

Cannabidiol in treating veterinary patients

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WRITER'S COMMENT: As any living thing grows older, bones begin to shrink and joints begin to wither. Osteoarthritis, one of the most common diseases associated with old age (estimated to affect 1 in 5 dogs), is as prevalent in geriatric dogs as it is in humans. The traditional treatment for pain relief is nonsteroidal anti-inflammatory drugs (NSAIDs), but people have been seeking alternative treatments due to the propensity for adverse side effects. Around the time of the literature review assignment in my UWP104E class, my brother had a sixteen year old corgi named Fripon that suffered from chronic kidney disease and osteoarthritic pain. NSAIDs were not an option due to risk for further kidney damage. My brother decided to treat Fripon's pain using CBD oil. Due to CBD's relative novelty for use in animals, I questioned its efficacy and decided to consult the veterinary literature. To my surprise, CBD's therapeutic effects in animals were largely uninvestigated, and information was quite limited, which prompted me to compile all the available information, at the time, into this review.

INSTRUCTOR'S COMMENT: In my Writing in the Professions: Science class, one of the major assignments is a literature review, and the goal is to write a paper that closely resembles a review by a working scientist. Ideally, such reviews make connections no one has ever made before, and so achieve a new understanding of the subject. I ask my students to do the same, to try to make connections in their reviews that are new to the world. In so doing, and surprisingly often, the

students create new knowledge—pretty good, for undergraduates in a writing class (it is hard to do bench science in a class with no bench). CBD has gotten a good deal of attention as a therapeutic agent for human use. Jeffrey had the wit to ask a question that is characteristically UCD: what does the research show about its efficacy in animals? No one had ever thought to do that. He pulled together the research on the subject, and what resulted is the very first literature review on CBD in veterinary medicine.

—Scott Herring, *University Writing Program*

Abstract

Cannabidiol (CBD) use in veterinary medicine is controversial due to both the complicated legal status of the drug and limited research on its efficacy. Historically, CBD has been considered a toxin to animals. The legalization of cannabinoids in several states has increased owner-interest in the use of CBD therapies to manage pain in their pets. Legal restrictions currently in place serve as obstacles to those who wish to study CBD's therapeutic effects. A small handful of studies have found positive results, but more research must be done before veterinarians can accurately give counsel on its usage.

Introduction

The cannabis plant contains two active chemicals that exhibit evidence of analgesic effects: tetrahydrocannabinol (THC) and cannabidiol (CBD). Both chemicals have been shown to provide pain relief; however, THC is a psychoactive agent whereas CBD is not (Łebkowska-Wieruszewska et al. 2018). THC in higher concentrations can cause toxicosis and even death (Fitzgerald et al. 2013). Possible CBD overdose is less severe due to its non-psychoactive nature, rendering it the favored compound in pain management (Brutlag & Hommerding 2018).

CBD is primarily employed to treat osteoarthritic pain, but it has also been used to treat a variety of other symptoms such as anxiety and epilepsy (Brutlag & Hommerding 2018). Traditional treatments of osteoarthritis (OA) are nonsteroidal anti-inflammatory drugs (NSAIDs)

which reduce inflammation of the joints, providing pain relief (Gamble et al. 2018). Although NSAIDs are quite effective in treating pain, they may cause unwanted side effects. A study on the efficacy of NSAIDs found that prolonged use caused adverse side effects in 55% of dogs with OA (Gamble et al. 2018). Owners have begun to look for alternative methods of pain relief due to the negative side effects of NSAIDs, as they have heard anecdotal evidence on the efficacy of CBD.

The legalization of marijuana in several states has made cannabis products much more available; however, restrictions on its research still remain. Empirical research on the use of CBD in treating veterinary patients is minimal due its complicated legal status in many countries (Kogan et al. 2019). Researchers in the United States who wish to study the effects of CBD and other cannabinoids must obtain approval from a large array of regulatory government agencies, further complicating the process (Kogan et al. 2019). Despite this lack of research, several companies have created commercially available CBD products, specifically marketed for use in animals, that are not currently FDA-approved (Moore 2016). This issue raises concern about the efficacy and relative safety of such products. The lack of regulation can be potentially harmful as usage increases among pet owners. The purpose of this review is to survey the current knowledge of CBD use in veterinary medicine and to highlight any gaps for further research.

Pharmacokinetics and efficacy of cannabidiol in dogs

Mechanism of action

The primary methods of delivery are: orally (microencapsulated oil beads and CBD-infused oil) or transdermally (CBD-infused creams). CBD affects the body via the CB1 receptor (found in the central nervous system) and CB2 receptor (found in the peripheral tissue) (Fitzgerald et al. 2013). The CB1 receptor is primarily responsible for the adverse effects from cannabinoids, whereas the CB2 receptor controls release of histamines and is the main therapeutic receptor. CBD inhibits histamine release which reduces inflammation and provides pain relief (Brutlag & Hommerding 2018).

Pharmacokinetics

Scientists measured serial cannabinoid concentrations in blood

plasma to determine the duration it remained in the blood. CBD concentrations in plasma are used as an indicator of the degree to as well as the length for which the drug is in effect. In a comparison among several modes of administration (transdermal/oral pill/oral oil), the oil variant had the highest degree of systemic exposure possibly due to its highly concentrated composition (Bartner et al. 2018). Bioavailability of CBD was low when given orally due to the liver's first pass effect (Bartner et al. 2018). The transdermal cream had the lowest plasma concentration, possibly due to inefficient absorption across the skin barrier (Bartner et al. 2018). In another study comparing absorption rates between fed and fasted dogs, fed dogs took much longer to absorb CBD and had a lower max concentration of CBD plasma than fasted dogs (Łebkowska-Wieruszewska et al. 2018). The elimination half-life of oral CBD oil was determined to be 4.2 hours (Gamble et al. 2018). Dogs can possibly undergo a dosing regimen of up to three or four times daily due to the short half-life and rapid elimination of CBD from the blood (Gamble et al. 2018).

A randomized, placebo-controlled study performed on 22 osteoarthritic dogs found that the use of oral CBD oil significantly decreased pain and increased physical activity within the first two weeks of administration with no observable side effects. Dogs on NSAIDs had reduced pain from the first week but demonstrated higher creatinine levels indicative of impaired kidney function. One effect noted was the slight elevation of liver enzymes, but its significance is still uncertain due to the brevity of the study (Gamble et al. 2018).

Current limitations of CBD therapy in veterinary medicine

As of August 2018, CBD remains a Schedule 1 drug in the United States, a classification that places heavy federal restrictions on distribution and research (Brutlag & Hommerding 2018). This has been an obstacle to those who wish to study its therapeutic effects. While the current research on CBD therapies is lacking, there is a sizeable amount of research on cannabinoid toxicology (Gyles 2016). There is currently a large amount of research on the negative effects of cannabis in animals going back decades whereas, in the last 5 years, only 3 studies have been conducted on its therapeutic effects. It has been suggested

that dogs have higher cannabinoid receptors than humans, making them more susceptible to overdosing (Brutlag & Hommerding 2018). The literature shows overwhelming evidence of cannabis' toxicity. After the legalization of marijuana in Colorado, two veterinary hospitals reported a 4-fold increase of marijuana toxicosis in dogs over a 5-year period (Gyles 2016). More studies must be done on CBD's therapeutic effects before veterinarians can give their recommendation.

Despite the lack of research and a confused legal picture, interest in CBD therapies has increased among owners and veterinarians as the legalization of cannabinoids spreads (Kogan et al. 2019). This trend has incentivized companies to produce CBD products marketed for veterinary use. None of these products is FDA-approved for use in animals, yet owners purchase and use them (Moore 2016). This practice can potentially be dangerous because there is no regulation on what actually goes in these products. The lack of quality control has created dishonest business practices. The FDA sampled a few CBD products on the market and discovered that the levels of CBD in the product did not match the indicated amounts on the label. In addition, some products were found to have contained THC despite not being listed (Brutlag & Hommerding 2018).

Conclusion

There is not enough empirical research being done at the moment for veterinarians to recommend the use of CBD. As it stands, the literature overwhelmingly reports on toxicology, so veterinarians can only be confident about that aspect. Veterinarians themselves have reported that 68.1% felt their knowledge was inadequate to counsel owners on the various CBD products (Kogan et al. 2019). Further research should look into the long term effects of CBD use. It could explore the findings of Gamble et al. (2018) and investigate the causes of the elevated liver enzymes and creatinine levels to gauge the safety of long-term use. There should also be studies that compare CBD treatments directly against traditional modes of pain management. First, however, thoroughgoing legislative changes must be made before researchers can put serious effort into studying cannabis' therapeutic effects in animals.

References

- Bartner LR, McGrath S, Rao S, Hyatt LK, Wittenburg LA. 2018. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Can J Vet Res.* 82(3): 178-183. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6038832/>.
- Brutlag A, Hommerding H. 2018. Toxicology of Marijuana, Synthetic Cannabinoids, and Cannabidiol in Dogs and Cats. *Vet Clin N Am-Small.* 48(6): 1087-1102. <https://www.sciencedirect.com/science/article/pii/S0195561618300871#bib20>.
- Fitzgerald KT, Bronstein AC, Newquist KL. 2013. Marijuana Poisoning. *Top Companion Anim M.* 28(1): 8-12. <https://www.sciencedirect.com/science/article/pii/S1938973613000263#bib1>.
- Gamble L, Boesch JM, Frye CW, Schwark WS, Mann S, Wolfe L, Brown H, Berthelsen ES, Wakschlag JJ. 2018. Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs. *Front Vet Sci.* 5(165). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6065210/>.
- Gyles C. 2016. Marijuana for pets?. *Can Vet J.* 57(12): 1215-1218. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5109620/>.
- Kogan L, Schoenfeld-Tacher R, Hellyer P, Rishniw M. 2019. US Veterinarians' Knowledge, Experience, and Perception Regarding the Use of Cannabidiol for Canine Medical Conditions. *Front Vet Sci.* 5(388). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6338022/>.
- Łebkowska-Wieruszewska B, Stefanelli F, Chericoni S, Owen H, Poapolathep A, Lisowski A, Giorgi M. 2018. Pharmacokinetics of Bedrocan, a cannabis oil extract, in fasting and fed dogs: An explorative study. *Res Vet Sci.* 123: 26-28. <https://www.sciencedirect.com/science/article/pii/S0034528818313158?via%3Dihub#!>.
- Moore S. 2016. Managing Neuropathic Pain in Dogs. *Front Vet Sci.* 3(12). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4762016/>.