WHAT ALL VETERINARIANS SHOULD KNOW ABOUT CANNABIS:

AN UPDATED REVIEW OF CANNABIS IN VETERINARY MEDICINE

Author's contact information:

Trina Hazzah, DVM, DACVIM(O), CVCH
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Blvd.
Los Angeles, CA 90025
Trina.hazzah@vca.com

Introduction

Marijuana laws are changing at a rapid pace with many states obtaining full legalization. Pet owners are now becoming more and more interested in utilizing cannabis (both hemp and marijuana forms) for their pets and are looking to veterinarians for guidance on the safety and efficacy of the variety of products that exist. It is essential for veterinarians to have a basic understanding of terminology, the endocannabinoid system, the components of the plant, clinical utilization and toxicity. This document will review these facts as well as touch on some recent veterinary publications and relevant legal updates.

Basic Terminology[1-2]

Cannabis:
The genus of a flowering plant that has three different species that have been recognized including *Cannabis sativa, Cannabis indica and Cannabis ruderalis.*

Both hemp and marijuana fall under the umbrella term, cannabis. However, there are several distinct differences.

Hemp/Industrial hemp:
Phenotypically the hemp variety of the cannabis plant is thin, tall with thin leaves and typically has strong and durable natural fibers. The stalk produces fibers that can be used to manufacture textiles, rope, food, clothes, paper, etc. Hemp contains <0.3% of Tetrahydrocannabinol (THC) by dry weight at the time of harvest, which is the highly psychoactive component of the plant. It also typically contains larger amount of Cannabidiol (CBD) compared to marijuana strains.

Marijuana:
Phenotypically the marijuana plant is shorter, with a thicker stalk and large broad leaves. The fibers in this plant typically have low tensile strength compared to its hemp counterpart. Marijuana contains >0.3% of THC by dry weight at the time of harvest.

Endocannabinoid system:
One of the body's most ubiquitous neurotransmitter networks found within all animal systems from nematodes to humans.[3]

Cannabinoids:
A class of diverse chemical compounds that act on cannabinoid receptors in cells that alter neurotransmitter release. Ligands for these receptor proteins include the endocannabinoids, the phytocannabinoids, and synthetic cannabinoids.

Terpenes:
Aromatic molecules found in the oils of all plants that also possess medicinal properties.

The Endocannabinoid System[3-7]

A complex regulatory system that is present in almost every system in the body that helps maintain balance and homeostasis. The endocannabinoids are generated on demand by the body, especially in times of stress, disease or injury.

The Endocannabinoid System is composed of 3 essential parts:

1) The endocannabinoid receptors (part of the G-protein coupled receptors)
    a. CB1- found predominantly in the CNS
    b. CB2- found predominantly in the spleen and immune system
2) Endocannabinoids (ligands)
    a. Anandamide- primary endogenous ligand for CB1 receptor
    b. 2-AG- primary endogenous ligand for CB2 receptor
3) Regulatory Enzymes
    a. Fatty Acid Amide Hydrolase (FAAH)-degrades anandamide
    b. Monoacyglcerol Lipase (MAGL)-degrades 2-AG
    c. COX-2 enzymes-degrades both anandamide and 2-AG

The *Cannabis Sativa* Plant[8-27]

Phytocannabinoids:

Phytocannabinoids consist of over 100 naturally occurring compounds with chemical structures related to the endocannabinoids. They are exogenous, plant-based compounds that bind to the endocannabinoid receptors as well as other receptors in the body. There are multiple phytocannabinoids that have been studied but the two most common ones are detailed below.

Δ^9-tetrahydrocannabinol (THC) is a partial agonist for both CB1 and CB2 and is largely responsible for the neurological effects noted with cannabis use. Some of the most notable physiologic effects of THC include:

- Analgesia
- Anti-convulsant
- Anti-inflammatory
- Anti-neoplastic
- Appetite stimulant/Anti-emetic (works peripherally and centrally)
- Bronchodilatory
- Gastrointestinal support
- Promotes sleep
- Reduces intraocular pressure

Cannabidiol (CBD) unlike THC does not have the profound psychoactivity on its own and in fact can reduce the psychotoxicity of THC via negative allosteric modulation of CB1 and CB2 receptors and inhibition of CYP450 (which slows the metabolism of THC to the potentially more psychoactive metabolite 11-hydroxy Δ^9 THC).[28-29,36] CBD is an antagonist, with low binding affinity at CB1 and CB2 receptors. CBD is also unique in that it has been shown to inhibit FAAH in mice, which can allow

anandamide (or THC) to act on the receptors longer. Some of the most notable physiologic effects of CBD include:

- Analgesia
- Anti-emetic
- Anti-diabetic
- Anti-inflammatory
- Anti-neoplastic
- Anxiolytic/Anti-depressant
- Cardioprotective
- Improves fracture healing
- Neuroprotective and anti-convulsant

There are several other phytocannabinoids that have been shown to have medicinal benefits, both in vitro as well as in vivo. For example, Cannabidiolic acid, or CBD-A is a precursor to CBD and has been shown to have potent anti-emetic, anti-neoplastic and anti-inflammatory properties. A 2008 study showed CBD-A had essentially equal COX-2 inhibition compared to two NSAIDs.[30]

Terpenes:[31]

Terpenes are aromatic oils that are responsible for giving cannabis varieties different smells and tastes. The development of terpenes within cannabis began for adaptive reasons, specifically to repel predators, protection (anti-bacterial and anti-fungal effects) and to attract pollinators. There are over 200 different terpenes that have been identified in the cannabis plant and every cultivar (strain) has a unique terpene profile. Terpenes have physiologic effects on the body. The most impressive characteristic of terpenes is their ability to interact synergistically with the other compounds within the plant to enhance the effect it has on the body.

The importance of understanding whole-plant medicine is to appreciate the phenomenon of the entourage effect. This is defined as the intricate synergy between the different parts of the plant (cannabinoids, terpenes, and flavonoids) that result in powerful medicinal benefits.

Clinical Utilization

Cannabis is being utilized for a variety of different disease processes in human medicine and there are multiple publications (both in vivo or in vitro) supporting its medicinal use. Due to the legal environment surrounding cannabis, there are only a few in vivo studies performed in veterinary medicine thus far. Here are a few examples of medical conditions, which represent the most common and scientifically justified clinical applications of cannabis:

Medical conditions:

- Anti-inflammatory
    - Eosinophilic dermatitis and hypersensitivity in cats[32]
- Analgesia
    - Osteoarthritis [33-34]
    - Neuropathic pain[35]
- Anti-convulsant [18,20,37-39]
- Neuroprotection[40-41]
- Anxiolytic[42-44]
- Anti-neoplastic[45-56]
- Gastrointestinal support[57-59]

Product Selection:

Selecting the correct product is critical for all patients, but especially veterinary patients. The following are a few important points that need to be considered when obtaining a medical cannabis preparation:

1) "Full spectrum" means the product contains the various components of cannabinoids, terpenes and flavonoids, in the original plant strain, which contributes to the entourage effect. Utilizing the entourage effect tends to provide the patient with the best chance of success. Avoid single compound isolates such as CBD alone (without other components of the plant, unless specifically indicated).
2) Be sure the product is free of pesticides, herbicides, heavy metals and solvents. This can be accomplished by reviewing a certificate of analysis (COA). *
3) The product should have labeled amounts (in mg) of each cannabinoid (THC, CBD, etc.) so that appropriate dosing is feasible.

*A Certificate of Analysis (COA) is a laboratory evaluation of a product that provides an objective measurement of ALL 3 of the above parameters.

Toxicity:

THC is the limiting factor when it comes to dosing veterinary patients and careful selection of products and proper dosing is essential. Dogs in particular have higher amounts of CB1 receptors in their cerebellum compared to any other species.[60] When dogs receive excessive amounts of THC (either via accidental ingestion or overdose) they develop a unique toxicity known as Static Ataxia. Dogs with this condition frequently present with severe ataxia and a sawhorse stance where they sway back and forth and abruptly catch themselves from falling.

Excessive THC exposure in dogs can also lead to urinary incontinence, severe lethargy/stuporous appearance, agitation, tachycardia or bradycardia (dose dependent), hypersalivation, and hypothermia.[61]

The majority of dogs experiencing intoxication after marijuana ingestion recover completely with supportive care and monitoring. However, dogs with severe clinical signs that are unable to eat or drink without support, intravenous fluids and even hospitalization may be warranted. The use of intralipid therapy to bind the highly lipophilic THC is another treatment option to reduce clinical signs in severe cases of toxicity.[61] Theoretically, dosing with CBD can also reduce the THC induced psychotoxicity.

Unlike opioid receptors, there are no cannabinoid receptors in the respiratory centers of the brain. Thus, even with extreme overdoses of cannabis, there is no chance of respiratory depression. One published study concluded there is no known LD_{50} for cannabis in dogs. Doses of greater than 3000 mg/kg of pure THC where given in dog research models without resulting in any fatalities directly relating to THC. Two of the dogs in the study however, died from aspiration pneumonia secondary to severe sedation.[62]

CBD, by contrast, has very few side effects in both humans and veterinary patients. A recent study found that CBD was well tolerated in dogs at a dose of 10-20 mg/kg/day. This is much higher then what is typically given in a clinical setting. The only hematological effect noted was an elevation in serum ALP, which was likely due to CYP450 interactions. Physiologic side effects were limited to mild gastrointestinal signs (diarrhea), pinnal erythema, and oculonasal discharge noted.[63]

<u>Dosing:</u>

The majority of medications in veterinary medicine follow a linear dosing curve. In other words, as the dose increases, drug efficacy increases (or reaches a plateau). Similarly, side effects develop with increasing dosage. With cannabis however, dosing follows a biphasic dosing curve, meaning after the "optimal" dose is achieved, and further increase in dosing leads to diminished clinical efficacy. Dosing cannabis beyond the optimal dose also increases the risk of developing side effects- particularly with THC.[64]

When considering the above information regarding biphasic dosing and realizing that THC is the dose limiting compound, it is imperative that pets are dosed with a full spectrum product initially at very low doses (starting at 0.1mg/kg q 12 hours of THC or CBD) and then gradually increasing the dose (every 5-7 days) until efficacy or dysphoria is noted. Overtime, as the receptors are "primed", higher doses of THC can absolutely be used in patients as tolerance to the intoxicating effects can occur. Depending on the disease state (i.e., cancer), higher amounts of THC may be warranted. Most cannabis products are dosed orally at an interval of every 12 hours, however depending on the disease state (i.e., seizures, anxiety, pain) every 6-8 hour dosing can be implemented. Based on a recent publication that evaluated pharmacokinetics of CBD, it was demonstrated that median half-life of elimination was approximately 4 hours for both a 2mg/kg and 8mg/kg dose.[33]

Legal environment

In late 2018, the Agriculture Improvement Act (2018 Farm Bill) removed hemp and all of its constituents from Schedule I status under the Controlled Substance Act (CSA) and became federally legal. Even though the new law de-scheduled hemp-based CBD under the CSA, the FDA still considers CBD to be a "drug."[65] There are currently no CBD products approved for use in animals. The FDA approved anti-convulsant CBD product Epidiolex, is available to veterinarians for extra-label use in animals under the Animal Medicinal Drug Use Clarification Act (AMDUCA). [66]

Note: Unless it is derived from hemp produced in a manner consistent with the Farm Bill, CBD remains Schedule I under the CSA. The only cannabinoid (natural and synthetic) containing products that are FDA approved for human use are Epidiolex, Dronabinol and Nabilone.

As federal cannabis law continues to change, so do regulations at the state level. Currently, medical marijuana laws apply to the use of products in human patients and do not authorize veterinarians to recommend, dispense or prescribe marijuana products. Until federal and state guidelines become well-defined for veterinarians, it is the current recommendation to NOT carry marijuana or hemp-derived CBD-containing products in your hospital/clinic.

Please contact your local veterinary medical board for more information on what the exact laws and guidelines are surrounding cannabis in your state.

Conclusion

As cannabis-derived medicines show therapeutic value in multiple disease conditions such as epilepsy, anxiety, cancer and osteoarthritis, pet owners are asking their veterinarians about the legality, safety and efficacy of available products. As veterinarians, we all took an oath to use our scientific knowledge for the benefit of society through the protection of animal health. As a profession, we must decide how to honor our oath and steer clear of potential legal obstacles. Should we refuse to provide guidance to pet owners, they will invariably turn to the internet or an uneducated budtender at the local dispensary. The reality is that cannabis is here to stay, and we all need to educate ourselves on the pharmacology and clinical applications of this plant in order to assist our clients and keep our patients safe.

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