

Medical Cannabinoids: A Review

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The endocannabinoid system (ECS) has been evolving since the beginning of multi-cellular species, but why did veterinary practitioners never learn about it in school? Just like our human counterparts' veterinary practitioners have no or only a cursory understanding of the ECS and cannabis therapy. Veterinary practitioners have also been echoing that there "is no evidence" in animals. To the contrary, we have numerous studies utilizing cannabinoids and other cannabis molecules for therapeutic relief and translational studies that could be considered for any vertebrate creature. Here we review some of the current and pertinent literature in utilizing cannabinoids in animals and discuss the future forecast of cannabis in veterinary medicine.

The ECS is a system comprised of naturally occurring ligands called endocannabinoids, catabolic and hydrolyzing enzymes, receptors CB1 and CB2, and other endocannabinoid *like* molecules. The function of the ECS is vast but is commonly known to maintain homeostasis. There has recently been an expansion of the ECS that include other receptors and ligands known as the *Endocannabinoidome*. This expansion includes a new understanding that the affinity of endogenous ligands and molecules from the cannabis plant known as phytocannabinoids also have affinity for other receptors we may be more familiar with such as opioid, dopamine, serotonin, TRPV, and several others. This speaks to the interest in using phytocannabinoids for several conditions.

There are some fundamental distinctions one must make on the topic of medical cannabis, and even specific terminology used when approaching medical cannabis as a valid medical therapy. The first distinction is between a "marijuana" plant versus a "hemp" plant. The hemp plant has much lower levels of THC (less than 0.3% by dry weight) and has found favor among veterinary professionals since there is a reduced risk of THC "toxicity". This distinction is particularly important for recommendations made by veterinary professionals. At the time this article was written there were no states that allow for medical marijuana prescriptions for veterinary use. Veterinarians are not allowed not need to "prescribe" or "dispense" OTC hemp CBD products as a prescription is not needed and these terms should not be applied to animal supplements in general. Since the legalization of medical marijuana in the United States began, the Animal Poison Control and Pet Poison Hotline has seen a >300% increase in THC toxicities. There is no question to the risk and occurrence of the most common and potent phytocannabinoid, THC, yet it should be noted there are no reported deaths that can be definitively attributed to THC or other phytocannabinoids without other factoring chemicals also present in the system in humans or animals. The suspected lethal dose of THC in dogs is >9 g/kg, a nearly impossible dose to achieve- in fact the study conducted in the 1970's didn't have any dogs die at this dose. A 2018 study investigating the susceptibility of cannabis-induced convulsions in rats and dogs, reported no seizures in dogs at dosages of THC and CBD around 25mg/kg orally, twice a day for

over a year. But central nervous system signs including ataxia, tremors, and hypoactivity were observed. In a more recent study with acute dosing at dosing up to ~62mg/kg of THC the dogs had dose related symptoms, but again no fatalities. When it comes to THC use in practice there is no doubt to its potential, however some of the most respected cannabinoid researchers (E. Russo, D. Meiri, etc.) have started changing the tone of THC use in clinical practice as there is nothing that the other non-intoxicating phytocannabinoids can't do that THC can. Levels of THC found in hemp (<0.3%) typically present little concern of intoxication or other adverse events- including proliferation of certain types of human cancers - despite anti-cancer affects in other cancer types. With this in mind and the several hemp products available we now have several "safe" products owners can choose from with limited THC. Cannabidiol (CBD) is another popular phytocannabinoid at the moment. It is one of numerous phytocannabinoids that the *Cannabis sativa* genus contain. Safety data is favorable. Interestingly, GW Parma did a long-term study in dogs for 39 weeks with a CBD isolate for 10-100mg/mg orally with some minor concern of elevating liver enzymes (ALP and ALT) and notable hepatocellular hypertrophy, commonly seen with steroid use also. They animals in this study did not require medical intervention. More recently, we have a 12-week study published showing the safety of using a hemp CBD product in healthy dogs and cats. The study concluded that at a dose of 2mg/kg, PO, BID is safe and well tolerated. However, one cat did have a transient spike in ALT that could not be directly correlated to the CBD product. Other than this one cat all other chemistry values in dogs and cats remained within normal limits.

A veterinary specific textbook is currently underway, with contributions from over 30 veterinary specialists. The textbook is expected to hit the shelves on 2021 and is being published by Springer Nature.

Long-term monitoring:

The author suggests liver enzyme monitoring for patients that will be on the product long-term, >3 months. They would include, ALP, AST, ALT and minimum. The addition of GGT and CBD may be considered in addition. C-Reactive protein may also be an interesting way to gauge success.

Common drugs where interactions may occur:

Benzodiazepines- This is one of the most common and sever drugs we see potentiating effects of even zero THC products. Animals may appear extremely lethargic or have symptoms similar to THC intoxication. Recommend significant decrease in either cannabis product of benzo, by at least 25%. Dose de-escalating or escalating over time is usually warranted for the small percentage of animals that may experience these symptoms.

Gabapentin, Acepromazine, Tramadol, Phenobarbital- in some patients you may see transient lethargy, inappetence, abnormal behaviors and in severe cases urination. Dose de-escalating or escalating over time is usually warranted for the small percentage of animals that may experience these symptoms.

Trazodone (other SSRI's)- theoretically we should keep serotonin syndrome in mind. However, this has not been described in animals with the combination of cannabinoids products and SSRI's and is not well described in human literature.

Response to cannabinoid products: The variance in response is heavily reliant on multiple factors known as the Endocannabinoid System Tone. The tone of the ECS is dependent on

- 1) The disease or injury and severity
- 2) Production of endocannabinoids
- 3) Product of catalyzing or hydrolyzing endocannabinoid enzymes
- 4) Number of ECS receptors and activity of the endocannabinoidome
- 5) Gene variant of receptors (Akt, CB1, CB2, etc.)
- 6) Formulation of the product being used and dose

*Dosing can be semi-fluid with maintenance dosing and “rescue doses” as needed.

Record writing template:

- Owner inquired about CBD product. Provided harm reduction counseling.

+/- Owner purchased XX product. Suggested dosing based of recent efficacy studies.

+/- Recheck appointment in 3-6 month for blood work.

- Owner asked about XX product. Reviewed COA and provided harm reduction counseling. Owner elected to use product at XX dose for ECS support.

What to look for in a cannabis product: *(written by Liz Hughston)*

While high-CBD products are available for the human market, many of them still contain levels of THC that may lead to intoxication in our patients (particularly dogs). This is especially true if a product is derived from marijuana, and not hemp. For this reason, products formulated specifically for veterinary species are better choices than those formulated for humans. Because these products are not regulated by the FDA (just as human vitamins and supplements are unregulated), look for a company that adheres to current [Good Manufacturing Practices](#), or one that has the National Animal Supplement Council (NASC) [Quality Seal](#) to ensure a clean supply chain and manufacturing environment.

Ask for a Certificate of Analysis (CoA) for any product you are thinking about purchasing. This is a third-party, independent laboratory analysis of the product. While there are issues with testing facilities and standardization, this is currently the best (only) way to evaluate the quality of a product.

The CoA should include:

- A breakdown of all cannabinoids present in the product

- We have good evidence that whole-plant (aka full-spectrum or broad-spectrum) products are more effective than products that contain **ONLY** CBD (such products are termed “isolates” and may require much higher doses to achieve the desired effect)
- The CBD:THC ratio in the product
- Terpene analysis
- Heavy Metal testing
- Herbicide / fungicide / insecticide testing
- Microbial testing
- Mycotoxin testing
- Residual solvent testing

The company should also provide the following information:

- The amount of CBD per mL (or teaspoon)
- A complete ingredient list
- Check for dangerous ingredients like xylitol or other flavorings
- Extraction method used

A company should provide all of the information listed above without hesitation and immediately upon request. As the market matures, purchasing a product that is backed by positive scientific studies using the product will be advisable.

Clinical Veterinary Cannabis Studies

To date, we have an ever-growing list of relevant studies for practical use of cannabis in companion animals. The author is aware of at least 9 canine pharmacokinetic studies in dogs, 2 in cats and 4 in horses. All data suggests absorption can range from 19-35% depending on the cannabinoid (and other phytoconstituents) profile and administration technique.

Osteoarthritis

For management of various conditions, we now have the results from 7 studies looking at the efficacy of different CBD products for the comfort levels of dogs with osteoarthritis. All the studies concluded that CBD has a minor to significant favorable impact on decreasing pain scores and increasing quality of life (QoL) for the pets. Dosages in these studies ranges from 0.25-2mg/kg PO BID. In most of these studies ALP became elevated in a percentage of the participants. However, none warranted clinical intervention. Unless multiple other liver enzymes are also increased it is difficult to assess if the elevations were a sign of hepatic insult or were related to the metabolism of the product. The researchers are more inclined to suggest

the elevations were related to the metabolism, also supported by human and rodent literature. Interestingly, CBD has been researched in rodent models for its bone healing properties where ALP did increase as bone density increased while on CBD treatment. The specific isoform of ALP warrants more study to find the etiology of this elevation in a smaller percentage of dogs.

Seizure Disorders

As it relates to neurological conditions, a pilot study was conducted in dogs. The study found that at a dose of 2.5mg/kg BID did not meet the study goals of 50% decrease in seizure activity, but there was an average of 33% decrease in the dogs that did respond. While the study was not a huge success it did show great promise. I personally believe the ongoing, longer term study with a higher dose will be much more successful. Epileptic patients generally require higher dosages compared to those needed for other conditions such as pain. Currently, there are a few other studies evaluating CBD for veterinary epileptic forms that should be published in the near future. Anecdotally the author has seen great success with CBD for seizure disorder in combination with other AED's. In fact, many owners are able to significantly decrease traditional AED dosages. Tolerance to CBD is not something typically described with CBD use, however in a recent human study, around 30% of patients did develop what appeared to be a CBD tolerance. Dosages were increased with good response.

Oncology

In vivo oncology studies in veterinary species are currently ongoing. There are two studies looking at the efficacy of CBD products for treating transitional cell carcinoma in dogs and a broader QoL study that the author is aware of. Cell culture studies have been conducted with great promise for *in vivo* application. Canine glioblastoma, canine lymphoma, canine mammary carcinoma and osteosarcoma cell lines are all responsive to CBD. In fact, there appears to be synergy with two chemotherapeutic agents that were tested, doxorubicin and vincristine. Dosages of phytocannabinoids based on scaled dosing from cell line work appear to be greater than 5mg/kg PO BID, but patients can benefit from symptomatic relief at dosages much lower. Human studies have found better response to chemo treatment and an improved QoL when phytocannabinoid product are used. The use of phytocannabinoids are found to aid in decreasing nausea and increase appetite related to chemotherapy in people.

Behavior/Anxiety

Animal models of CBD utility for anxiety or panic attacks are supported by studies placing a prey species in front of a predator species and conditioned escape responses in mice and rats. According to these studies, anxiety or panic attacks would be related to the flight and freezing defensive responses elicited by threats which expression was decreased in both models. There are multiple canine studies and one feline study currently ongoing. Experience feline practitioners have hailed CBD as a novel, yet effective treatment for cats with chronic cystitis.

Dermatological

Finalized and pre-liminary results from at least three canine studies have shown around a 50% decrease in canine atopy lesions and itch scoring when a CBD product was used. Topical and systemic forms have been used with success.

Gastrointestinal

While clinical studies in companion animals are lacking, receptor identification studies in cats and dogs show the potential therapeutic benefit for diagnosis such as IBD and IBS. Human studies show good efficacy for chronic forms of colitis. It is important to note oils may be better tolerated for GI conditions to not cause flare-ups. Other studies looking at ECS distribution in various tissues are those interested in gastrointestinal function. One study published by Glaizzo and colleagues looked at CB1, CB2, GPR55, and PPARa in canine gastrointestinal tissue, giving us deeper insight to the anatomical basis of supporting therapeutic cannabis in relieving motility disorders and visceral hypersensitivity in canine acute or chronic enteropathies. We have also seen studies looking at protective effects, specifically for gastrointestinal mucosal lesions secondary to acute pancreatitis in rat models. This is of particular interest in companion animals because pancreatitis is a common occurrence.

Renal disease

Human patients have been using cannabinoid product with chronic renal conditions for years with great success and not adverse warning in the literature. This may be a great option for stimulating appetite and keep the often-geriatric patient comfortable if NSAIDS are a concern.

Conclusion

While the legal status of cannabis and hemp products continues to play out it is critical that we continue to push for quality scientific data to support therapeutic evidence. Just like in human medical cannabis circles, the veterinary side of things will continue to evolve, looking for specific cannabinoid and terpene profiles for various ailments or ECS support. As scientists, consumers, and animal lovers, we must pressure cannabis/hemp manufacturers to produce products following good manufacturing guidelines, use safe ingredients for animals, and be transparent with what is in their products. To that end, manufacturers should suggest dosing regimens based on science instead of anecdotes. It is critical to note dose extrapolation from one tested product to the next would not necessarily provide the same efficacy or have the same safety profile as mentioned in the conclusions of a specific study based on the wide array of cannabinoid and terpene profiles on the market. We must also pressure local governments, mainly state veterinary and pharmacy boards, to adopt legislative language to allow veterinary professionals to discuss, recommend, and, in some cases, prescribe cannabis product for our pets. Lastly, we must encourage the veterinary profession to educate themselves on this topic.

General Condition Category	Favorable cannabinoids & terpenes (Broad or Full Spectrum CBD dominant products)	Dose- Bases off total cannabinoid concentration -Felines (use higher end)
Chronic Pain (Arthritis, CKD, Atopy)	CBGA, CBDA, or THCA. Myrcene, Linalool, Pinene, Caryophyllene, Carene, *Humulene (can be appetite suppressing)	0.5-1mg/kg +/- Loading dose for a week of 1-2mg/kg BID
Acute Pain	CBDA, CBGA or THCA. Myrcene, Linalool, Pinene, Caryophyllene, Bisabolol	1-2mg/kg BID, rescue
Seizures (Epileptic form)	CBG, CBC, CBDV, CBN + Myrcene, Linalool, Geraniol	2-10mg/kg BID-TID
Cancer Symptoms (Appetite, comfort, nausea)	THCA, CBDA, CBGA + Myrcene, Limonene, Caryophyllene	1-5mg/kg BID
Anti-Cancer	CBG, CBGA, Carene, Borneol, Limonene	2-10mg/kg BID
Chronic Anxiety	CBN + Myrcene, Nerolidol, Linalool	0.25-1 mg/kg BID, rescue
Acute Anxiety	CBN + Myrcene, Nerolidol, Terpeneol, Linalool	1-3 mg/kg BID, rescue
Cognitive Decline	CBGA + Limonene, Caryophyllene, Pinene	0.5-2 mg/kg BID

References: References available upon request or by access the files section here.

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