

THE WONDERFUL WORLD OF CANNABINOIDS IN SMALL ANIMAL PRACTICE

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Hemp Cannabinoids: An overview

The use of cannabinoids in veterinary medicine is growing daily endocannabinoid system is a long-standing complex receptor mediated system that includes the cannabinoid receptor 1 and 2 systems (CB receptors) that are primarily involved in controlling local synaptic transmission and potentially hormone and cytokine release in peripheral tissues. But this system extends into other receptor systems including; transient receptor potential receptors (TRPV), adenosine reuptake in cells, glycine receptor activity and peroxisomal proliferation receptor (PPAR), G protein orphan receptors (GPR55 and others) and 5-hydroxytryptophan receptor (5-HT) biology. To this end there is significant interest in the TRPV system as it relates to mitigation of nociceptive responses in acute and chronic neuropathic pain. (1-3) The glycine receptor inhibition may also be important in spinal cord transmission of the pain response and endogenous and exogenous cannabinoids may play a role in the mitigation of pain perception from the spinal cord to the brain. (2) Lastly, the serotonin receptor system may be equally important as it relates to issues of pain perception and mentation as potential targets of all cannabinoids. (2)

Hemp cannabinoids are derived within the plant primarily in the flowering bud with tetrahydrocannabinol (THC) as a long sought after recreational and medicinal cannabinoid due to its psychotropic activity in what is known as marijuana and is the major differentiator between federally legal hemp versus illegal cannabis (higher than 0.3% THC as measure in the plant). The cannabinoid synthesis (and terpene profile) are what differentiate strains of *Cannabis sativa* spp. Hemp will produce cannabidiolic acid (CBDA) through cannabidiol synthase activity in the hemp cultivars which when heated will decarboxylate into cannabidiol (CBD) during processing of hemp. Much of today's industry focuses on CBD while the research into molecules like CBDA, cannabichromic acid (CBCA), cannabichromene (CBC), tetrahydrocannabinolic acid (THCA), and cannabigerol (CBG) and cannabigerolic acid (CBGA) are burgeoning showing similar and slightly different actions at these receptor systems above as well as antioxidant and even antibacterial properties. Resulting in the "endocannabinoidome" being a term to encompass all of the targets for CBD and CBDA. (4)

When these minors and other molecules such as terpenes and flavonoids from the plant are in an extract it is considered to be "Full Spectrum". This lends to the idea of "the entourage effect", where some researchers postulate that these additional molecules may act synergistically, or improve absorption of cannabinoids to provide the benefits of pain mitigation. (5) Considering the multiple receptors/channels being affected this endocannabinoid system is now being referred to as the endocannabinoidome (2) An example of this concept is a study in steers, where whole hemp containing little to no CBD or THC, but rich in CBDA and THCA was provided to cows, alongside other acidic molecules; these researchers showed that cows displayed lower overall cortisol, prostaglandin E2 and improved comfort levels. (6) Interestingly, in the few studies examining CBDA absorption and retention in dogs and cats, there is a 3-5 fold better absorption of CBDA than CBD across species. (7-9)

Chronic OA Pain – The current Data in Dogs and Cats!

If we examine the current clinical literature on pain mitigation in dogs and primarily focus on randomized, blinded placebo-controlled studies, there are now 4 studies in dogs evaluating osteoarthritis pain and one in cats. In dogs, the first study used a full spectrum CBD/CBDA rich hemp product, which contained an equal mix of CBD and CBDA, dosed at 2 mg/kg every 12 hours. Results showed benefits based on validated subjective measurements using the Canine Brief Pain Index (CBPI) with an approximately 25-point drop in pain scores at weeks 2 and 4, that were not observed in the placebo group. In addition, Hudson Activity scores were also evaluated, demonstrating a 20-point increase in the activity index during treatment, while during placebo treatment there was a mild worsening of scores. (10) On veterinary evaluation at the 2 and 4 week time point there were improvements in pain scores on examination in the dogs when treated with the full spectrum CBD/CBDA mixture.

A second study utilized a smaller cohort of dogs using a CBD-rich hemp product. There were 4 groups of 5 dogs receiving either a placebo or two different forms of CBD oil (11) The trial was for 1 month, utilizing the Helsinki Pain Index, which was performed at the end of the treatment period. All dogs in the groups treated with 50 mg/day dose of CBD-rich hemp in MCT oil and 20 mg dose of microsomal encapsulated formulation showed a significant drop in pain index scores. Both the 50 mg and 20 mg treatment groups given products once a day showed improvements according to owner surveys and veterinary assessment.

A third, randomized placebo-controlled study, examined dogs with clinical arthritis that were concurrently managed on firocoxib or low-dose prednisone, in addition to amitriptyline and gabapentin. (12) This drug choice could not be changed during the 12 week trial. Dogs were provided 2 mg/kg every 12 hours orally of the CBD product. Evaluation via canine brief pain inventory by clients showed a significant difference when compared to the placebo group. More importantly, this was the longest study utilizing a CBD rich hemp product to date, and it appeared to demonstrate safety with concomitant use of other commonly utilized medications.

Recently published results from another 6-week placebo cross over design study, utilizing 42 dogs with a dose of CBD isolate of 4.5 mg/kg twice daily in an MCT oil base, for 6 weeks in each arm of the trial. A secondary assessment was to better understand its use in conjunction with carprofen as a standard NSAID treatment for OA. The measures included standard subjective owner and veterinary assessments at 6 weeks of each treatment, as well as objective kinetics around ground reaction forces. What was evident is that both subjective owner and veterinary assessments regarding pain were improved when on this CBD product, compared to placebo treatment. They also recognized sporadic increases in ALP associated with some of the treatment group dogs, as well as a statistically significant increase in ALT in dogs with concomitant use of carprofen, although there were no differences in dogs above the reference range interval in either placebo or treated dogs. These results are different from Gamble et al. who used a different product at a lower dose, where ALT rises were not associated with NSAID use, and in fact were associated with lower serum creatinine concentrations in dogs using CBD-rich hemp and carprofen together. (13) These conflicting results may be due to the product, or dosing being higher in the most recent study.

A recent study by Ellevet in cats with OA using their paste product at 2 mg/kg BW every 12 hours showed similar efficacy as in the dog study with client specific outcomes being different from placebo and no alterations in serum chemistry or blood counts in a cross over design for 6 weeks in each arm of the study. (14) Another pain indication suggests some mild benefit in cats with chronic gingivostomatitis when using ~1 mg/kg of a CBD based powder diluted in water and administered orally once daily. Although the healing and oral lesions were no different between the placebo and treatment groups, it was found that weight improved in the treatment group and decreased in the placebo group. Exactly whether this was due to pain mitigation or appetite stimulation is undetermined but does suggest some utility in cats. Further investigations in cats are sorely needed.

Anticonvulsant properties:

CBD has been used for over 10 years in the treatment of childhood seizures with the FDA approved product for humans called Epidiolex. This product is often used with other anti-convulsants and shows relative efficacy with about 30-40% of children showing a 50% reduction in seizure activity. This has led CSU researchers to do two studies in dogs with refractory seizures. In the first pilot study dogs were given 2.5 mg/kg of a CBD rich hemp product for 12 weeks vs placebo and in the treatment group 33% (3 of 9) showed a 50% reduction in seizure activity. (16) This led to a larger study using a slightly higher dose at 4.5 mg/kg in a 12 week crossover design to placebo. The major findings were that dogs on placebo during the add on to their current treatment showed higher seizure rates of 25-30% over 12 weeks while CBD treated dogs did not show increases or decreases. (17) More interestingly, dogs on CBD showed approximately 30% fewer days with seizures suggesting mild efficacy.

Similarly, using a full spectrum CBD/CBDA product was studied in 14 dogs with refractory epilepsy using a 2 mg/kg equal mix of CBD and CBDA in a cross over design versus placebo for 12 weeks in each arm of the study. Surprisingly, the CBD/CBDA treatment showed an over 40% response rate of dogs with a 50% decrease in seizure activity, and average seizures during the 12-week treatment with CBD over the time period was less than 5 while the placebo treatment resulted in approximately 8 seizures during this period. Interestingly, owners reported that seizures were not as lengthy and pre or post ictal periods were reduced across the cohort further supporting that CBD/CBDA rich hemp was useful during the treatment period. (18)

From a neurologist's perspective, the important point to study was whether other anti-convulsants were influenced by CBD since cytochrome p 450 activity can be increased with CBD treatment resulting in ALP rises which was

observed in the first two studies mentioned but not the study using full spectrum CBD/CBDA. That said, in the last study serum levels of zonisamide, phenobarbital and bromide showed no changes in the serum levels over the 12-week period suggesting no interactions. Further evidence of higher doses of CBD at 10 mg/kg has also been studied to examine its effects on phenobarbital and there appear to be no interactions providing peace of mind that CBD can be used safely during refractory epilepsy. (18,19)

Atopic Dermatitis – really?

Targeting dermal diseases is relatively untapped human realm using these cannabinoids to alter disease progression in dermatology. Interestingly, there has been some examination of these receptor systems in atopic dermatitis in dogs and it has been shown that the CB receptors, GPR 55, TRPV and PPAR are found in keratinocytes and inflammatory cells of canine atopic patients suggesting these may be targets for helping control this disease. (20) To that end, there has been one observational study using a natural palmitoylethanolamide nutraceutical that targets the CB receptors suggesting that this nutraceutical may help resolve atopic dermatitis pruritus. (21) The cannabinoids that target these alternative receptors systems have not been examined until recently. A recent clinical trial using a CBD/CBDA full spectrum hemp oil was used to examine the resolution of atopic dermatitis in refractory cases that were on a spectrum of other treatments. After completion of a double blind placebo controlled study using this oil at a dose of approximately 2 mg/kg body weight for 4 weeks there were encouraging results where 10 of 17 pet owners on the full spectrum CBD/CBDA oil found positive results the warranted continuing the treatment while only 2 of 12 in the placebo group wanted to continue treatment. (22) The study examined not only the pruritus but also the dermal lesions based on dermatologic CADESI scoring. Interestingly, the owners reported reduced pruritus while dermal lesions were no different. In addition, when looking at serum cytokines there was no reduction in the pro-inflammatory cytokines examined with treatment, while pruritus was diminished. These and other data suggests that pruritus is the definitive target which may be through neural control rather than controlling the inflammatory response.(22,23) But, at the typical dose of 2 mg/kg neural transmission of pain and pruritus can be controlled. More importantly, when regression analysis was performed on pruritic response and serum CBD/CBDA concentrations that there was a significant correlation between serum concentrations and the pruritic response suggesting that dosing and inherent metabolism of cannabinoids may be important in clinical response to hemp derived cannabinoids as well as the product used.

Anxiety/Stress Relief

In human medicine CBD rich hemp product use has been pretty well established as a mild anxiety-like agent across different forms of anxiety. (24,25) This makes is a popular supplement to treat dogs with however dosing and anxiety model studies in dogs and cats appear to be mixed in the response. Car ride, noise phobia and separation anxiety studies in colony dogs have been largely negative to mixed and the doses studied have been in the 1-4 mg/kg for situation and in long term treatment studies. (26-29) The problem with many of these studies is the fact that colony dogs do not have the severity of anxiety that many of our clinical patients exhibit and studies need to be done on clinical cohorts. Interestingly, in one cat study over time for aggressive behaviors showed that CBD rich hemp at 2 mg/kg was as efficacious as fluoxetine without the adverse effects observed with fluoxetine suggesting that maybe cats respond better or that the severity of the anxiety was real and was being studied from a clinical perspective.(30) Recently endeavors looking at a CBD/CBDA product are suggesting the dosing may be part of the issue. Humans usually take 10 mg/kg for situational anxiety while dog studies have not gone this high with dosing which may be necessary.(24) To observe anxiolytic effects using between 4-6 mg/kg one hour before stress event was more useful than lower doses and a recent longer term shelter study using 3 mg/kg every 12 hours led to decreased kennel activity and trends toward ethogram video assessment as being effective. (Besengher under review) For situational anxiety a recent study in dogs with clinical thunderstorm aversion showed that a dose of 6 or 9 mg/kg was effective at reducing stress behaviors while 12 mg/kg was not suggesting there may be a sweet spot or U shaped curve for efficacy which requires practitioners to start at the lower dose and work towards an effective dose like so many other anti-anxiolytic agents that we typically use clinically. (Albright manuscript under preparation)

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