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Introduction to Veterinary Cannabinoid Medicine

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The interest in the therapeutic uses of cannabis for people and animals has grown considerably in the past few years. Many pet guardians that see the benefits reported in humans are turning towards cannabis products to administer to their pets. With legalization in Canada occurring in October 2018, these products have become even more accessible. Although veterinarians are not yet allowed to recommend, prescribe or dispense cannabis products to our patients, we should be prepared to educate our clients on the legal aspects, safe use and potential toxicity of these products.

History of Cannabis

Cannabis is one of the oldest cultivated plants and has been used for thousands of years in traditional medicines and for both industrial and religious purposes. The hardiness of this weed and its numerous applications, along with wind pollination, were key elements in its global spread. Evidence of prehistoric use in the form of rope and clothing remnants and fiber and seed impressions in pottery have been found throughout central Asia.¹ Current research suggests that cannabis cultivation began at least 12,000 years ago in Mongolia and southern Siberia and quickly spread across Asia, Europe, India, reaching Africa by 2,500 BCE.

Hemp appears to have been an important crop in Chinese history as it is referenced in classical literature as early as 475 BCE. The first recorded use of cannabis for medical purposes appears roughly 2,000 years ago in Chinese *bencao* (materia medica) texts.² Cannabis appears to have been used extensively in Ayurvedic medicine traditions and is referenced in the *Bhagavad Gita* (ca. 200-400 BCE).³

Cannabis use is well documented by classical Greek physicians. Dioscorides (40-90 AD) included cannabis in his *De Materia Medica* as a remedy for oral and ear pain.³ Both the physician Galen (131-201 AD) and the historian Pliny the Elder (23-79 AD) noted the widespread use of cannabis throughout the Roman Empire.³ During the medieval ages, cannabis is referenced in numerous medical texts and was used frequently in the Islamic world during the

eighteenth centuries as a diuretic, anti-epileptic, anti-inflammatory, antipyretic and pain reliever.⁴

Cannabis was an important crop to the New World as well, as farmers in both Canada and the United States were required to grow hemp as early as the 1600s, mostly for textiles.⁵ The period of cannabis prohibition began in 1923 as cannabis was made illegal in Canada by the Opium and Narcotic Drug Act. Cannabis, along with its derivative and preparations, is currently classified as a Schedule II drug by the Controlled Drugs and Substances Act. Industrial hemp was banned as well from 1938 until 1998. In 2001 the first edition of the country's medical marijuana laws (Medical Marijuana for Medical Access Regulations) came into effect allowing physicians to prescribe marijuana for their patients.⁵ The Cannabis Act came into effect October 17, 2018 which has legalized recreational use of cannabis, making Canada the second country to do so. The medical access and recreational use laws apply only to humans. **There is no legal pathway for veterinarians to prescribe, dispense or recommend cannabis products to their patients at this time.**

Cannabis: What is it?

Cannabis nomenclature and terminology is confusing due to the extremely diverse genetic variation of this plant. The cannabis genus belongs to the *Cannabaceae* family of plants which contains about 170 species, including hops and nettle trees. The number of species of cannabis is still controversial but there is one widely recognized species, *Cannabis sativa*. Until recently it was thought that there were one to two other species, *Cannabis indica* and *Cannabis ruderalis*, but it is now proposed that these are variants of *C. sativa*.⁶

To further confuse the issue, there are many cultivars and hundreds (if not thousands) of strains that differ in chemical composition. Genetic stock, soil composition, wind pollination, age and maturity at harvest all contribute to each strain's unique chemical components.⁷

Much research is currently devoted to analyzing the chemical components of the cannabis plant. To date, there have been over 500 different compounds isolated. The pharmacologic properties of cannabis appear to be mostly due to three groups of ingredients: cannabinoids, terpenes and phenylpropanoids.⁶

Cannabinoids are chemicals that act on the body's cannabinoid receptors to affect neurotransmitter release. Cannabinoids coming from plant sources are known as phytocannabinoids, or exogenous cannabinoids, and differ from endogenous or synthesized cannabinoids. Phytocannabinoids can be found in other plants and spices (echinacea, hops, black pepper, etc) in trace amounts.⁸ These terpenophenolic compounds are derived by decarboxylation of their respective 2-carboxylic acids and are found concentrated in the resin produced by the plant's trichomes.⁹ To date, over 120 cannabinoids have been identified in cannabis.⁹ The classes of known cannabinoids are listed in Table 1 along with their main pharmacologic actions (when known).¹⁰

Each cannabinoid appears to have different physiologic effects and actions. The best studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is recognized as the primary psychotropic agent in cannabis. CBD is purported to be non-psychotropic and appears to have widespread physiologic effects throughout the mammalian body.⁶ Psychotropic is defined as a substance capable of affecting mental activity, behavior or perception. As CBD does interact with serotonin receptors and many neurotransmitters that influence behavior, CBD is very much a psychotropic substance. It is more accurate to term CBD a non-intoxicating substance.

Table 1: Classes of cannabinoids

<p><u>Cannabichromenes</u></p> <ul style="list-style-type: none"> ● Cannabichromene (CBC): anti-inflammatory, antibiotic, antifungal, analgesic ● Cannabichromenic acid (CBCA) ● Cannabichromevarin (CBCV) ● Cannabichromevarinic acid (CBCVA) <p><u>Cannabicyclols</u></p> <ul style="list-style-type: none"> ● Cannabicyclol (CBL) ● Cannabicyclolic acid (CBLA) ● Cannabicyclovarin (CBLV) <p><u>Cannabidiols</u></p> <ul style="list-style-type: none"> ● Cannabidiol (CBD): anxiolytic, antipsychotic, analgesic, anti-inflammatory, antioxidant, antispasmodic. ● Cannabidiol monomethyl ether (CBDM) ● Cannabidiolic acid (CBDA): antibiotic ● Cannabidiorcol (CBD-C1) ● Cannabidivarin (CBDV) ● Cannabidivarinic acid (CBDVA) ● Cannabidiol-C4 (CBD-C4) <p><u>Cannabielsoins</u></p> <ul style="list-style-type: none"> ● Cannabielsoic acid B (CBEA-B) ● Cannabielsoin (CBE) ● Cannabielsoin acid A (CBEA-A) <p><u>Cannabigerols</u></p> <ul style="list-style-type: none"> ● Cannabigerol (CBG) ● Cannabigerol monomethyl ether (CBGM) ● Cannabigerolic acid (CBGA): antibiotic, antifungal, anti-inflammatory, analgesic ● Cannabigerolic acid monomethyl ether (CBGAM) ● Cannabigeroverin (CBGV) ● Cannabigeroveranic acid (CBGVA) <p><u>Cannabinols and cannabinodiols</u></p> <ul style="list-style-type: none"> ● Cannabinodiol (CBND) ● Cannabinodivarin (CBVD) ● Cannabinol (CBN): sedative, antibiotic, anticonvulsant, anti-inflammatory ● Cannabinol methyl ether (CBNM) ● Cannabinol-C2 (CBN-C2) ● Cannabinol-C4 (CBN-C4) ● Cannabinolic acid (CBNA)

- Cannabiorcool (CBN-C1)
- Cannabivarin (CBV)

Cannabitriols

- 10-Ethoxy-9-hydroxy-delta-6a-tetrahydrocannabinol
- 8,9-Dihydroxy-delta-6a-tetrahydrocannabinol
- Cannabitriol (CBT)
- Cannabitriolvarin (CBTV)

Delta-8-tetrahydrocannabinols

- Delta-8-tetrahydrocannabinol (Δ 8-THC)
- Delta-8-tetrahydrocannabinolic acid (Δ 8-THCA)

Delta-9-tetrahydrocannabinols

- Delta-9-tetrahydrocannabinol (THC): euphoriant, analgesic, anti-inflammatory, antioxidant, antiemetic
- Delta-9-tetrahydrocannabinol-C4 (THC-C4)
- Delta-9-tetrahydrocannabinolic acid A (THCA-A)
- Delta-9-tetrahydrocannabinolic acid B (THCA-B)
- Delta-9-tetrahydrocannabinolic acid-C4 (THCA-C4)
- Delta-9-tetrahydrocannabiorcol (THC-C1)
- Delta-9-tetrahydrocannabiorcolic acid (THCA-C1)
- Delta-9-tetrahydrocannabivarin (THCV)
- Delta-9-tetrahydrocannabivarinic acid (THCVA): analgesic, euphoriant

Miscellaneous cannabinoids

- 10-Oxo-delta-6a-tetrahydrocannabinol (OTHC)
- Cannabichromanon (CBCF)
- Cannabifuran (CBF)
- Cannabiglendol
- Cannabiripsol (CBR)
- Cannbicitran (CBT)
- Dehydrocannabifuran (DCBF)
- Delta-9-cis-tetrahydrocannabinol (cis-THC)
- Tryhydroxy-delta-9-tetrahydrocannabinol (triOH-THC)
- 3,4,5,6-Tetrahydro-7-hydroxy-alpha-alpha-2-trimethyl-9-n-propyl-2,6-methano-2H-1-benzoxocin-5-methanol (OH-iso-HHCV)

Terpenes are aromatic organic hydrocarbons produced by plants and some insects. Terpenes and terpenoids (terpenes denatured by oxidation) not only provide the fragrance in many perfumes and essential oils but are also used in many pharmaceutical products. There are 140 known terpenes in cannabis and these appear to have not only independent physiological effects but also work synergistically with cannabinoids.⁶ The most common terpenes found in cannabis are β -caryophyllene, β -myrcene, (E)- β -ocimene, terpinolene, limonene, and β -pinene.⁶

Phenylpropanoids are organic compounds synthesized by plants from phenylalanine and include flavonoids, lignols, coumarins, phenolic acids and stilbenes. Vital to plant structure, growth and development they also have shown to have multiple beneficial effects for humans and animals. Flavonoids are known for their anti-cancer, antioxidant and anti-inflammatory properties. Cannabis has 23 known flavonoids, the major ones being quercetin, apigenin, luteolin and cannaflavin A and B.⁶

So what is the difference between hemp and marijuana?

Hemp refers to a variety of *C. sativa* that has been cultivated primarily for numerous consumer products such as paper, textiles, clothing, biodegradable plastics, paint, insulation, biofuel and animal feed. It typically has higher concentrations of CBD and only trace concentrations of THC. The legal definition of hemp is that it contains less than 0.3 percent THC.

Marijuana refers to the varieties of *C. sativa* that, due to their unique chemical composition and higher concentrations of THC, have narcotic and psychoactive properties.

Due to enormous variation within this one species, a new classification system has proposed four groups of cannabis (Table 2).¹¹

Table 2: Proposed classification of cannabis

- Group 1: Non-narcotic plants, domesticated for stem fiber and/or oils seed in western Asia and Europe. Low THC and high CBD.
- Group 2: Non-narcotic plants domesticated in east Asia, mainly China. Low to moderate THC, high CBD.
- Group 3: Narcotic plants domesticated in South Central Asia. High cannabinoids, mostly THC.
- Group 4: Narcotic plants domesticated in South Asia (Afghanistan and neighboring countries), contains both THC and CBD.
- Two groups (at least) of stabilized hybrids with intermediate characteristics between the four groups.

The Endocannabinoid System

A full discussion of the endocannabinoid system (ECS) is beyond the scope of this lecture, but a brief introduction is necessary in order to understand the therapeutic implications of cannabis. The ECS is thought to be the largest receptor system in the mammalian body and consists of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the enzymes necessary for synthesis and degradation of these chemicals.

Research continues to investigate this widespread neuromodulatory system since the first endocannabinoid was identified in 1992.¹² Anandamide, or N-arachidonylethanolamine, was first identified in porcine brains and named after the Sanskrit word for 'internal bliss'.¹² At the present, there are six endogenous cannabinoids that have been recognized (Table 3).¹³

Table 3: Known endocannabinoids

- Anandamide (*N*-arachidonoyl-ethanolamine, AEA)
- 2-AG (2-arachidonoyl-glycerol)
- 2-AGE or Noladin (2-arachidonoyl-glyceryl ether)
- Virhodamine (*O*-arachidonoyl-ethanolamine)
- NADA (*N*-arachidonoyl-dopamine)
- Lysophosphatidylinositol

Endogenous cannabinoids are long chain polyunsaturated fatty acids (eicosanoids) that are derived from arachidonic acid. When changes in intracellular calcium levels are detected, endocannabinoids are synthesized from cell membrane phospholipids and released into the extracellular space.¹⁴ This differs from classical neurotransmitters which are produced and stored in synaptic vesicles until needed.¹⁴ Once released, endocannabinoids act as ligands, binding cannabinoid receptors to ultimately cause a physiologic response. The synaptic interaction is proving to be extremely complex but it appears that retrograde signaling is the primary method of action, meaning that endocannabinoids are synthesized post-synaptically then bind to presynaptic receptors.¹⁵

Elucidating cannabinoid receptors and their mechanisms is an ongoing topic of research as well. In addition to the specific cannabinoid receptors, the endocannabinoid system appears also to have interactions with other receptor systems and neurotransmitters.¹⁴ To date there have been two principal G-protein-coupled receptors identified: Cannabinoid Type 1 (CB1) and Cannabinoid Type 2 (CB2).¹⁵

The highest concentration of CB1 receptors are found mostly in the central nervous system and are primarily responsible for the psychotropic effects of cannabis. These receptors are found in high numbers in areas of the brain in charge of pain modulation (spinal cord, periaqueductal grey), movement (basal ganglia, cerebellum) and memory (hippocampus, cerebral cortex).¹² They can also be found in the gastrointestinal tract, heart, lungs, urinary bladder, reproductive organs, adrenal glands, adipose tissue, hair follicles, salivary glands and within immune cells and sympathetic ganglia.¹⁶ These receptors act to inhibit the release of acetylcholine, dopamine, gamma-aminobutyric acid (GABA), histamine, serotonin, cholecystokinin and other neurotransmitters.¹² The activation of these receptors also appears to affect opioid, N-methyl-D-aspartate (NMDA) and GABA receptors.¹²

The CB2 receptors are located in the immune system (primarily in B and Natural Killer cells), tonsils, spleen and both the central and peripheral nervous systems. These receptors appear to be important with regards to inflammation as they inhibit the production of pro-inflammatory cytokines while increasing the release of anti-inflammatory cytokines.¹²

There are numerous enzymes involved in the ECS that work to produce, regulate and degrade endocannabinoids and act on phytocannabinoids as well (Table 4).¹⁷

Table 4: ECS enzymes

- Fatty acid amide hydrolase (FAAH)
- Monoacylglycerol lipase (MAGL)
- Diacylglycerol lipase (DAGL α , β)
- Phospholipase C (PLC)
- Phosphatase
- Phosphatidylinositol
- N-arachidonoyl phosphatidylethanolamine (NAPE)
- N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD)
- N-acyl phosphatidylethanolamine-hydrolyzing phospholipase C (NAPE-PLC)
- 1, 2-diacylglycerol (DAG)
- N-acetyltransferase (NAT)
- Cyclooxygenase-2 (COX2)
- Lipoxygenase (LOX)
- 2-arachidonoylglycerol hydrolase (ABDH6)
- \square , β -hydrolase-12 (ABDH12)

Although research of the endocannabinoid system is still in the early stages, this system appears to be very complex and has a role in many physiologic reactions necessary to homeostasis. (Table 5)¹⁶

While endocannabinoids are still being discovered within the body and synthetic cannabinoids are being developed, the cannabis plant provides the greatest concentration of phytocannabinoids that can interact with the endocannabinoid system. THC, the main endocannabinoid in marijuana, will bind to both CB1 and CB2 receptors.⁶ CBD, the main endocannabinoid in hemp, has little affinity for CB1 and CB2 receptors but acts on the ECS through interaction with serotonin receptors, peroxisome proliferator activated receptors (PPARS) and vanilloid receptors (TRPV1 or transient receptor potential cation channel subfamily V) among others.¹⁸

The other components of cannabis, chiefly the terpenes and phenylpropanoids, can act on the ECS through various non-cannabinoid receptor-mediated systems.¹² This combination of chemical ingredients results in ‘the entourage effect’, describing the synergistic relationship that results in enhanced therapeutic benefits when used together compared to each component used separately.¹⁸

Table 5: Endocannabinoid system dependent activities

- Nervous system repair/maintenance
- Pain management
- Inflammation

- Apoptosis
- Carcinogenesis
- Appetite
- Metabolism
- Pruritus
- Emesis
- Cognition
- Emotional memory
- Motor behavior
- Sensory
- Anxiety
- Neuroendocrine processes (induce hypotension, bradycardia)
- Inhibit cell growth
- Modulate immune response
- Exert pro-inflammatory actions
- Enhance migration of eosinophils, PMNS, NK T cells (all important in early stages of inflammation)

Phytocannabinoids Interaction with the Endocannabinoid System

Although there are other cannabimimetic plants that can affect the endocannabinoid system, cannabis is unique in containing the largest amount of phytocannabinoids. Research continues into the mechanisms of how phytocannabinoids, terpenes and flavonoids interact with the endocannabinoid system. THC and CBD remain the most studied to date.¹⁹

THC has been found to interact with the ECS in the following ways:

- CB1 receptor agonist
- CB2 receptor partial agonist
- Inhibits prostaglandin E2 synthesis
- Stimulates lipoxygenase
- Inhibits glutamine release
- Interacts with the serotonergic system to increase cerebral serotonin production
- Has dopaminergic blocking actions
- Stimulation of β -endorphin release
- Neuroprotective antioxidant activity
- Allosteric modulation of opioid receptors (μ , δ)

CBD has been found to have the following functions:

- Low affinity for CB receptors
- Negative allosteric modulator of CB1 receptors in the presence of THC
- Inhibits FAAH
- Inhibits anandamide reuptake
- Inhibits metabolism of THC

- TRPV1 agonist
- Inhibits TNF- α
- Activates 5-HT_{1A} receptor
- Inhibits voltage gated calcium channels
- Inhibits glutamate neurotoxicity
- Inhibits adenosine transport

Current research and Therapeutic Implications

While there are numerous human and laboratory animal studies and controlled clinical trials connected to cannabis, companion animal studies are scarce. As the legal scheduling of cannabis occurs, we should expect to see numerous studies in the future. A good review of the recent animal studies can be found in Dr. Landa's (et. al) paper 'The use of cannabinoids in animals and therapeutic implications for veterinary medicine: a review' published in *Veterinarni Medicina Journal* in 2016.¹²

To date, it appears that cannabinoids have the potential to be beneficial for a number of clinical signs and diseases. There have been positive studies in rodent models involving cannabinoids and cardiovascular disease, cancer, pain, asthma, vomiting, diabetes, retinitis pigmentosa and weight loss. Therapeutic potential has been demonstrated in many symptoms and disorders in humans including pain, cancer, chemotherapy induced nausea, multiple sclerosis, asthma, glaucoma, Parkinson's disease and epilepsy.¹²

In Canada, the legality of cannabis has prevented any companion animal studies until recently. There are several projects announced:

- The University of Saskatchewan's The Cannabinoid Research Initiative of Saskatchewan has announced plans to partner with the Western College of Veterinary Medicine to study the use of cannabinoids in companion animals and veterinary applications.²⁰
- Dr. Sam Hocker from the oncology department of the Ontario Veterinary College reportedly has several studies underway:
 - In vitro effects of cannabidiol (CBD) on canine urothelial carcinoma.
 - Effects of cannabidiol on chemotherapy response in canine urothelial carcinoma cells.
 - Effects of cannabidiol on external beam radiation therapy response in canine urothelial carcinoma cells.
- Canopy Animal Health has studies approved and underway to research the effectiveness of cannabidiol (CBD) to treat anxiety in certain animals.
- CBDBioVet, Inc., a Calgary based company, has announced the following clinical trials:²¹

- An investigation of the efficacy of cannabidiol therapy on the relief of pain and inflammation in the canine osteoarthritis patient.
- An investigation of the efficacy of cannabidiol therapy on the relief of seizures in the canine epilepsy patient.
- An investigation of the efficacy of cannabidiol therapy on the relief of pain and inflammation in the canine colitis patient.
- Liberty Leaf Holdings, Ltd, a Canadian based cannabis company, in connection with ESEVResearch, have announced completion of a CBD research on canine pain management (August 2018). Although not published, the study reportedly found that 15 out of 16 dogs with osteoarthritis improved with a CBD supplement.²²

Currently in the United States there are several cannabis related studies underway in veterinary schools:

- Colorado State University of Veterinary Medicine
 - Dr. Stephanie McGrath and team in connection with Applied Basic Science Corporation and a grant from the American Kennel Club Canine Health Foundation have three studies completed:^{23, 24}
 - ‘Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs’; published in the Canadian Journal of Veterinary Research July 2018.
 - ‘Efficacy of cannabidiol for the treatment of epilepsy in dogs.’
 - ‘Efficacy of cannabidiol for the treatment of osteoarthritis in dogs.’
- Cornell School of Veterinary Medicine
 - Dr. Joe Wakshlag and team in connection with ElleVet published ‘Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs’ in the Frontiers of Veterinary Science Journal July 2018.²⁵
- Mississippi State University College of Veterinary Medicine
 - Dr. Barbara Kaplan is currently studying how cannabinoids can alter immune function. A previous project demonstrated that phytocannabinoids can suppress T-cell dependent humoral immunity.²⁶
- University of Illinois College of Veterinary Medicine
 - Dr. Timothy Fan and Dr. Adit Das identified a new group of omega 3-fatty acid metabolites named endocannabinoids epoxides (EDP-EAs) that appear to decrease inflammation and slow osteosarcoma metastasis in mice. Preclinical studies in dogs are planned. Other current studies include:²⁷
 - Metabolism of phytocannabinoids by cytochrome P450s.
 - Biochemical mechanisms of cytochrome P450 epoxygenases.
 - Discovery of endocannabinoid epoxides as anti-inflammatory compounds.
- The University of Florida College of Veterinary Medicine
 - Dr. Amandine Lejeune: A pilot study to determine the safety and efficacy of CBD oil use during chemotherapy in dogs with lymphoma.²⁸

- Dr. Gabriel Garcia: Use of Hemp Based Nutraceuticals as an Adjunctive Agent in Dogs with Epilepsy.²⁹
- AgTech Scientific in connection with The University of Kentucky began a three year pet research/clinical trial and equine study in 2018 using hemp based additives.³⁰

There have been several international studies of note as well:

- University of Pisa Department of Veterinary Sciences
 - Dr. Mario Giorgi and colleagues from the University of Life Sciences in Lubin, Poland, The University of Queensland School of Veterinary Science and Kasetsart University School of Veterinary Medicine in Bangkok published a study ‘Pharmacokinetics of Bedrocan®, a cannabis oil extract, in fasting and fed dogs: An explorative study’ in the Research in Veterinary Science Journal.³¹
 - Dr. Miragliotta and team has published two studies that suggest cannabinoids may be helpful with dermatitis in dogs and cats:
 - ‘Cannabinoid receptor types 1 and 2 and peroxisome proliferator-activated receptor- α : distribution in the skin of clinically healthy cats and cats with hypersensitivity dermatitis’ in the Veterinary Dermatology Journal (June 2018).³²
 - ‘Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis’ American Journal of Veterinary Research (July 2012).³³
- University of Perugia Department of Biopathological Sciences
 - Dr. Mercati and team ‘Identification of cannabinoid type 1 receptor in dog hair follicles’ Acta Histochemica Journal.³⁴
- CannPal Animal Therapeutics, Australia
 - The company has recently finished phase one of clinical trials on their product for pain and inflammation in dogs and have plans to begin a clinical trial of a dermatologic cannabis product to support skin health in dogs.³⁵

Anecdotally, there are numerous stories of cannabis products affecting the quality of life of cats and dogs with cancer, arthritis, seizures, anxiety and chronic inflammatory conditions. In 2018, the American Holistic Veterinary Medical Association released a survey of US pet owners on their use and perceptions of cannabis products.³⁶ Almost eighty percent of respondents reported using cannabis products on their dog, mostly for pain and anxiety. Side effects were reported by fewer than 5 percent and the majority (86.6%) said they would recommend cannabis to other dog owners. A smaller study of 120 Canadian dog owners was published in the Canadian Veterinary Journal in July 2019. Of this group, almost eighty percent said they had purchased cannabis products for their dogs most commonly for pain and anxiety. Similar to the American

study, a majority of the respondents (92.9%) would recommend these products to other pet owners.³⁷

Caveats and Concerns

Legal status: Currently veterinarians are not allowed to recommend, prescribe or dispense any cannabis products. The Cannabis Act that went into effect on October 17, 2018 legalized cannabis only for humans. Health Canada has added all phytocannabinoids to the prescription drug list. It is likely that veterinarians may, in the future, be able to prescribe a product but these products will have to be approved by Health Canada and have a DIN (drug identification number). Veterinarians are cautioned to provide a ‘Client Initiated Harm Reduction’ approach when questioned about cannabis products by clients.

Quality controlled products: As cannabis products for pets are illegal and not federally regulated, finding a reliable, quality controlled product is challenging. In 2016, the US Food & Drug Administration found that 11 out of 13 products tested did not match the label claims and many products did not contain any measurable amount of CBD. Results from 2015-2017 can be found on the US FDA website:

<https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm>. A 2017 study funded by the Institute for Research on Cannabinoids found that nearly 70 percent of all cannabidiol products sold in the United States were mislabeled.³⁸ Blind testing programs in Spain, Austria and the Czech Republic have reported issues with mislabeled products as well.

In Vancouver, CBD pet products are readily available at every corner dispensary and pet stores. Two of my patients have gone to the emergency hospital with signs of THC intoxication after taking a ‘CBD-only’ labelled product. Until cannabis becomes a prescription only veterinary product, pet owners should be cautioned to evaluate any supplement critically before giving it to their pet. Pet products should be clearly labelled with the amount of CBD in the product, the ratio of CBD to THC and how the cannabis is prepared (whole plant, isolate, distillation, solvent extraction). A Certificate of Analysis (CoA) should be readily available that provides a profile of the supplement’s cannabinoids, terpenes and flavonoids. The CoA will also list any traces of herbicides, fungicides, insecticides or bacteria and should include testing for residual traces of solvents. Products should be absent of other harmful ingredients, such as xylitol or alcohol. Many pet supplements are mixed in with coconut, hemp or olive oil which may be of concern for patients prone to pancreatitis or gastrointestinal issues. Supplements that are certified organic, non-GMO and adhere to Canada’s Good Manufacturing Practices guidelines may indicate products of better quality.

Dosing: At this point in time there have not been enough pharmacokinetic studies in companion animals to have established appropriate dosages for dogs and cats. Recent studies have used 2 - 6 mg/kg ranges. There does appear to be a wide range of therapeutic dosages as in what works for one patient may not be effective in another.

Dosing will also depend on a myriad of factors: the patient's overall health, the condition(s) being treated, concurrent medications and supplements being used and the product formulation. The current advice is 'Start low, go slow' meaning start with a very low dose and titrate to effect. The general dosing schedule used with my patients using CBD rich formulas is as follows:

Day 1: Start with 0.5 mg/kg once daily, given in the evening.

Day 3-5: Give 0.5 mg/kg every 12 hours.

Day 6-8: Give 0.5 mg/kg in the morning, 1 mg/kg in the evening.

Day 9-11: Give 1 mg/kg every 12 hours, etc.

Clients are instructed to call weekly with a progress report and the pet's dose is adjusted based on whether there have been improvements or adverse effects noted. It can take up to two weeks for CB receptors to upregulate. A slower schedule can be used for fragile or sensitive patients while a quicker titration used for patients who are painful or facing euthanasia.

Products that have higher levels of THC are reserved for more severe cases. Due to the high risk of intoxication, THC products are started at much lower doses: 0.05-0.15 mg/kg once daily and then titrated slowly (every 3-7 days) to every 8-12 hours.

It is also important to note that cannabis can have biphasic effects and produces a U shaped dosing curve. This means that lower doses and high doses can have little to know effect. The 'perfect' dose will be one that promotes homeostasis in that individual patient. Cannabis can often cause opposite responses in different individuals, meaning that while it may cause appetite stimulation in one patient, it may suppress appetite in another. Needless to say, **dosing is EXTREMELY experimental and individualized.**

Product applications: It can be confusing navigating the number of available preparations. The following can be used as a general guideline:

Hemp seed products: While these products contain no active phytocannabinoids, they can be a good source of omega 3 EFA and fiber and provide nutritional support for younger adult animals.

Hemp based products or CBD isolates: These products contain mostly CBD with a THC content of less than three percent or only CBD. These products can be helpful for anxiety, cognitive decline, seizures, cancer and diabetes regulation.

High CBD ratios: this includes products that have ratios of CBD to THC in the amounts ranging from 1:4 to 1:20. These can be helpful for the same list of conditions as listed above with the hemp based products.

Even ratios: these products have a 1:1 ratio of CBD to THC. These products can be helpful for more severe disease or pain: spinal cord or brain injury, cancer, inflammatory bowel disease, pancreatitis, colitis.

High THC: these products include ratios of 4:1 to 20:1 THC to CBD. Due to the high risk of side effects, these products are reserved for severe pain, cancer, advanced osteoarthritis, appetite stimulation and palliative care cases.

Side effects: While most of my patients have done extremely well with cannabis products, there have been a handful who have not. Clients have reported that CBD has made their pet appear restless, 'wired' or 'stoned'. Many clients have reported changes in stool product, lethargy and a few dogs have appeared to become quite pruritic. Many cat owners have had difficulty medicating their pets with the oils or capsules. Some animals have had increased ALP elevations.

Drug interactions: Cannabis is primarily metabolized in the liver and excreted in bile. Drug interactions can occur through the cytochrome P450 family and P-glycoprotein activity. The CYP family of enzymes plays a role in metabolizing a majority of clinical medications. Drugs that cause P450 inhibition (omeprazole, ketoconazole, itraconazole) can potentially lead to higher concentrations of CBD in the body. THC and CBD are metabolized by CYP3A4. Drugs that inhibit this enzyme (phenobarbital, rifampicin, phenytoin) can lead to increased levels of CBD and THC. Drugs that induce the CYP2C9 enzyme (warfarin, diclofenac) can lead to decreased levels of CBD and THC. CBD is metabolized by the CYP2C19 enzyme. This enzyme also acts on 10% of the medications in current clinical use, primarily the proton-pump inhibitors and anticonvulsant medications.³⁹

As a potent inhibitor of CYP3A4, CBD may lead to increased serum concentrations of medications metabolized by this enzyme, such as macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, antiretrovirals and some statins. CBD is known to also inhibit CYP2D6 which can lead to increased concentrations of SSRIs, tricyclic antidepressants, beta blockers and opioids.³⁹ There is still much more research needed to elucidate the interactions between cannabis and clinical medications.

Toxicity: Unfortunately the number of accidental intoxications in pets has skyrocketed as cannabis becomes more accessible. The ASPCA has reported a 765% increase in marijuana ingestion calls.⁴⁰ Signs of intoxication can vary and include lethargy, ataxia or agitation, bradycardia or tachycardia, mydriasis, hypothermia or hyperthermia, urinary incontinence and seizures. Ataxia, lethargy and urinary incontinence are most commonly seen in dogs. Roughly 25% of patients may show signs of hyperactivity or aggression.

A presumptive diagnosis is based on clinical signs and history. Human urine drug tests can be used but false negatives are possible due to the timing of the test and the difference in human and canine urine metabolites. The urine drug test is designed to screen for the human

metabolite 11-hydroxy THC (11-OH- Δ^9 -THC) while dogs produce 8-hydroxy THC (8-OH- Δ^9 -THC). However, a positive result is reliable for cannabis intoxication. Gas chromatography/Mass spectrometry can be used for a definite diagnosis but this is often not feasible due to cost and test turn around.⁴¹

Management is supportive. Inducing vomiting is usually not recommended as cannabis can be a powerful antiemetic and most animals have central nervous depression on presentation making vomiting unsafe. Decontamination can be accomplished by gastric lavage followed by repeated doses of activated charcoal. Supportive care consists of IV fluids, managing body temperature, respiration, heart rate, oxygenation and blood pressure. Sedatives may be needed for agitations and anticonvulsants may be needed for seizures.

Conclusion

As our understanding of this complex plant increases so do the potential therapeutic benefits. Veterinarians should be prepared to answer more questions from pet owners and, unfortunately, to treat more cases of marijuana intoxication. One benefit of legalization, once the legal barriers of research are removed, is that we should expect to see a plethora of companion animal studies in the future.

Additional Resources

Canadian Association of Veterinary Cannabinoid Medicine: cavm.com

Veterinary Cannabis Academy on Facebook

Veterinary Cannabis Education and Consulting: veterinarycannabis.org

International Cannabis and Cannabinoid Institute: <https://www.icci.science/en/>

Endnotes

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