The Safety and Use of Cannabidiol Products in Dogs and Cats: A Literature Review

by
Cassidy Parker

A THESIS

submitted to
Oregon State University
Honors College

in partial fulfillment of
the requirements for the
degree of

Honors Baccalaureate of Science in Biology
(Honors Scholar)

Presented August 26th, 2021
Commencement June 2022
This literature review aims to discuss the safety and use of cannabidiol (CBD) products for dogs and cats. The most prominent issue with CBD products for pets is the limited amount of resources and information available to the veterinary community. Another consideration for the control of CBD on the market is that, none of the products currently available have obtained approval from the Food and Drug Administration (FDA) (U.S. Food & Drug Administration, 2021). Some of these products have even faced warnings from the FDA regarding their marketing claims about the therapeutic value of CBD for pets. To address this issue, the content of this literature review will include peer-reviewed research, webinar information, accounts from the FDA, and commentary from experts. The objective of this literature review is to make the information accessible to all members of the veterinary community including licensed veterinarians and pet owners. After examining these resources, a conclusion will be drawn as to the overall safety and uses of CBD products specifically for dogs and cats. In comparing conclusions reached by published studies, many studies suggest CBD has the potential to be a beneficial substance for
dogs and cats, although further research is needed to determine the exact parameters of those benefits. It is important to note that unless the topic is mentioned by the client, licensed veterinarians are not permitted to discuss CBD products as a treatment option for pets. In addition, as of this point in time, the lack of clinical trials in dogs and cats explains the challenges in determining appropriate dosing to fulfill clinical outcomes. Although science-based information is scarce, it may be possible for veterinarians to discuss potential uses and safety concerns with clients who have indicated an interest in using CBD for their animals.

Key Words: Cannabidiol, Small Animal, Veterinary Medicine

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I understand that my project will become part of the permanent collection of Oregon State University, Honors College. My signature below authorizes release of my project to any reader upon request.

_____________________________________________________________________
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Introduction

Frequent solicitation by pet owners has highlighted the need for a summary of information regarding cannabidiol (CBD)-containing products manufactured and marketed for cats and dogs. Scientific research is necessary to provide the information needed for veterinarians to inform their clients about the use and safety of CBD products. Cannabidiol comes from the cannabis plant, which is also known for producing tetrahydrocannabinol (THC). The extracted CBD portion of the plant is found in many types of products made for consumption by people, dogs and cats (Boothe D. M., 2017). CBD products include treats or oils for oral administration and ointments for topical use. To this day, much is still being discovered about CBD and its uses for household pets as well as potential side effects and safety precautions.

This project aims to summarize the available science-based literature and community opinion of the safety and use of CBD products for dogs and cats. This task will be accomplished by first defining CBD, including its structure and chemical formula, where it comes from, and how it is derived. Second, a summary of the current research on CBD in dogs and cats will be outlined. Third, products marketed for dogs and cats available on the market will be reviewed. Fourth, information about the safety of use and the Food and Drug Administration (FDA) involvement in regulating the production and distribution process will be analyzed. Finally, a conclusion will be drawn based on the research analyzed. The sources reviewed in this project are peer-reviewed published research studies, abstracts and webinar sources from licensed veterinarians, company websites, and official communications from the FDA. The objective of this review is to reveal connecting themes and summarize the studies on
CBD for the veterinary community to use as a reference for informing consumers and clients about the scientific research revolving around CBD products for dogs and cats.

**Overview of Cannabidiol**

The *Cannabis sativa* plant is used to produce both hemp and marijuana (Kogan, Hellyer, & Robinson, 2016). Both plant-products contain the necessary plant chemicals to produce the popular cannabinoid compounds CBD and THC, but hemp can produce a significantly higher percentage of CBD in comparison to marijuana. Cannabidiol has a chemical formula of C₂₁H₃₀O₂. Although CBD shares the same chemical formula as THC, the structural arrangement of the molecules differs between the two. The cannabis species is known to contain a minimum 480 distinct compounds, the maximum number is not currently known (Boothe, et al., 2020). Cannabinoids are lipophilic and have a low molecular weight. The two-dimensional outline of the CBD molecule structure is shown in Figure 1. A three-dimensional representation of the cannabidiol molecule with the attached hydrogens is shown in Figure 2.
Figure 1 | A 2-Dimensional representation of the CBD molecule (PubChem, n.d.). The figure contains both of the 6 carbon rings and demonstrates the structure of CBD in the skeletal formula. The black and grey triangle shapes show the orientation of those bonds.
Even though CBD originates from the *Cannabis sativa* plant, it has no psychoactive effects, unlike its well-known relative THC. The particular reason for this circumstance is that CBD does not alter an organism’s mental state compared to THC (Greb & Puschner, 2018). To further distinguish CBD from THC, previous studies demonstrated that even at the highest dose administered (640.5 mg; ~62 mg/kg) CBD did not cause death and only mild side effects in dogs (Vaughn, Kulpa, & Paulionis, 2020). THC is understood more comprehensively due to the increased interest from the general population (Boothe, et al., 2020). A visual representation of the difference in chemical structure between CBD and THC can be observed in Figure 3.
CBD is obtained from its precursor, cannabidiolic acid (CBDa), through a conversion process performed on the flower part of the plant. This process is conducted when the plant is being baked, heated, smoked, or vaporized. In addition to extraction from the plant, CBD can also be manufactured in synthetic form (Kogan, Hellyer, & Robinson, 2016). To summarize the process, the decarboxylation of the CBDa will yield CBD which is the subject compound of this review.

CBD is thought to have analgesic and anti-inflammatory properties. CBD is a multi-target compound that has been used in research to treat conditions in people, including epilepsy (Podell, 2015). Studies have demonstrated the potential for CBD to be used as a muscle relaxer, antipsychotic, and anticonvulsant substance in people. However, a larger quantity of research is required to fully determine the safe uses for
CBD for these conditions (PubChem, n.d.). Unless noted on the label, it was determined by a research study from Colorado State University that the CBD used in available products on the market for people will contain a maximum of only 0.3% of THC (Kogan, Hellyer, & Robinson, 2016).

Current Research on the Use of CBD in Dogs and Cats

The venture of CBD into the veterinary world is still relatively recent. Although products are widely available, the research to back up their efficacy is far behind the actual speed of product production. Recent publications of peer-reviewed literature show an overall trend of promising results for the future of CBD in veterinary medicine. Although, many of these studies explicitly state that further research is needed to fully understand CBD’s place in the treatment of dogs and cats, each new study brings forth an insightful discovery. The areas that are most widely covered by current veterinary research include dosing information, delivery method, and potential uses.

CBD has been evaluated in the treatment of epilepsy in dogs. The use of CBD in the management of epileptic seizures is one of the major conditions that is currently under investigation (McGrath, 2019). Such studies have identified a significant decrease in frequency of seizures with the use of CBD. The type of CBD used in this study was CBD-infused oil. The dose was 2.5 mg/kg administered by mouth at a rate of twice a day for the duration of 12 weeks. The dogs in the CBD group demonstrated a 33% reduction is the frequency of seizures. Although between the treatment and placebo group there was a similar number of dogs considered to be responders to the
treatment. Although more research is needed to assert the use of CBD as the key factor in these results. Additional investigation into confirming the effect, determining effective dosing, the length of treatment, and other factors may aid the assertion of CBD as a key factor in the treatment of intractable idiopathic epilepsy in dogs.

CBD has also been evaluated in the treatment of osteoarthritis in dogs. In a single-dose pharmacokinetics study using 2 and 8 mg/kg CBD enriched oil, the results indicated a notable pain decrease as well as an increase in activity among the treatment group as opposed to the placebo group (Gamble, 2018). The resulting clinical significance was stated that, “This pharmacokinetic and clinical study suggests that 2 mg/kg of CBD twice daily can help increase comfort and activity in dogs with OA.” Other studies have used similar doses of CBD mentioned above, leaving the question about higher dosages as a possible treatment pathway. On the other hand, the delivery method has been called into question by several research groups (Boothe, et al., 2020). The main concern lies in the intersection between the bioavailability of CBD products and the delivery method.

Side Effects and Safety of Use

For this investigation, it will be necessary to cover the concerns of safety and side effects. There are few reported side effects of CBD in dogs and cats. When dosing CBD for dogs and cats with anxiety, there were observed changes in behavior; for example, the pet may have a lapse in memory of house training or suddenly begin to
exhibit aggressive behaviors (Gellman, 2019). These effects are specifically associated with the micro-dosing of CBD. Micro-dosing is the practice that allows administration of a substance at a small enough scale that a whole-body response is unlikely to be produced (Anderson, et al., 2019). However, the dosage is enough that effects at a cellular level can still be studied. Most experts agree the time period in which the effects of CBD can be observed greatly depends on the purpose of treatment. Additionally, diarrhea is a reported side effect and is associated with particularly high doses of CBD. For a simple representation of the most common dosage recommendations for dogs and cats, as calculated per body weight one may refer to Table 1 below.

<table>
<thead>
<tr>
<th>Dose Label</th>
<th>Amount CBD (per kg body weight) for daily administration.</th>
<th>Reason for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro</td>
<td>0.1 mg/kg</td>
<td>anxiety, fear, stress, behavioral issues, mild pain, muscle tension</td>
</tr>
<tr>
<td>Medium</td>
<td>0.2-0.5 mg/kg</td>
<td>osteoarthritis, moderate pain, muscle spasms</td>
</tr>
<tr>
<td>High</td>
<td>0.5-1 mg/kg</td>
<td>moderate to severe pain, neurogenic pain, degenerative myelopathy, tremors, idiopathic epilepsy, diabetes regulation, Inflammatory bowel disease</td>
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</tr>
<tr>
<td>Ultra</td>
<td>1.0-5.0 mg/kg</td>
<td>refractory epilepsy, anti-neoplastic, refractory pain, hospice care</td>
</tr>
</tbody>
</table>

For a more comprehensive comparison of research studies on dosage between species, refer to Table 2 below.

Table 2 | A comprehensive comparison of CBD dosage information based on species.

<table>
<thead>
<tr>
<th>Species</th>
<th>Human</th>
<th>Dog</th>
<th>Cat</th>
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Side Effects and Safety of Use: Cats

In a recently published abstract, researchers reported the safety of orally administered CBD in healthy cats (Rozental, 2020). Eight cats were included in the study and received a single dose of CBD oil at variable doses, ranging from 2.5-80 mg/kg. No severe effects were noted in any of the 8 cats. Head shaking and excessive salivation was noted in several cats and at high doses (40-80 mg/kg) mild lethargy was appreciated (Rozental, 2020). No hematologic or biochemical abnormalities were
appreciated after a single dose. For escalating doses in healthy cats, a study titrated to maximum doses of 30.5 mg/kg CBD (CBD oil), 41.5 mg/kg THC (THC oil), or 13.0:8.4 mg/kg CBD: THC (CBD/THC oil) with no need for medical intervention. In addition, only mild side effects were observed including mild lethargy and hypothermia (Kulpa, Paulionis, Eglit, & Vaughn, 2021). This study is the first of its kind to test cats for the maximum tolerability of CBD, THC, and a combination of both.

_Side Effects and Safety of Use: Dogs_

In contrast to cats, dogs have not exhibited excess salivation or head shaking with CBD oil (Deabold, 2019). Another study on canines conducted with CBD oil by mouth at 2 or 8 mg/kg twice daily concluded that no side effects were observed, and CBD may have been effective in increasing comfort and activity in dogs with osteoarthritis (Gamble, 2018). In addition to benefiting dogs with osteoarthritis, a study involving dogs with intractable idiopathic epilepsy involved 2.5 mg/kg CBD oil administered twice daily and resulted in 2 cases of ataxia and a 33% reduction in seizures with no adverse behavioral effects (McGrath, 2019). For a study on different administration methods, including oral oil beads, infused oil and transdermal cream, the highest exposure was the oral CBD oil formulation (Bartner, McGrath, Rao, Hyatt, & Wittenburg, 2018). The doses used were 75 or 150 mg every 12 hours at 2, 4, and 6 weeks for a 6 week period. A preliminary study on escalating CBD doses in healthy dogs observed 10 escalating doses of CBD oil containing 18.3-640.5 mg per dose as the safety profile with oils containing the least amount of THC to be the most favorable (Vaughn, Kulpa, & Paulionis, 2020). In another study, evaluating the safety
of CBD in healthy dogs, neither the CBD oil, topical cream or oral microencapsulated oil beads used in the study resulted in life-threatening side effects (Bartner, 2017), however, all test subjects had diarrhea. The diarrhea was unrelated to the dosage of CBD. However, further research is necessary to determine if this was the fault of the CBD itself or the oil administration method.

When considering dosing information, it is important to note that a CBD tolerance may develop with regards to cellular and biochemical changes within a dog or cat (Boothe, et al., 2020). Although it was stated above that the mechanisms have not been fully defined, studies are proposing that changes in the CBD receptors and how they bind may occur due to down-regulation and desensitization. In addition, there is a potential for side effects from drug interactions with CBD use. Although there is currently a lack of published studies on this specific occurrence, the latest summary of Cannabis in Veterinary Medicine from the American Veterinary Medical Association (AVMA) indicates the biggest concern is the trace amounts of THC found in CBD products which have known negative side effects (Boothe, et al., 2020).

**Bioavailability of CBD**

For products intended for human consumption, it is common to find CBD in consumable items such as hemp seed oil. In most cases, these items are taken orally but can alternatively be administered topically to areas of concern on the body in the form of a lotion or ointment (Greb and Puschner, 2018). When humans receive CBD by mouth, there is a wide range of variation in levels of absorption and blood
concentration. On the contrary, for dogs, CBD products have poor oral bioavailability (Samara, Bialer and Mechoulam, 1988). The suggested reason for this is first-pass effect, where the drug encounters the liver after oral administration, and biotransformation of the drug occurs which reduces the bioavailability (Pelly, 2007). Since the liver metabolizes the CBD, increasing the bioavailability in dogs is accomplished by an intravenous administration of the cannabidiol (Greb and Puschner, 2018), however, this is not a feasible route of administration for pet owners or for the long-term management of chronic disease.

In addition, cats differ from humans and dogs by the pathway in which CBD is oxidized. Studies have identified the receptors of CBD as the CB1 and CB2 receptors (Greb and Puschner, 2018). Each receptor has a unique relation to the body. The CB1 receptor is associated primarily with the central nervous system. The CB2 receptor is associated with specific parts of the central nervous system including the microglia, in addition to the immune system and testes (Kendall and Yudowski, 2017). Dogs possess both receptors mentioned above. Cats are known to only possess the CB1 receptor, and it remains unclear if there is a presence of CB2 receptors in felines. The difference in bioavailability for felines was noted as significant between different delivery methods such as oil vs gel (Strunk, 2020). To further discuss bioavailability in relation to delivery method, several studies suggest that the bioavailability of CBD oil is low compared to other oral products (Boothe, et al., 2020). While the receptor pathways have been identified as different between dogs and cats, it is suggested that the receptors respond better to oral rather than topical administration (Boothe, et al.,
2020). Some ways this is accomplished is by pet owners mixing CBD intended for oral consumption into a pet’s food or by giving a pet treats containing CBD.

**Available Products, Regulation, and FDA Involvement**

According to the FDA, drugs are classified as any substance intended to alter bodily functions (Boothe, et al., 2020). As of January 2021, according to the American Veterinary Medical Association, “under current federal and state law, veterinarians may not administer, dispense, prescribe or recommend cannabis or its products for animals” (Burke, 2021) This means veterinarians are not legally permitted to prescribe or recommend CBD as a treatment to their clients. This is due to THC’s status at the federal level of a Schedule 1 controlled substance as determined by the Drug Enforcement Administration. This is the same classification of substances such as heroin. The reason CBD is available on markets for consumers is that many states legalized THC for use by humans. No appointment or conversation is required with a healthcare professional for a consumer to obtain CBD products. To vet the usage of CBD more thoroughly for dogs and cats, an examination of the specific products available to consumers is required. Multiple companies produce products containing CBD that are intended for use in pets. Some examples of these manufacturers are Canna-Pet, Hemp Genix, and Treatibles (Greb & Puschner, 2018). Each manufacturer offers background research, selected, and paid for by them, on how CBD is beneficial to the pet for the purpose of generating demand for the product. A pet owner would find items in the form of oils, treats, and biscuits (Edwards & Verdino, 2019). Each product offers a variety of dose options depending on what form it takes and how it is administered to the pet, whether that is topically or orally. The shelf life of most
products is typically listed as one year (Glow CBD, n.d.). A majority of current data available for consumer products is largely testimonial based on customers that have chosen to administer CBD-containing products to their pets (Greb & Puschner, 2018). While testimonial reviews may have a small amount of usefulness, the observations of the owners are not as a whole conducted in a controlled environment. This actively demonstrates that there could be any number of variations present to influence their observations. One study asked pet owners to make a general comparison on the effectiveness of CBD vs prescribed medications they had used for their pets in the past (Kogan, Hellyer, & Robinson, 2016). A vast majority of pet owners reported that CBD was comparable or superior to the prescribed medications. However, this study is inherently biased due to the lack of a placebo comparison group, therefore, the findings of this study should be interpreted cautiously. Dr. Mark Verdino, who is the senior vice president and chief of veterinary staff at North Shore Animal League America, recently discussed navigating CBD products for pets in an interview (Edwards & Verdino, 2019). When a customer goes to choose a product, Dr. Verdino offers the two following pieces of advice. The first is that a pet owner should never use any products marketed for humans due to the possibility of xylitol being present, which is a toxic compound to pets. A consumer should always choose a product designated for their specific animal. The second piece of counsel is to note that CBD has yet to pass the FDA approval process, therefore no official recommendations for dosing currently exist. Dr. Verdino recommends pet owners who chose to use CBD for their animals that should begin with very small doses and be closely observant of their reactions and possible symptoms.
In addition to the lack of FDA approval for CBD, some companies have also received formal warnings regarding their usage of CBD. In 2015 the FDA issued a formal warning to seven companies who manufacture CBD products including some who sell products manufactured for pets (Downs, 2015). One specific warning letter was addressed to Canna Pet LLC by the Center for Veterinary Medicine United States (Nelson, 2015). In summary, the letter includes a description of how several of Canna-Pet’s marketing statements make claims about the unapproved CBD that violates the FD & C Act. To add to the warning presence of these letters, a study from Pennsylvania State University has demonstrated that around 70% of available CBD products are mislabeled (Loflin, Thomas, Marcu, Hyke, & Vandrey, 2017). As a result, consumers may fall victim to false information about CBD products due to the lack of FDA involvement and the large presence of information on CBD that is easily accessible being authored by the corporations that sell the products. Some have even gone as far as to claim they have verified their products by scientific studies (Consumer Reports Inc., 2019). However, further research demonstrates that these studies have been paid for and influenced by the companies so a bias in the interpretation of results and conflict of interest is clearly demonstrated in their claims.

In addition, the FDA has made it clear that CBD or THC is not allowed to be an ingredient in any food product (Boothe, et al., 2020). CBD is also not permitted to be marketed as a dietary supplement due to the Federal Food, Drug, and Cosmetic Act (FDCA) based on evidence that CBD does not “increase total dietary intake,” meaning, it does not contribute to daily nutrient, vitamin, mineral, or caloric intake.
At an international level, CBD is not under international control due to its lack of psychoactive properties.

**Conclusion**

As cannabidiol products intended for pets continue to be researched as well as sold, it is ultimately at the discretion of the pet owner to determine if using one of these products is the right choice for their pet. Veterinarians may be able to discuss the use of these products based on appropriate science-based information but only if the topic is brought up by a client (Consumer Reports Inc., 2019). While studies have demonstrated promising potential for CBD to be used in the future as a treatment, there is no concise conclusion that can currently be drawn on the precise and appropriate method and dose for any dog or cat. Understanding that CBD has demonstrated positive effects when used in animals is equally important as knowing the potential side effects it may cause. If a member of the pet-owning community does decide to explore CBD as an option for their pet, it is recommended they read the appropriate studies and educate themselves on the most credible and up-to-date dosing and product information available. Although more research on dosing is required one may conclude that CBD could have benefits for their pet as seen with previous studies. The sources included in this literature review are provided to create a summary of information so that the community may make an educated decision on the results of the use of cannabidiol as a treatment for their pets.
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