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[SEARCH RESULT # 1] Assessment of Safety, Toxicity, and Pharmacokinetics of Cannabidiol in Healthy Dogs (Abstract P02)

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Source: Conference Proceedings : Am College Vet Internal Med Forum : ACVIM 2017. Lisa Bartner
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Assessment of Safety, Toxicity, and Pharmacokinetics of Cannabidiol in Healthy Dogs (Abstract P02)

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Our purpose was to determine the pharmacokinetics (PK) and tolerability of cannabidiol (CBD) in healthy dogs. We hypothesized oral and transdermal delivery would be well tolerated and provide measurable systemic levels of CBD.

Thirty, healthy Beagle dogs were randomly assigned to receive one of three CBD formulations (capsule, oil, or transdermal cream), twice daily for a total dose of 150 or 300 mg/day (approximately 10 and 20 mg/kg/day), over 6 weeks. Blood was collected for 12 hours following the first dose for CBD PK. At 2-, 4-, and 6-weeks, blood was collected for CBC, chemistry panel, bile acids, and CBD plasma levels. Daily observational notes and weekly physical examinations were also performed.

Pharmacokinetic analysis demonstrated that the oil formulation resulted in higher plasma concentrations and systemic exposure, with less variability. Cannabidiol exposure was dose proportional. Elimination half-life of the oil formulation following a dose of 75 and 150 mg was 199.7±55.9 and 127.5±32.2 minutes, respectively. Twice-daily administration maintained plasma CBD levels until study completion.

There were no significant abnormalities on CBC, urinalysis, or pre- and postprandial bile acids. Mild elevations in serum alkaline phosphatase (ALP) occurred at 4 and 6 weeks, more frequently with capsule and oil formulations at 300 mg/day. All dogs experienced diarrhea; presence, onset, and severity did not correlate with formulation or dose.

Cannabidiol appears to be well tolerated in dogs. Exposure is proportional to dose and oil formulation provides more favorable PK. These results provide a framework for future efficacy studies of CBD in dogs.

[SEARCH RESULT # 2] Medical Cannabinoids: Prophecy or Prayer?

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Source: Conference Proceedings : Am College Vet Internal Med Forum : ACVIM 2017. Dawn Merton Boothe

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Medical Cannabinoids: Prophecy or Prayer?

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Introduction

The legalization of medical marijuana (*Cannabis* spp.) for treatment of human diseases has been accompanied by an increased use in animals. Much of this use is implemented without veterinary supervision by pet owners able to purchase animal dietary supplements derived from marijuana or its constituents. However, this use is largely accomplished by clients who access them through internet sites marketing products specifically for use in dogs and cats. Although such use is not currently evidence-based, support for medical use of marijuana-based products is increasing emerging in human medicine and most of the indications should extrapolate to animal diseases. The purpose of this manuscript is to describe the types of products being marketed, the regulations surrounding their use, and provide a scientific bases for their use based on presumed mechanisms of action. Finally, evidence supporting use for various indications will be summarized.

Marijuana Ingredients

Marijuana refers to the dried leaves and tops of the hemp plant (*Cannabis sativa*) (Svienska 2008). It has been a part of recreational, religious and medical activities of a variety of cultures for over 5,000 years and was among the most commonly prescribed medications in the United States Pharmacopeia until declared illegal in the 1930s (Krietzer 2009; Burns 2006). *Cannabis* sp is a pharmacologically (and toxicologically) diverse herb, containing at least 480 distinct compounds with their proportions varying between each subspecies, the part of the plant, and how that product is cured or prepared. Plant products include, in addition to marijuana, hashish and hashish oil, formed from the resin secreted by the plant. Hemp is commonly used to refer to the stem of the marijuana plant. However, marijuana is one of several varieties of hemp plants grown and harvested specifically for the stem which is used for a variety of products such as ropes, animal bedding. Unique to *Cannabis* are close to 70 different terpene phenolic compounds referred to as cannabinoids. Phytocannabinoids are unique to *Cannabis*. These lipophilic, low-molecular-weight compounds (300 Da) (Hosking 2008) are structurally similar to the **eicosanoid arachidonic acid**, the precursor of prostaglandins and leukotrienes. The most important of the phytocannabinoids are: Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) (Grotenhermen 2003). In addition to phytocannabinoids, marijuana contains approximately 140 different terpenoids. These compounds are responsible for a variety of actions as well as its scent. The specific terpenoids yielded from a particular marijuana plant depend on the type of *Cannibis* (determining the fiber content), the part of the plant, its sex and age, whether or not it is cultivated in or outdoors, when it is harvested and the conditions at harvest, and how it is dried and stored. The serotonergic effects of marijuana (5-HT1A and 2A) may reflect the impact of these essential oils, contributing to analgesia and mood modification. Other components in the plant include nitrogen containing compounds (n=70: alkaloids, amines); carbohydrates, including common monosaccharides (n=13: fructose, glucose, mannose), selected disaccharides (sucrose, maltose), and several polysaccharides (e.g., cellulose, pectin) as well as several sugar alcohols (n=12; mannitol, sorbitol, glycerol). A number of flavonoids also are present (n=23); among them, apigenin has a wide variety of effects, including interaction with benzodiazepine receptors, resulting in an anxiolytic effect. Other ingredients include fatty acids (n=33) and others.

Proposed Mechanisms of Action

The Endocannabinoid System

Among the phytocannabinoids, Δ^9-THC is the most understood as it is the main property of psychogenic producing behavior and pharmacological activity against pain (Grotenhermen 2003; Di Marzo 2007). Its discovery and elucidation of its role in the human body paralleled that of the discovery of the opioid receptors, leading to a description of the endocannabinoid system, including endogenous cannabinoid ligands (endocannabinoids) and their respective endocannabinoid (eCB) receptors (Hosking 2006; Di Marzo 2006; Di Marzo 2007). The major **cannabinoid receptors**, CB_1R and CB_2R, are G-protein coupled receptors found within the cytoplasm of the cell. The CB_1R receptor is ubiquitous and commonly found within the central and peripheral nervous tissue as well as in peripheral tissues associated with the immune system (e.g., tonsils and spleen) (Burns 2006; Grotenhermen 2003; Hosking 2008). Similar to opioids, endogenous endocannabinoid ligands are capable of acting as agonists or antagonists on their corresponding receptors (Di Marzo 2006). CB2r are located principally on immune cells, but this includes microglia. The cannabinoid receptors are influenced by both endocannabinoids and phytocannabinoids. At least 5 **endogenous cannabinoids** have been described, with anandamide (CB1 and 2 agonist, but higher affinity for CB1) being the most thoroughly studied. It is synthesized by post-synaptic neurons, acting as a retrograde messenger to influence neurotransmitter, and particularly GABA, release. It is extremely unstable, being rapidly hydrolyzed to ethanolamine (an antihistamine) and arachidonic acid. Cannabinoids are able to disrupt short-term memory, impair cognition and time perception, alter mood while enhancing body awareness, discoordination, sleepiness, and reduce attention focus and the ability to "filter" irrelevant information.

Although interaction with cannabinoid receptors is unique among plants to hemp, cannabinoids do not necessarily cause their effects by direct interaction with CBR. Other receptors are also targeted (e.g., benzodiazepines, serotonin, others). Cannabinoids can influence the release of other neurotransmitters.

Pharmacodynamic Effects

The endocannabinoid system is a known contributor to physiology, but has been recognized for only about 25 years. In general, it contributes to homeostasis (*Relax, Eat, Sleep, Forget and Protect*; McParland 2014).

Endocannabinoids appear to be important as neuroprotectants (e.g., antioxidants, inhibition of calcium influx and excessive glutamate production), for example, that associated with CNS ischemia or hypoxia, or the presence of neurotoxicants. These effects appear to be mediated predominantly by CB1 (located particularly in the dorsal horn of the spinal cord) although CB_2 also plays a role, depending on the tissue (Svizenska 2008). Cannabinoids also inhibit neuroinflammation (see therapeutic indications). Although not all effects of cannabinoids are mediated by CBR, their extensive distribution contributes to a variety of physiologic responses. The dopaminergic reward pathway is stimulated by CB1 receptors, motivating eating, smoking and substance abuse. A variety of clinical effects occur, including but not limited to inhibition of nociception (sensation and pain), decreased anxiety and emesis, manipulation of gastrointestinal and cardiovascular function, and stimulation of appetite.[4] The CB_2R receptors are principally found in cells and organs of the immune system, including leukocytes, monocytes, B and T cells, spleen, and tonsils. Activation of CB_2R receptor receptors do not cause the effects on mentation that activation of CB_1R produces, and has become a target for therapeutic use in human medicine by reducing inflammation, immune suppression, and as a chemotherapeutic (Burns 2006; Grotenhermen 2003; Hohmann 2006).CB_1R receptors often modulate other signals. For example, they inhibit voltage-activated calcium channels, decreasing excitatory (acetylcholine)

and increasing inhibitory (GABA) neurotransmitters. CB_2 also is located on neurons where it may be associated with cell differentiation (Svizenska 2008).

Specific Cannabinoids

Cannabidiol (CBD) was the first isolated phytocannabinoid to be isolated from the *Cannabis* plant in 1930–1940s. In 1960s, CBD was employed as an anticonvulsant due to having similar pharmacologic effects as phenobarbital and diphenyldantoin (DPH) (Mechoulam 2002). CBD, has very low affinity for the cannabinoid receptors; however, it serves as an antagonist for CB_1R and CB_2R agonists (Mechoulam 2007). The natural CBD (-) does not bind to CB_1R; however, the synthetic (+) has been shown to bind to both CB_1R and CB_2R (Mechoulam 2002). Besides anti-convulsant effects, CBD has been used for its anxiolytic, antipsychotic, and antinausea effects (Mechoulam 2002). Interestingly, after oral administration of CBD in a murine model for rheumatoid arthritis, researchers saw a diminished interferon gamma (IFN-γ), decreased release of tumor necrosis factor alpha (TNF-a) and nitrous oxide (Mechoulam 2002; Malfait 2000). CBD also works as a potent antioxidative agent, showing greater protective nature against glutamate neurotoxicity than either ascorbate (vitamin C) or α tocopherol (vitamin E) (Mechoulam 2007). These antioxidative effects may have explained why CBD was successful in correcting hypermotility in mice, with no effects on the control population (Capasso 2008). On a smaller scale, CBD has been shown to stimulate mesenchymal stem cells responsible for bone formation and fracture healing, while also controlling bone resorption (Izzo 2009). Although CBD has very low toxicity on rhesus monkeys after IV administration, it has been reported to have very low oral bioavailability (9 h), which may be due to first pass metabolism (Mechoulam 2002). Cannabichromene (CBC), one of the non-psychotropic cannabinoids, has been shown to have strong anti-inflammatory properties through indirect activation of CB_1R, through inhibition of the endocannabinoid inactivation (Shinjyo 2013). Most recently, CBC was determined to normalize the intestinal motility of an experimental model of intestinal inflammation in mice, but not alter the rate of transit in control animals (Izzo 2001; Izzo 2012). **Cannabigerol** (CBG), whose mechanism of action has not been completely elucidated, has a wide variety of therapeutic targets from antitumor activity as well as potent antibacterial effects towards selected microbes, including methicillin resistance staphylococci (MIC of 0.5 to 2 mcg/ml) (Appendino 2008; Rock 2011; Izzo 2009). Traditionally, cannabinol (CBN), the primary product of Δ^9-THC breakdown, was been used to predict the age of the marijuana plant. CBN has recently been discovered to have an immunosuppressive effect by decreasing the production of interleukin-2 (IL-2) by decreasing T cell activation (Faubert 2000).

Untoward Pharmacologic Effects

As with many CNS active drugs, marijuana is associated with both tolerance (higher concentration needed to impart a similar pharmacologic effect) and withdrawal (a clinical syndrome of nervousness, tension, restlessness, sleep disturbance and anxiety). However, the long elimination half-life of the most active ingredient, THC (and others) appears to preclude a clear cut abstinence syndrome (Svizenska 2008). As with other addictive agents, laboratory rodents have been demonstrated to self-medicate, suggesting an addictive component. Tolerance also should be expected: dogs exhibit a unique ataxic response to IV CBD. However, tolerance to this effect rapidly emerges within one week of repetitive treatment.

Cannabinoids in Dogs or Cats

Cannabinoid receptors have been studied in a limited fashion in dogs. Initial studies focused on relevance to humans and provide evidence that dogs may react with unique behaviors. **Receptors**: In 1975, tritium-labeled Δ-9 THC (0.5 mg/kg IV) radioactivity was distributed throughout canine cerebellum and cerebral cortex, with increased concentrations in grey matter versus white matter noted; up to 50% of the signal reflected metabolites (28). Peripherally,

radioactivity occurred in all organs save the vitreous humor. Peripheral tissues with the highest concentrations (relative) were bile (8), adrenal gland (3, 5), liver, auricle and ventricle of the heart, renal cortex, and pancreas (1), with the least concentration in the fat, trachea, and testis. The canine CB_2R has been relatively cloned and characterized and shows 76% homology with other species (31). CB_1R is located in the apical region of the striated cells of parotid and mandibular salivary glands (12). Both CB_1R and CB_2R were demonstrated in various cells of canine epidermis and dermis of dogs; both receptors increased in atopic dogs (8).

Marijuana and Pets

Legalization in states has yet to include veterinary medicine. Legalization of medical or recreation marijuana among the states is likely to be associated with an increased incidence of toxicity, with a 4-fold increase cited in one study although toxicity may reflect additional ingested foods (e.g., chocolate) (Meola 2012). THC is among the compounds cited as a toxicologic hazard in detection (police) dogs (Llera 2008). It is the most common drug to which detection dogs are exposed. Both dogs and cats may become intoxicated with smoke inhalation as well as ingestion of food containing marijuana (or hashish). It is absorbed rapidly following either oral or inhalant administration with clinical signs evident within 30 to 60 minutes of ingestion, although one reference (Osweiler 2008) indicates onset as long as 12 hours after exposure. Cannabinoids of medical significance appear to undergo first pass metabolism and as such, the risk of toxicity with inhalant products is much greater compared to oral. The implication for medical use is that oral administration may not be cost effective. The drug is eliminated by hepatic metabolism and biliary excretion with elimination being complete in 5 days in dogs; duration of toxicity ranges from 30 minutes to 3 days, but 18–24 is the average. Enterohepatic circulation may contribute to the prolonged half-life. The most common signs of toxicity following ingestion in dogs include tachycardia, hypotension, depression, ataxia, vomiting (inducing emesis is not recommended in clinically depressed dogs because of the risk of aspiration), altered behavior, bradycardia, hypersalivation, weakness, hypothermia and seizures. Treatment is largely supportive, with sedation with benzodiazepines or phenothiazines as needed. Antiemetic therapy may be indicated.

Pharmacologic Manipulation

The system can be manipulated by interfering with endogenous receptor ligands with cannabinoid or cannabinoid-like drugs, and enzymes responsible for endocannabinoid synthesis and degradation.

Regulatory Considerations

Currently, at least 24 (PRO-CON). States have approved marijuana in some form. According to NORML (www.norml.org/states), a site dedicated to law reformation, 34 states have some type of conditional use, 15 states of decriminalized use, 14 states of medical marijuana laws. Several states have passed Industrial Hemp bills, with such plants being legal under some conditions as long as they contain less than 0.3% THC (DMW). However, cannabinoids themselves, included the oil CBD concentrate from these plants remains as a Class 1 Schedule substance, meaning it has a high risk of abuse potential and no recognized medical benefit. 10 different pharmaceutical cannabis products (including synthetic) have or are undergoing some level of approval (http://medicalmarijuana.procon.org/view.resource.php?resourceID=000883).

Medical Uses

The proposed indications for medical marijuana have included, but are not limited to behavioral, sleep and gastrointestinal disorders, neuroprotection, antispasmodic but prokinetic, anorexia, nausea, glaucoma, diabetes, immunosuppression, malaria, anti-inflammatory and, of course, pain (Table 1, Izzo 2009). A proposed advantage of medical marijuana compared to a single drug (e.g.,

dronabinol, a synthetic THC [Marinol®]), is the multiple compounds contained in the plant. Two advantages are offered: 1. The compounds might act synergistically (a "synergistic" shotgun or entourage effect) to provide an enhanced desired pharmacologic effect, while 2. at the same time, mitigating (one compound acting on another) undesirable effects. However, evidence for a synergistic benefit is lacking based on the lack of differences when THC is consumed as marijuana, versus Marinol® (humans) (Brenneisen 200X). Presumably, because marijuana contains so much THC, it may not be the most effective portion of the plant and it may contribute to more side effects. Cannabinoid deficiency has been linked as an etiology of a variety of illnesses: ("eCB deficiency syndrome") as an etiology in migraine, fibromyalgia, irritable bowel syndrome, psychological disorders, and others (McParland 2014). However, finding evidence to support either the negative or positive effects of *Cannabis* can be difficult because such information is often tainted with emotionally mediated opinion. PRO-CON (http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881) is a useful site that provides links to evidence using a categorical approach, as well as information on approval status among the states.

Pain Management

Cannabinoid use has been best prescribed for its use in controlling neuropathic pain. Peripherally, CB2R receptors, and to a much lesser extent CB1R, have been effective in modulating the inflammatory response as well as tissue and nerve injury (19, 33). CB2R, present on both mast cells and leukocytes, play multiple key roles in the modulation of the local inflammatory response including preventing mast cell degranulation, diminishing neutrophil migration, and decreasing the release of nitric oxide from macrophages (33). Cannabinoids have an analgesic effect on neuropathic pain in rodent models (thought to be mediated via the CB1 and CB2 receptors) in addition to other receptors, such as transient receptor potential vanilloid type 1 (TRPV1). Secondary to nerve injury, cannabinoid induced antinociception is more effective in alleviating pain than opioid drugs by suppressing wind up and noxious stimulus induced central sensitization (Hohmann 2006). The mechanism of action is hypothesized to be due to loss of opioid receptors along the traumatized nerve tissue being either removed or compromised secondary to the injury, where CB_1R remain intact (Bridges 2001; Rice 2002). Recently, studies of the interactions between the cannabinoid and the opioid systems indicates that co-administration of two agents may produce favorable synergistic effects, and may offer a new treatment strategy for multi-modal analgesia (MacPherson 2000; Ripamonti 2001). Recent findings have also suggested that NSAIDs may also owe some of their therapeutic success to their interaction with the endocannabinoid system either by inactivation of proteins or by encouraging biosynthesis. Rofecoxib, a cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory, synergizes with anandamide (the endogenous agonist of CB_1R and CB_2R), in a positive-feedback loop to further elevate levels of anandamide as well as other analgesic fatty acid ethanolamide levels (Di Marzo 2007).

Neurologic

Suppression of convulsions/seizures: While the exact mechanisms resulting in suppression of epileptic seizures by cannabinoids are unknown, there are many receptors for cannabinoids (particularly CB1) in areas of the brain known to be sites where partial seizures originate CBD reduces calcium oscillations in hippocampal neurons *in vitro*, and may exert its antiepileptic action by reducing calcium available for cell excitation. CB1 receptors have been detected with strong immunoreactivity in the hippocampi, skin and salivary glands of normal dogs. Experimentally, CBD attenuates experimentally-induced seizures in animals; this may reflect reduced calcium fluxes (Izzo 2009). THCV also has been associated with some anticonvulsant effects by virtue of its inhibitory effects on CB1. **Anxiolytic**: These effects have been demonstrated in healthy human volunteers (Izzo 2009). CBD exerts benzodiazepine independent effects, possibly by activating post synaptic 5-HT1A receptors. **Neuroprotection**: CBD is an antioxidant and as such has been proposed for treatment of Alzheimer's disease, Parkinson's disease and Huntington's disease.

Restoration of calcium homeostasis may prevent apoptosis (Izzo 2009). In rodents, CBD reverses brain damage associated with ischemia. **Emesis and appetite**: Control of emesis and approved appetite are among the approved indications for FDA-approved cannabinoids. Emesis involves, among other signals, release of serotonin and subsequent stimulation of 5HT that activate neurons in the area postrema. CB1 receptors in the cerebrum, vestibular nuclei, and other brainstem nuclei involved in emesis suppress vestibular nuclei signals associated with nausea. Among the mechanisms of improved appetite is facilitated olfaction. Appetite is an approved indication for FDA-approved cannabinoid products.

Other

Cancer: In addition to control of adverse clinical signs associated with cancer and its treatment, a number of the cannabinoids have antiproliferative-antiapoptotic effects in a number of tumor cell lines. The National Cancer Institute has a link describing ongoing studies: www.cancer.gov/about-cancer/treatment/cam/patient/cannabis-pdq. **Diabetes mellitus**: CBD inhibits development of diabetes in non-obese diabetic mice, including ameliorating clinical signs of disease. This appears to reflect, in part, control of pancreatic inflammation, but also reduction of oxidative stress in target tissues (e.g., retina). **Bone formation**: A number of cannabinoids (essentially all in Table 1) stimulate mesenchymal stem cells responsible for bone formation and fracture healing. CBD Aldo controls bone resorption, reducing bone loss (Izzo 2009). Antimicrobial: CBC and CBG have demonstrated potent antibacterial effects towards selected microbes, including methicillin resistance staphylococci (MIC of 0.5 to 2 mcg/ml).

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[SEARCH RESULT # 3] Medical Marijuana - What Every Veterinarian Needs to Know

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Source: Conference Proceedings : Wild West Veterinary Conference : Wild West Veterinary Conference 2015. Robert J. Silver

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Medical Marijuana - What Every Veterinarian Needs to Know
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Background Information

Cannabis sativa L., more popularly known as: marijuana, Mary Jane, pot, weed, ganja, bhang, reefer, dope, grass, *Cannabis*, etc. has been a part of human history since before the written word. Archeological and anthropological evidence supports the fact that *Cannabis* was cultivated by humans since the beginnings of agriculture more than 10,000 years ago. During the Neolithic

period ancient peoples used every part of the plant: the stems and stalks for fiber for cordage and cloth; the seeds which are high in protein and omega 3 fatty acids, for nourishment, and the roots, leaves and flowers for medicinal and ritual applications.

The *Cannabis* plant contains hundreds of compounds, many of them medicinally beneficial. This fact is what led Raphael Mechoulam, to call *Cannabis*: "A pharmacological treasure trove." Mechoulam, in 1964, was the first researcher in the world to determine the structure of Δ-9-tetrahydrocannabinol (Δ-9-THC). As of this writing, it has been found that the *Cannabis* plant contains more than 421 individual compounds.[1] These constituents include: cannabinoids, terpenes and terpenoids, flavonoids, non-cannabinoid phenols, nitrogenous compounds and compounds commonly found in plants.[2] This diversity of constituents helps to explain the multitude of effects that have been historically, anecdotally and scientifically described for *Cannabis*. Different parts of the *Cannabis* plant have different constituents in them, and different strains and growing conditions can alter the phytochemical profile in a given plant.

There are two main cultivars of *Cannabis sativa L*. which are defined by the dominant cannabinoids present and the amount of fiber contained in the stalks: 1) "Hemp," is non-psychotropic and contains higher levels of the cannabinoid, cannabidiol (CBD) than 2) "Marijuana," which is psychotropic and which, inversely to hemp, contains higher levels of the cannabinoid Δ-9 THC than CBD, and significantly less fiber. Within both cultivars are strains that differ from each other genetically and produce differing amounts of the many different phyto-constituents of *Cannabis*. Throughout most of the world, marijuana is illegal to grow and sell, and hemp is legal to both grow and sell. This is excluding the US, where hemp growing was illegal, until the recent passage of the Farm Bill of 2014. Marijuana growing in many states is not illegal when following regulatory guidelines. But, paradoxically, in many states you can legally sell marijuana grown locally, but locally grown hemp is still illegal.

Legal Considerations for Veterinary Use of *Cannabis sativa L*. in the US

Marijuana has been illegal for over 70 years. The prohibition of marijuana in the United States, which started in 1937, just following the end of the prohibition on alcohol, lasted until November 5, 1996, in California, with passage of the Compassionate Use Act, which allowed for the legal use of *Cannabis* for medicinal applications in California alone.

Since 1996, and as of this writing in Spring 2015, there are now 36 states that have legalized the medicinal use of marijuana or extracts of cannabidiol (CBD); of these 36 states, 23 states and the District of Columbia allow medical marijuana, which contains substantial amounts of Δ-9 THC and has the potential to be psychotropic; 12 states allow the medical use of extracts containing CBD which is not psychotropic; 5 allow recreational use for citizens of the state that are 21 years of age or older; and 9 states currently have pending legislation in 2015 for medical marijuana. 2016 looks to be a pivotal year in the legalization of marijuana. California will vote on legalizing recreational marijuana, and, if this large state passes this bill, it is thought that the rest of the nation will follow. Only time will tell.

Many states' legislation allowing the medicinal use of *Cannabis* differ with other similar state's legislation as regards specific aspects of regulation, and which specific extracts of *Cannabis* are legislated to be legal for medicinal use. Thus, for the most accurate information, this author urges the reader to check with their individual state's requirements and regulations for the legal parameters regarding the use of *Cannabis* and its extracts in that specific state.

Useful and accurate websites to check for this information include:

1. **NORML**:
   http://norml.org/states

2. **PRO-CON**: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881
3. **GOVERNING**: www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html

In spite of this groundswell of public opinion in favor of the legalization of *Cannabis* and its extracts in the US, state by state, federal law and the Drug Enforcement Agency (DEA) still consider all of the *Cannabis* plant and its extracts, including CBDs to be illegal, Schedule I controlled substances.

For veterinarians and their clients, this is the problem. The medical marijuana laws, state by state, are for human physicians and their human patients, not for veterinarians or their patients. In fact, if a veterinarian were to prescribe or dispense *Cannabis* to palliate an animal suffering from terminal cancer and its associated pain, or breakthrough cluster seizures, in the case of refractory epilepsy, they could lose their license, or worse, be sent to jail.

Currently there is "bipartisan" legislation pending in congress to reschedule *Cannabis* to a more "legal" DEA scheduling such as Schedule II or hopefully, lower schedules such as III or IV. Recently a federal judge ruled against a civil suit to reschedule *Cannabis*, saying that it was up to a higher court or congress to change the law. Things are moving forward, (although too slowly for many who have urgent medical needs for this emerging therapy) with regards to a more consistent federal legal stance relative to individual states' legislation allowing the legal medical or recreational use of *Cannabis*.

Plant Constituents and their Biological Counterparts (Exo- and Endo-Cannabinoids)

There are several plant constituents in *Cannabis* of medicinal interest. Of most interest are the phytocannabinoids, which consist of more than 100 terpenophilic compounds, found mainly in *Cannabis*, but recently has been described in several other plants in the family Linaceae (flax), and Asteraceae (Echinacea and Helichrysum). Other phyto-constituents such as terpenes, terpenoids, and flavonoids also contribute to the medicinal profile of *Cannabis*.

Cannabinoids exist in the plant mainly as carboxylic acids, which are called cannabinoid acids and are all non-psychotropic. The acidic form is converted to neutral molecular analogs by light, heat and combustion.[2] The phytocannabinoid that has gotten the most attention in this plant is Δ-9 THC, which provides its psychotropic qualities, and, subsequently, has resulted in its value, notoriety and illegality. However, the other phytocannabinoids, which are divided into multiple classes based on chemical structure, are not psychotropic, but contain the majority of the medicinal properties of this plant.

Table 1. Major and minor cannabinoids

Δ-9-tetrahydrocannabinol (Δ-9 THC)	Analgesic (reduces pain), antiinflammatory, antioxidant, bronchodilatory, improves symptoms of Alzheimer's disease, benefit duodenal ulcers, muscle relaxant, anti-itch, cholestatic jaundice.
Δ-9 tetrahydrocannabinolic acid (Δ-9 THCA)	THCA is the acidic or carboxylated form of THC. It is the predominant cannabinoid in psychoactive strains. It is non-psychotropic until activated or decarboxylated, smoked or cooked at temperatures greater than 245°F. Also has medicinal benefits, similar but also separate and different than THC.

Δ-9 tetrahydrocannabivarin (Δ-9 THCV)	Antiinflammatory, anticonvulsant, analgesic properties, antioxidant, neuroprotective in model of Parkinson's in one study, improved glucose tolerance and insulin sensitivity *in vivo*
Δ-8 tetrahydrocannabinol (Δ-8 THC)	Stable in air, much less psychotropic than Δ-9 THC; at low doses, Δ-8 THC (0.001 mg/kg PO was found to induce appetite stimulation without psychotropic effects.)
Δ-8 tetrahydrocannabinolic acid (Δ-8 THCA)	The carboxylated (acidic) form of Δ-8 THC.
Cannabidiol (CBD)	Antianxiety, anticonvulsant, Parkinson's disease, Huntington's disease, psychosis, MS, Alzheimer's, cytotoxic for breast cancer, effective against MRSA, reduces oily skin, treatment of addiction.
Cannabidiolic acid (CBDA)	Acidic form of CBD, carboxylated form of CBD. Has medicinal properties but not well studied at this point in time.
Cannabichromene (CBC)	Antiinflammatory, analgesic, antifungal, antidepressant, Anandamide reuptake inhibitor.
Cannabigerol (CBG)	Antifungal, GABA uptake inhibitor (calming), antidepressant, analgesic, antiinflammatory, reduces scales in psoriasis, effective against MRSA.
Cannabidivarin (CBDV)	Anticonvulsant
Cannabinol (CBN)	Sedative, effective versus MERSA, helps with burns, reduces scales in psoriasis, helps with breast cancer. May be a degradation product of THC or CBD.

Other, equally important phyto-constituents of *Cannabis* are the terpenes and terpenoids. These organic compounds are produced by a variety of plants. It is thought they serve a protective function for these plants. They are a significant component in plant essential oils. These molecules are responsible for the aroma of *Cannabis*, and because they, like cannabinoids, are lipophilic, they also cross the blood-brain barrier and contribute to the medicinal benefits of *Cannabis*.

The US FDA considers terpenes and terpenoids to be generally recognized as safe (GRAS), as they are flavor and fragrance components common to human and pet diets. Cannabinoids, terpenes and terpenoids are all produced in the same glandular structure on the *Cannabis* plant, the trichome, from the same chemical precursor, geranyl pyrophosphate. Hops (*Humulus lupus*) is a member of the same Cannabaceae family as *Cannabis*, and they share many of the same

terpenes and terpenoids such as β-myrcene, β-pinone, humulone, and β-caryophyllene. Cannabinoids are virtually odorless, emitting only a slight pitch-pine scent.

The biological effects of *Cannabis* are due to interactions among the many various phyto-constituents of cannabinoids, terpenes and terpenoids. This phytochemical interaction has been termed the "entourage effect," and is believed to explain the multiple biological activities of the *Cannabis* plant, and the differences that are seen in bioactivity of the different strains of the *Cannabis* plant. The entourage effect states that the potency of the whole plant extract is the sum total of the interaction of all of the plant constituents involved, and is different than the effect of any individual plant component alone.

Strains are subsets of the *Cannabis sativa L*. genome, which contain differing distributions of fiber, phytocannabinoids, terpenes and terpenoids. The number of possible combinations among these *Cannabis* phyto-constituents is close to infinite. These strains are much like breeds of dogs. All are *Canis familiaris*, but there are definite differences between a Chihuahua and a Saint Bernard, in spite of the similarity of 99% of their shared genome.

The Endocannabinoid System and Cannabinoid Receptors

Following the determination of the structure of the first cannabinoid Δ-9 THC in 1964, researchers started looking for the membrane receptors that could mediate the activity of the cannabinoids. In 1988, the first cannabinoid receptor was discovered in the rat brain using a radioactive-labeled THC derivative. This receptor, termed cannabinoid receptor 1 (CB1), was determined to be a G-protein coupled receptor with the highest density in the rat cerebral cortex, hippocampus, hypothalamus, cerebellum, basal ganglia, brain stem, spinal cord and amygdala. This receptor is present in all vertebrate species, indicating that that the endocannabinoid system has been in existence for over 500 million years.

The endocannabinoid system (ECS) consists of: 1) the cannabinoid ligand, which binds to the cannabinoid receptor, 2) the receptor itself, and 3) the enzymes that synthesize and degrade the ligands.

The CB1 Receptor

The CB1 receptor is found in its highest concentrations on neurons that release gamma amino butyric acid (GABA), the main inhibitory neurotransmitter. It is located near the synapse. The discovery of this endocannabinoid receptor was a water-shed moment in neurophysiology in that it led to the discovery of the body's own endogenous cannabinoid molecules (endocannabinoids).

Mechoulam, who discovered THC, also discovered the first endocannabinoid, which he called "anandamide" after the Sanskrit word for bliss. Anandamide binds to the CB1 receptor and creates the similar effects as the phytocannabinoids naturally occurring in *Cannabis*. A second endocannabinoid was subsequently discovered, 2-arachidonoyl glycerol (2-AG). There are several other compounds currently under investigation as additional endocannabinoids.

The endocannabinoid receptors evolved along with the endocannabinoids to constitute a naturally-occurring cellular communication system, which is the endocannabinoid system. It is sheer coincidence that the phytocannabinoids found in the *Cannabis* plant resemble the endocannabinoids enough to activate the cannabinoid receptors.

The cannabinoid receptor CB1 is the most abundant G protein-coupled receptor expressed in the brain, with particularly dense expression in (rank order): the substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum and amygdala. This distribution has been determined for the human brain. Detailed studies in the dog using PCR technology are forthcoming, but not yet available.[4,5]

The endocannabinoid system's major homeostatic functions were summarized by DiMarzo as: "**relax, eat, sleep, forget and protect**." The endocannabinoid system has an effect on embryological development, neural plasticity, neuroprotection, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, hunger, feeding and metabolism.[10]

The endogenous agonists for cannabinoid receptors are long-chain polyunsaturated fatty acids (eicosanoids) that are derivatives of arachidonic acid, and have varying degrees of selectivity for either one or both of the cannabinoid receptors. Endocannabinoids are unlike other neurotransmitters in that they are lipids versus aqueous in nature. They also are not stored, but are manufactured ad hoc from the cellular membrane.

Endocannabinoids are released as calcium levels increase inside the neuron or when G-coupled protein receptors are activated. Endocannabinoids function as neuro-protectants by virtue of their antioxidant activity and by inhibiting calcium influx and excessive glutamate production. There are both cannabinoid receptor-dependent and cannabinoid receptor-independent actions of endocannabinoids.

Activities that are cannabinoid receptor-dependent include cognition, memory, appetite control, emesis, motor behavior, sensory, anxiety, and autonomic and neuroendocrine processes. Endocannabinoids induce hypotension and bradycardia, inhibit cell growth, affect energy metabolism and modulate immune responses, as well as being involved in fat accumulation, glucose and lipid metabolism. Endocannabinoids can also exert proinflammatory actions such as enhancing the cellular migration of eosinophils, neutrophils and natural killer T cells.[3]

Endocannabinoids use a previously undiscovered form of neuronal communication: "retrograde signaling," which is the opposite to the normal direction of neurotransmitter release from presynaptic neuron to reception on the postsynaptic neuron. Endocannabinoids released from the postsynaptic neuron actually bind at CB1 receptors on the presynaptic GABA neurons to modulate neuronal activity. This novel discovery of retrograde signaling was termed: depolarization-induced suppression of inhibition or DSI.

DSI helps to explain a number of previously unexplained aspects of brain activity. When you temporarily dampen inhibition, a form of learning termed, "long-term potentiation" occurs, which is a process by which information is stored through the strengthening of synapses. It was also found that CB1 receptors can, in some cases, block presynaptic cells from releasing excitatory neurotransmitters. This is true in the cerebellum where endocannabinoids located on excitatory synapses help to regulate neurons involved with motor and proprioceptive control of movement. This helps to explain, in part, the "static ataxia" uniquely observed in dogs only. The canine species have the highest density of CB1 receptors in the cerebellum of any other species studied to date.

Cannabis Research in Dogs

Research performed in the 1970s by the Department of Defense, explored whether marijuana could be "weaponized." Dogs were administered radioactive-labeled THC intravenously at escalating dosages. As a result, researchers found that dogs, as compared to pigeons, monkeys, guinea pigs, rats and mice, had the highest concentration of THC (now known to be bound to CB1 receptors) in the cerebellum, the canine molecular layer was found to be more dense than the molecular layer in any of the other species studied. The hippocampal formation was also very dense in specific locations.[4] Previous work had found that the minimum dose of THC administered IV to create static ataxia was 0.5 mg/kg IV.[5]

Tolerance to the "behavioral" effects of THC in the dog developed after daily injections were given. McMillan found that a dose of 2 mg/kg IV produced marked static ataxia, evidenced by

"swaying movements, hypersensitivity to moving objects and a prance-like foot placement." However, some dogs in this study group developed tolerance rapidly after the first administration of 2 mg/kg of THC. Subsequent injections continued to increase the degree of tolerance to THC in this study group. The magnitude of tolerance developed in these canine studies was in excess of 100 fold.[9]

CB1 receptors are found primarily in the central nervous system, but also have been found in the GI tract (perhaps explaining why we see appetite stimulation with *Cannabis* administration), cardiovascular system and reproductive system. In the dog, localization of the CB1 receptors was found in the hippocampus, structures of the skin including mast cells, hair follicles and salivary glands.[6]

CB2 Receptors

A second, G-protein coupled receptor for cannabinoids is the CB2 receptor. These receptors have been found to be strongly expressed in cells of the immune system, including the microglia, the peripheral nervous system and the organs. CB2 immunoreactivity was found in the B cell zones of lymphoid follicles in the dog, as well as in structures of the skin including mast cells, and hair follicles.[6] CB2 receptors are up-regulated during the early phases of inflammation in cells of the CNS and peripheral tissues, suggesting a role for cannabinoids in the management of inflammatory conditions of those tissues.

Non-CB Receptor-Dependent Activity

In addition to the receptor-dependent mechanism of action of the cannabinoids, terpenes and terpenoids, their activity can also be mediated through non-receptor dependent interactions. The endocannabinoids exert multiple pharmacological effects through a number of different mechanisms not restricted to modulation of the endocannabinoid system through receptor-ligand binding.

A partial list of these non-receptor dependent actions include:[1]

- Transient receptor potential (TRP) channel activation
- Peroxisome proliferator-activated receptor λ (PPAR λ) GPR55
- Abnormal-CBD receptor 5-hydroxytryptamine receptor subtype 1A (5-HT1A)
- Glycine α1 and α1β receptors
- Adenosine membrane transporter phospholipase A1
- Lipoxygenase (LOX) and cyclooxygenase-2 (COX-2) enzymes
- Calcium modulation
- Inhibition of anandamide inactivation by CBD, CBG and CBC

Terpenes and terpenoids exert strong biological effects by themselves, but have been found to interact synergistically with phytocannabinoids in the treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including MERSA).[7]

Potential Clinical Applications for *Cannabis* (Boothe 2015)

1. Pain, inflammation and immunomodulation:
    a. Effective for both acute and chronic pain by centrally and peripherally modulating nociception.
    b. CBD affects T-cells resulting in a mild generalized immunosuppressive effect.
    c. CBD has been found to have potential benefit for arthritis and psoriasis in humans.
2. Epilepsy:

a. CBD attenuates seizures in experimental models of epilepsy in animals.
b. THCV inhibits CB1 receptor activity resulting some anticonvulsant activity.

3. Anxiolytic:
    a. CBD exerts benzodiazepam-independent activity, postulated to be via post-synaptic 5-HT1A receptors.
4. Neuroprotection:
    a. CBD acts as an antioxidant and as such has been suggested for Alzheimer's, Parkinson's and Huntington's diseases.
5. Antiemesis:
    a. CBD in animal models has been found to be effective for the control of vomiting that is unresponsive to 5-HT-3 agonists such as metoclopramide or ondansetron.
6. Diabetes mellitus:
    a. CBD inhibits development of diabetes in experimental models of diabetes in mice. Reduction of pancreatic inflammation and antioxidant effects are credited with this benefit.
7. Bone formation:
    a. Cannabinoids stimulate the stem cells responsible for fracture healing and bone formation, as well as reducing bone loss by controlling bone reabsorption.
8. Cancer:
    a. Many of the cannabinoids have antiapoptotic effects and reduce neoplastic proliferation in selected tumor cell lines.
    b. Anecdotal reports from both human and veterinary patients indicate the potential for complete remission and possibly even cure of a number of different neoplastic diseases.
9. Antimicrobial:
    a. Both CBC and CBG have potent antibacterial effects including against MERSA (MIC of 0.5–2 mcg/ml).

Client Education Regarding the Use of *Cannabis* in Veterinary Patients

Medical marijuana has become a common topic for news and media broadcasts, as more states enact laws allowing its use for human medical problems and recreational use. Many of the same conditions that have been discussed in the media regarding human applications for cannabinoids also affect pets. Thus, it's not unusual that many pet owners, (especially those with dogs who have intractable epilepsy, chronic pain and cancer) have been considering the use of medical marijuana for their four-legged family members.

It behooves the veterinarian to be in possession of credible information to share with their client, specific to their pet and its diagnosis, and specific to the marijuana regulatory environment in their specific state. It's important for pet owners to know that even though medical marijuana is legal in a number of states for people to use under the supervision of a physician, it is not legal for a veterinarian to prescribe, and, depending on where the veterinarian is in practice, it may not be ethical based on local standards for the veterinarian to even recommend the use of medical marijuana for their patient, no matter how ill the patient is, or how close to death it may be.

The Nevada legislature, in March of 2015, introduced legislation creating a similar legal access to medical marijuana for veterinarians and their patients as for physicians and their human patients. This has not, as of this writing, come up for a vote. This is the first state in the United States to recognize that pets have medical needs for cannabinoid therapies just as humans. It will be interesting to see how that vote goes, and whether other states will follow suit.

At this point in time, to be compliant with legal regulations, the best a veterinarian can do is to: 1) Explain to their clients the risks associated with THC to dogs, based on the evidence that dogs have increased sensitivity to low doses of marijuana as compared to people, 2) Warn them of the risk of toxicity and an expensive ER visit if their pets get into marijuana products accidentally or are given too much THC, and 3) Suggest they consider trying legal industrial hemp extracts that contain nearly no THC (which is why they are legal), and which contain therapeutic levels of CBD and other non-psychotropic cannabinoids, terpenes and terpenoids.

A number of products are available on the Internet that are non-psychotropic and have been sent through the mail across state lines without problems to date. As of this writing, though, no credible, unbiased data exists documenting effective doses of CBDs and other cannabinoids in veterinary species. An abundance of anecdotal information exists suggesting an effective therapeutic range for CBDs from 0.1 mg/kg/day to 10 mg/kg/day based on studies in laboratory animals, humans, dogs and cats. Anecdotal reports with a commercial industrial hemp extract product suggests that dosages even lower than 0.1 mg/kg/day may be effective in certain patients for certain conditions. Definitive research is needed in veterinary species for more accurate dosing of cannabinoids.

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