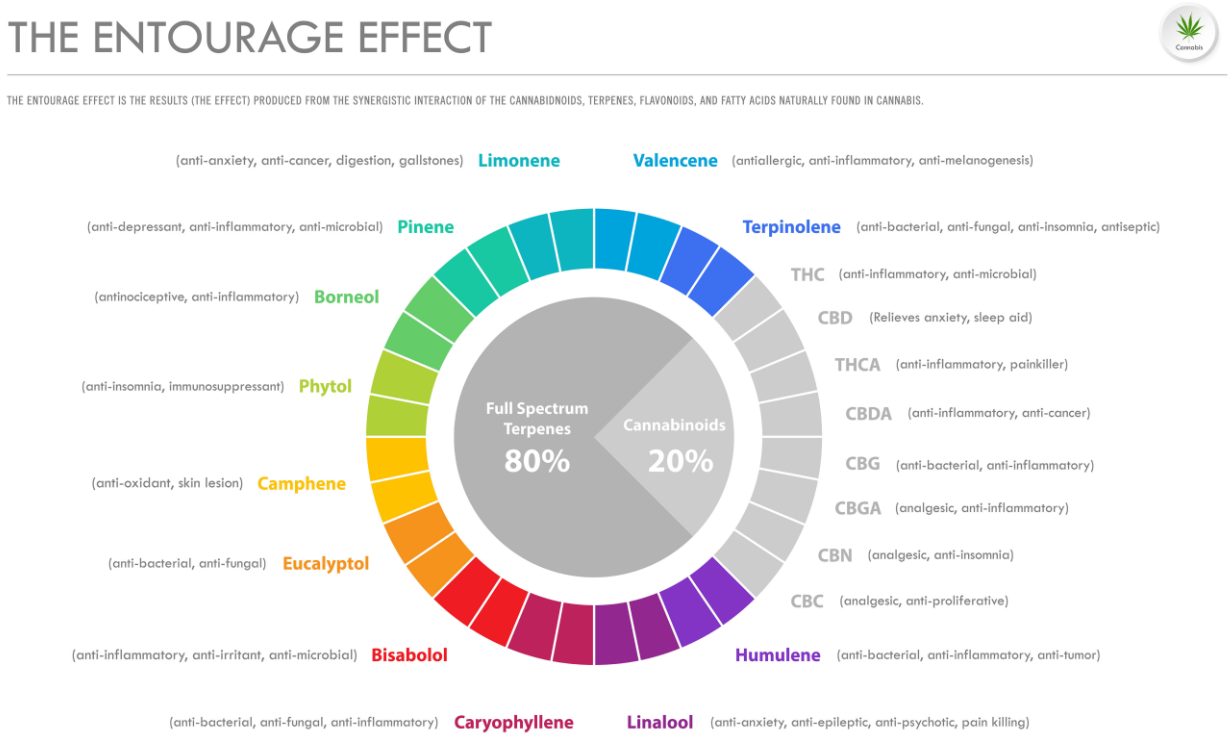
- Starting Dose:
  - Osteoarthritis:
    - 1.0 mg/kg-2.0 mg/kg BID
    - Recheck with owner after 3-5 days, if no observed difference, I increase the dose by 50%
    - Most patients who are going to respond will do so by 2-3 mg/kg, unless a comorbidity is present
  - Neuropathic Pain:
    - 1.0-4.0 mg/kg BID
  - Anxiety Disorders:
    - 3mg/kg-6mg/kg BID
- Seizures:
  - 2.5-10 mg/kg BID
    - Possibly as high as 20mg/kg
- Neurodegenerative Conditions
  - Central: 4- 10 mg/kg BID
  - Peripheral: 1-4 mg/kg BID
- CNS Neoplasia
  - 6-10mg/kg BID
- Atopy
  - 1-4 mg/kg BID
- Post-op Pain/Anxiety
  - 1-4 mg/kg BID
- GI Disease: TBD

CBD Dosing Guidelines to Canine Patients (continued)

- I recommend a starting dose of 2mg/kg BID for OA/NP and a starting dose of 2.5-5mg/kg BID for patients with seizures
  - My starting dose for patients with OA/NP is the same whether it is administered as a single-agent or along with other meds
  - I advise owners to give patients 7-10 days before considering an increased dose, I have administered doses as high as 4mg/kg BID for OA
  - Advise clients of the possible need to escalate the dose of CBD to 5 mg/kg BID or higher with seizure activity based on the human experience
  - In a patient with tumor induced seizures I have used a dose as high as 10mg/kg bid for adjunct seizure control
- Thus far there does not seem not be any adverse reaction when using CBD w/ NSAID's that is clinically significant, I have yet to observe any
- **Anxiety disorders-** I have found a starting dose of 3mg/kg BID to be more effective, an increase to 4 mg/kg BID not uncommon
  - Used as a sole-agent and adjunct to SSRI/TCA without clinical side effects
- **Atopic Dogs** – I have used CBD concurrently w/ apoquel, cytopoint, cyclosporine and steroids with observing any side effects, starting dose is 2mg/kg BID
- In all patients who use CBD on a long-term basis, I recommend evaluation of liver enzymes q 6 months
- I have patients/clients that use CBD on an as-needed basis for traveling, stressful events and recommend that it be administered at least 2 hours prior, based on the known Tmax
- In those patients that have an auto-immune condition, little is published, but I have explored doses of 2-4 mg/kg BID as an adjunct to immunosuppressives' at the owner's request
- I have used CBD as an adjunct to manage patients with Lymphoma, HSA, OSA, SCC , glioblastoma for its anti-inflammatory properties

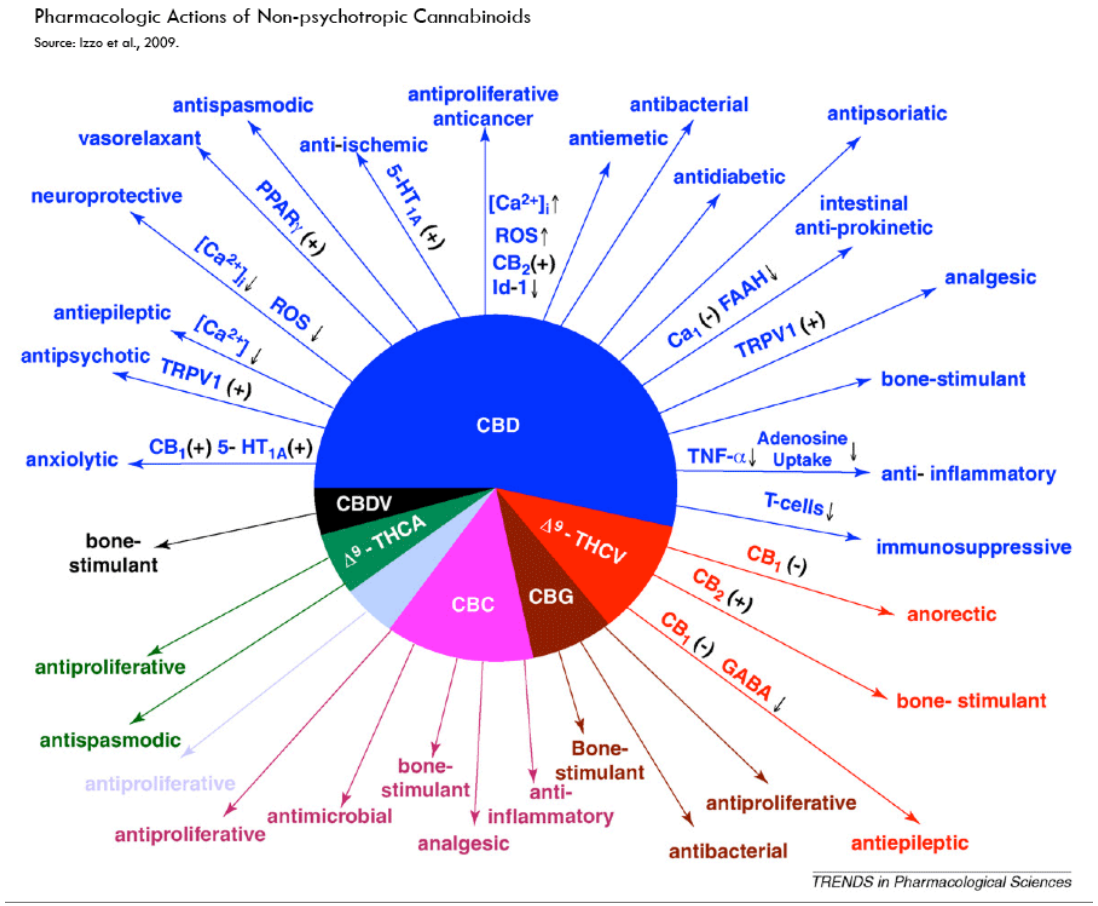
The Entourage Effect: What is it?

- Entourage Effect: The improved therapeutic effect that may result when whole plant extracts from the cannabis plant, a mixture of phytocannabinoids, terpenes, flavonoids, etc., are administered versus the administration of single-agents (e.g. CBD).
  - The entourage effect may also be referred to in reference to administration of a hemp product that is " full-spectrum"; in other words it includes all of the constituent compounds that are extracted from the hemp plant when the oil is removed from the plant.
- There is a conflict that exists between proponents of the "entourage" effect and the people that study it: the marketing claims for its effect are not yet firmly established in the scientific literature.
- Single-agent administration still has real demonstrated benefit
- We don't know which cannabinoids to "mix and match" or at what doses this may necessary



Future Directions and Challenges in Cannabinoid Medicine

- Exploration of the pharmacokinetics and mode of action of other cannabinoids
- Entourage Effect?
- Standardization of clinical study compounds
- Individualized nature of dosing
- FDA?
- Other species
- “Bad Actors”



Contact info for additional questions or follow-up

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