

Medical Cannabis for Veterinarians—Risks & Benefits

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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 Fall of 2016, there are now 28 states that have legalized the medicinal use of marijuana; and 9 states including the District of Columbia allow recreational use of marijuana for citizens of the state that are 21 years of age or older.

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:
<http://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 “bi-partisan” 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 (Phyto- 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 (Echinaceae and Helichrysum). Other phytoconstituents 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.

Other, equally important phytoconstituents 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-pinene, 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 phytoconstituents 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 phytoconstituents 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 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 neuroprotectants 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 pro-inflammatory 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 1970's 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 denser 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 $\alpha 1$ and $\alpha 1\beta$ 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 MRSA) (7)

Potential Clinical Applications for Cannabis (Boothe, 2015)

Pain, Inflammation and Immunomodulation

- Effective for both acute and chronic pain by centrally and peripherally modulating nociception
- CBD affects T-cells resulting in a mild generalized immunosuppressive effect
- CBD has been found to have potential benefit for arthritis and psoriasis in humans

Epilepsy

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

Anxiolytic

- CBD exerts benzodiazepam-independent activity, postulated to be via post-synaptic 5-HT1A receptors

Neuroprotection

- CBD acts as an antioxidant and as such has been suggested for Alzheimer's, Parkinson's and Huntington's diseases.

Anti-emesis

- 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

Diabetes Mellitus

- CBD inhibits development of diabetes in experimental models of diabetes in mice. Reduction of pancreatic inflammation and antioxidant effects are credited with this benefit

Bone formation

- Cannabinoids stimulate the stem cells responsible for fracture healing and bone formation, as well as reducing bone loss by controlling bone reabsorption

Cancer

- Many of the cannabinoids have anti-apoptotic effects and reduce neoplastic proliferation in selected tumor cell lines
- 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

Anti-microbial

- Both CBC and CBG have potent anti-bacterial 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.

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.

Dosages

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.

This author has found that dosing for CBD content in a hemp extract has been effective in the range of 0.1 mg/kg BID- 0.5 mg/kg BID for most conditions. Starting with the lower end of the dosing scale and staying at the low end for 2 weeks to evaluate for change, and then if not, enough change has been observed to try for two weeks at the 0.25 mg/kg BID dosage, and if in sufficient benefit has been observed at that dosage to go to the upper end of dosages at 0.5 mg/kg BID.

Seizures and tonic clonic contractions associated with brain tumors have been extinguished at 0.5 mg/kg/BID. Simple uncomplicated seizures have been found to be more easily addressed by CBDs than refractory seizures that are not responsive to even very strong sedative medication.

References

1. Izzo AA, Borelli F, Capasso, R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in Pharmacological Sciences*;2009;30(10):515-527.
2. American Herbal Pharmacopoeia: Cannabis Inflorescence: Standards of Identity, Analysis, and Quality of Control (2013); www.herbal-ahp.org
3. Svizenska I, Dubovy P, Sulcova A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures: A short review. *Pham Biochem Beha* 2008; 90: 501-511
4. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. Cannabinoid receptor localization in the brain. *Proc Natl Acad Sci.* 1990;87:1932-1936.
5. Martin BR, Dewey WL, Harris LS, Beckner JS. $^3\text{H}-\Delta^9$ -Tetrahydrocannabinol tissue and subcellular distribution in the central nervous system and tissue distribution in peripheral organs of tolerant dogs. *J Pharm Exper Ther.*1976;196(1):128-144
6. Campora L, Miragliotta V, Ricci E, Cristino L, DiMarzo V, Albanese F, della Valle MF, Abramo F. Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis. *Am J Vet Res* 2012;73:988-995.
7. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Brit J Pharmacol* 2011;163:1344-64.
8. Boothe, DM. The High Points of Medical Marijuana. *Western States Veterinary Conference Proceedings*, February 2015.
9. McMillan DE, Dewey WL and Harris LS. Characteristics of Tetrahydrocannabinol tolerance. *Annals NY Acad Sci.* (1971)191:83-99.
10. McParland JM, Guy GW and Di Marzo V. Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System.(2014)PLoS ONE (9)3:e89566. doi:10.1371/journal.pone.0089566.