MEDICAL CANNABINOIDS: AN ANALGESIC ALTERNATIVE TO OPIOIDS?

Dawn Merton Boothe, DVM, PhD, DACVIM (Internal Medicine), ACVCP
Auburn, AL

INTRODUCTION

(No portion of this handout can be copied). 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 refers to the dried leaves and tops of the hemp plant (*Cannibus sativa)* (Svienska 2008). It has been a part of recreational, religious and medical activities of a variety of cultures for over 5000 years (Krietzer 2009;Burns 2006 and was among the most commonly prescribed medications in the United States Pharmacopeia until declared illegal in the 1930s. *Cannibus* 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 terpenephenolic 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 **eicosonoid 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 serotinergic 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 monosacharides (n=13: fructose, glucose, mannose), selected disaccharides (sucrose, maltose), and several polysaccharides (eg, 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.

PHARMACODYNAMICS: THE ENDOCANNABINOID SYSTEM

The Endocanabinoid 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). In nervous tissue, the receptors predominate in the mitochondria of the neuron. These manufacturers of energy are negatively impacted by THC, but these effects of THC are largely blocked by CBD, demonstrating the yin/yang effects of these compounds. 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 antimistamine) 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 (eg, 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 CB2 also plays a role, depending on the tissue (Svizenska 2008). Cannibinoids 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 CB2R receptor receptors do not cause the effects on mentation that activation of CB1R 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. CB2 also is located on neurons where it may be associated with cell differentiation (Svizenska 2008).

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.

Drug interactions are a possible complication. The cannabinoids appear to inhibit multiple drug metabolizing enzymes based on in vitro studies. To date, the clinical relevance of this effect is not clear. CBD has been demonstrated to increase adversities associated with warfarin and combined use with clobazam resulted in higher clobazam concentrations in a child. Prudence dictates caution and perhaps monitoring.

Specific cannabinoids: Cannabidiol (CBD) was the first isolated phytocannabinoid to be isolated from the Cannabis plant in 1930-1940s. CBD-acid (CBD-A) is the prodrug form in the plant, but it is rapidly metabolized to CBD. In 1960s, CBD was employed as an anticonvulsant due to having similar pharmacologic effects as phenobarbital and diphenydantion (DPH) (Mechoulam 2002). CBD, has very low affinity for the cannabinoid receptors (often manifested as antagonistic), however, it serves as an antagonist for CB1R and CB2R agonists (Mechoulam 2007). The natural CBD (-) does not bind to CB1R, however, the synthetic (+) has been shown to bind to both CB1R and CB2R (Mechoulam 2002). Besides anti-convulsant effects, CBD has been used for its anxiolytic, anti-psychotic, and anti-nausea 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 anti-oxidative agent, showing greater protective nature against glutamate neurotoxicity than either ascorbate (Vitamin C) or α tocopherol (Vitamin E) (Mechoulam 2007). These anti-oxidative 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 CB1R, 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, cannibinol (CBN), the primary product of Δ9-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).

Cannabinoids in Dogs or cats: Cannabionid 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 ∆-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 stuates 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 (eg, 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 (http://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). This includes those predominantly cannabidiol (CBD) products derived from “industrial hemp”. Note that laws that legalize marijuana in selected states do not (and are likely not) to apply to veterinary medicine. Further, simply because marijuana has been legalized does not necessarily mean that they can be purchased in those states easily, nor that they can be transported across state lines. Until such laws are clear in what veterinarians can and cannot do, having clients purchase the products online is prudent.
In December, Congress passed the 2018 Farm Bill that specifically addressed industrial hemp. Some important points about the impact of this Bill on cannabinoid use in animals:

> The Farm Bill of 2014 had already legalized industrial hemp (less than 0.3%THC DMW) for pilot programs; the 2018 bill removes the pilot distinction and now any one can grow it. But there are some important caveats: (LongLink @ www.brookings.edu...)
>
> Regarding Industrial Hemp:
>
> 1. States must regulate the cultivation of IH. Each state's regulatory program must be approved by the Secretary of USDA. This includes verifcation that a plant being grown meets the definition of industrial hemp. This begins with the Secretary of USDA who will oversee states' regulatory plans for IH. These plans must be followed by the cultivators in the respective states. As such, although any person can grow IH, it will require a license and as such, not be will not be as easy as growing tomatoes.
>
> 2. The protections for hemp (not necessarily CBD; see below [heavy sigh]) research established in 2014 have been extended.
>
> Regarding CBD:
>
> 3. Hemp-derived products (I assume IH derived products) have been removed from Schedule 1 status, but CBD is NOT generally legalized. This is because the DEA and FDA have not dropped CBD from Schedule I status - yet. However, along with the DEA, some exceptions have been made: any cannabinoid (THC, CBD, etc) derived from hemp will be legal if produced

in a manner consistent with the Farm Bill, that is, it is from IH that has been grown according to state and thus Federal regulations.

Some (Boothe's take): this suggests that any CBD product, regardless of CBD content, is legal as long as it is derived from appropriately regulated IH (meaning all the above restrictions are met). However,

4. the Farm Bill does not change the fact the Federal Government's still considers all state programs that have legalized cannabis products to be illegal. So while there is a potential for a broad expansion of commercially available CBD products because of the bill, CBD is not in general "legal". Each producer is going to have to demonstrate that the CBD used in their products is derived from approved IH. Those current commercial producers that obtain their product from crops meeting the 2014 Farm Bill (presumably?) may have a jump on the industry.

Hopefully, a movement toward change in this aspect (more general legalization of CBD) can occur when the democrats come to power in the House.

4. Unfortunately (and ironically), under currently law, any research involving CBD must be obtained from research grade cannabis which currently can be obtained only from University of Mississippi School of Pharmacy. Before (presumably) any more research goes forward, the dEA and FDA are going to have to provide guideance. (Heavy sigh).

5. Still be worked out is the impact of pharmaceutical grade CBD such as that found in Epidiolex (which remains regulated by DEA as a Schedule V product) on CBD in IH. The approval of Epidiolex means that an active pharmaceutical ingredient that is in an approved drug is being sold commercially as supplements (which reflect either concentrated CBD oil or supplements which have been modified with the addition of CBD oil). Even if the CBD oil in these products has been derived from appropriately grown IH, the pharmaceutical manufacturers are not likely to take lightly the widespread availability of products containing an active pharmaceutical ingredient available in an approved drug. Expect some regualatory push back as the FDA tries to make Pharma and Dietary supplement manufacturers happy.

Summary:
The Farm Bill continues what the 2014 Bill began. The next step is putting into play Federal regulations for IH which will include approving the plants, and state regulatory programs. No CBD will be federally legal until the manufacturer can demonstrate that the product being sold is derived from CBD obtained from IH demonstrated to be as such. This will take some time (unless some of our current manufacturers, as I indicated above, already did that to be in compliance with the 2014 Bill).

Congress generally understands the safety of CBD; whether and when it can find a path to deregulate CBD without impacting THC is not clear. There is likely to be a lot of continued discussion as the implications of the Bill are discussed and the regulations surrounding the bill are promulgated and implemented.

Other considerations: Note that there is not regulatory mechanism for assuring the quality of currently marketed products. Indeed the FDA has demonstrated that many “dietary supplements” containing cannabinoids do not contain the labeled content, some being too high, others too low and some containing THC. This is among the reasons to consider monitoring CBD (https://www.vetmed.auburn.edu/veterinarians/clinical-labs/).

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®]), iis 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 emotionaly-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, CB_2R receptors, and to a much lesser extent CB_1R, have been effective in modulating the inflammatory response as well as tissue and nerve injury (19,33). CB_2R, 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 CB_1 and CB_2 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). 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). Cannabinoids may have antagonistic effects at NMDA receptors. 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. Rofenicoxib, 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). In human medicine, cannabinoids have demonstrated to be effective for treating neuropathic pain associated with diabetic neuropathies. In general, their efficacy is best when used in combination with other anagescis.

STUDIES IN DOGS: One study has demonstrated efficacy of cannabidiol in dogs for control of pain associated with chronic osteoarthritis (https://www.ncbi.nlm.nih.gov/pubmed/30083539) when used orally at 2 mg/kg q 12 hrs . Pharmacokinetics support this dose in achieving presumably therapeutic concentrations and maintaining these concentrations for 12 hrs. Treatments for epilepsy are currently ongoing.

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 CB_1) in areas of the brain known to be sites where partial seizures originate. 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. CB_1 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. One study (JAVMA, McGrath 2019) has demonstrated potential efficacy of CBD when added to other AED in dogs with refractory epilepsy).

Other: Cancer: In addition to control of adverse clinical signs associated with cancer and its treatment, a number of the cannabinoids have antiprolierative-anti apotopic effects in a number of tumor cell lines. The National Cancer Institute has a link describing ongoing studies. http://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 (eg, 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).