Scooby's Doobies: Cannabis Use in Veterinary Medicine
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As medical cannabis becomes legal in more states, and public opinion continues to shift toward acceptance of the use of cannabis for both medical and recreational use, more and more patients are using cannabis not only for their own medical conditions, but also for their pets’ conditions. In order to support our clients and our patients, it is necessary for the veterinary staff to be aware of available products and their uses in small animal veterinary medicine. These proceedings will also discuss the issue of inadvertent cannabis ingestion by dogs leading to toxicities and treatment methodologies.

TERMINOLOGY

*Cannabis* is the plant from which both “marijuana” and hemp derive; the difference is in the way the plant is bred. Some strains are cultivated to maximize the content of psychoactive substances and other cannabinoids (“marijuana” or “cannabis”), while others are cultivated primarily for fiber, oil, or other substances (“hemp”). **Industrial hemp** is defined by the Federal government as a *Cannabis sativa* plant with <0.3% of the psychoactive component or cannabinoid (specifically THC). These proceedings will refer to medical cannabis, rather than medical marijuana, as the word “marijuana” has many negative connotations and was given to the plant by people only interested in banning its use (see History/Timeline, below). A **cannabinoid** is any chemical compound that interacts with receptors found throughout the body and can be divided into three main categories: endocannabinoids, phytocannabinoids, and synthetic cannabinoids. **Endocannabinoids** are produced in cellular membranes throughout the body on an as-needed basis. **Phytocannabinoids** are found in plants like *Cannabis sativa*, *Echinacea purpura*, and others that interact with receptors in the endocannabinoid system. **Synthetic cannabinoids** are created outside of the body and designed to interact with cannabinoid receptors. **Terpenes** are compounds that provide plants with their aroma. Similarly, **flavonoids** are compounds that provide plants with their flavor.

HISTORY / TIMELINE (adapted from medicalmarijuana.procon.org)

2900 BC - AD: The first written mention of the use of cannabis as a medicine is found in China in 2900 BC. Chinese herbalists and medicine practitioners continue to explore the use of cannabis for many conditions and the earliest written reference to medical cannabis is published in the Chinese Pharmacopeia in 1500 BC. Cannabis is used extensively throughout Asia, India, and the Middle East for conditions ranging from glaucoma, to leprosy, earaches, edema, and inflammation. It was also used as an anesthetic agent.

30 AD: Chrism, a cannabis-based anointing oil, is mentioned in the New Testament as the oil Jesus used to anoint his disciples. The recipe for this oil – found in Exodus – calls for between six and nine pounds of cannabis to be steeped in oil and then used for both anointing and fumigations.

70 – 1700s: References to cannabis for medical use/treatments continue to be found throughout China and the Middle East with some calling it medicine and others warning of the psychotropic effects. In the Middle Ages in England, hemp was crucial for every herbalist to carry and in China it is used to treat vomiting, parasite infections, hemorrhage, diarrhea and dysentery, and as an appetite stimulant. As the Jamestown settlers arrived in North America, they brought hemp with them and hemp fiber was an important export for the colonies; so much so that in 1762 Virginia imposed penalties on any who did not produce hemp on their land. Both George Washington and Thomas Jefferson grew hemp on their plantations. In 1799, Napoleon invaded Egypt and returned to France with cannabis, which was studied for its pain relieving and sedative effects, making cannabis more accepted in Western medicine.

1800s – 1905: Dr. William O’Shaughnessy was a British army surgeon serving in India who re-introduced cannabis into British medicine upon his return to England. It was used widely for many conditions including muscle spasms, menstrual cramps, and rheumatism. It is rumored that Queen Victoria may have used cannabis tincture (extract in alcohol) to treat her own menstrual cramps as her personal physician wrote extensively on the use of cannabis for many ailments. Additionally, cannabis was used as an anti-convulsant for those suffering from tetanus, rabies, and epilepsy. Several studies at this time were
published including those by French psychiatrist Jacques-Joseph Moreau showing that cannabis was an appetite stimulant, a sleep aid, and a treatment for headaches. In 1850 cannabis was added to the United States Pharmacopeia as a treatment for neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, insanity, menstrual and uterine bleeding, appetite stimulation, and many others. In 1889, a study was published in *Lancet* on the use of cannabis to relieve symptoms of opium withdrawal.

1906: President Roosevelt signed the Food and Drugs Act (aka the Wiley Act), which established regulations for product labeling and specifically stated that packaging must have a statement of the quantity of alcohol, morphine, opium, cocaine, heroin, chloroform, cannabis, or any derivative thereof.

1911 – 1929: Fifteen US states pass anti-marijuana laws while US pharmaceutical farms grow 60,000 pounds of cannabis annually. This made the US self-sufficient in hemp. In 1925, the League of Nations signed a multilateral treaty that restricted the use of cannabis to scientific and medical purposes only and in 1928 cannabis is added to the UK’s Dangerous Drugs Act.

30s: Parke-Davis and Eli Lily were selling standardized extracts of cannabis for analgesia, sedation, and as an anti-convulsant. In 1930, Harry Anslinger was appointed as the first Commissioner of the Federal Bureau of Narcotics. Anslinger was the architect of national prohibition and believed that cannabis caused insanity and increased criminality. In 1933 publisher William Randolph Hearst joined the anti-cannabis fray, publishing sensationalized stories linking violence to cannabis consumption. In his newspapers, he dropped the terms “cannabis” and “hemp” and replaced them with “marijuana” which linked cannabis to minorities (most notably Mexicans who were immigrating into the west in large numbers). Both Anslinger and Hearst used racially charged language and blamed marijuana use for everything from rape to dissolution to murder. The film Reefer Madness is released in 1936 which purported to prove that marijuana ruins lives and leads to violence and promiscuity.

In 1937 the Marihuana Tax Act is passed, with strong support from Anslinger and over the objections of the American Medical Association who argued for the medicinal use and effects of cannabis. This law imposed registration and reporting requirements on growers, sellers, and buyers of cannabis, leading to a decline in prescriptions because doctors found it too difficult to deal with the extra work imposed by the law. By 1938, both cannabis and hemp are illegal in all states.

1964: Dr. Raphael Mechoulam is the first person to identify delta-9-tetrahydrocannabinol (THC) as the primary psychoactive component of cannabis. He is also the first to synthesize THC.

1970s: In 1970, Congress passes the Controlled Substances Act, which established the scheduling structure used for controlled drugs to this day. Cannabis was placed in Schedule I: drugs with a high potential for abuse, no currently accepted medical use, and a lack of accepted safety data. A presidential commission (Schafer Commission) recommended removal of cannabis from the scheduling system in 1972 but President Nixon rejected this recommendation, having declared war on drugs in 1971.

1980s: Marinol, the first synthetic cannabinoid, is approved by the FDA for the treatment of nausea. Patients in the clinical trial reported less nausea and fewer unwanted side effects when using the whole plant, however.

1990s: In 1990 researchers at the National Institute of Mental Health discover the cannabinoid receptor system in the human brain and in 1992 Dr. Mechoulam identified the first endogenous cannabinoid (aka endocannabinoid): anandamide. In 1996, California becomes the first state to legalize the use of cannabis to aid in the treatment of AIDS, cancer, muscular spasticity, migraines, and other disorders. California was followed by Alaska, Oregon and Washington which all legalized medical cannabis in 1998.

2000s: Research into the endocannabinoid system continues and more and more states are legalizing cannabis for medical use. The DEA is currently considering rescheduling cannabis to a less-restrictive schedule, which should boost research and the development of new pharmaceuticals to take advantage of the largest receptor system in the human body.
THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is believed to be the largest receptor system in the mammalian body. Receptors are located in the brain and throughout both the central and peripheral nervous system; they are also expressed on the membranes of immune cells throughout the body. The ECS serves as a neuromodulatory and immunomodulatory system and is vital to maintaining homeostasis and aiding the body’s own stress-recovery systems. The ECS has many functions including neuroprotection, pain modulation, motor activity regulation, cardiovascular controls, and antiproliferative actions in neoplastic cells. In the central and peripheral nervous system, the ECS reduces the influx of calcium at the presynaptic neuron, which inhibits the release of excitatory neurotransmitters. This inhibitory effect lessens pain responses, as well as other excitatory processes such as muscle tremors and spasticity. In the case of inflammation specifically, the ECS increases receptor expression and local endocannabinoid levels at the site of inflammation, leading to a down-regulation of the production of inflammatory proteins and chemotaxis of inflammatory cytokines.

The ECS has two primary receptor types known as cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). CB1 receptors are highly expressed in the brain but are also found in organs and tissues throughout the body. In the mammalian brain, CB1 receptors are one of the most abundant G protein-coupled receptors found, allowing both endocannabinoids and exogenous cannabinoids to cross the blood brain barrier (BBB) and exert effects on the brain. CB1 receptors in peripheral organs including adipocytes and Kupffer cells in the liver may exert some control over metabolism, and CB1 receptors in the gastrointestinal (GI) tract modulate motility, inflammation, and secretion. These receptors are also found in vagal nerve terminals in the GI tract involved in gut-brain signaling and perhaps playing a role in modulating feeding behavior. CB2 receptors are expressed almost exclusively in immune and blood cells, where they perform immunomodulatory functions and mediate cytokine release. They have also been found to inhibit the activation of the cell-mediated immune process (e.g. IMHA) and to inhibit chemotaxis. CB2 receptors are also found throughout the GI tract and are a potential therapeutic target for a number of inflammatory bowel diseases, with CB2 agonists proving to reduce gut motility in human irritable bowel syndrome patients. CB2 receptor agonists are currently being researched as treatments for both inflammatory and neuropathic pain. Interestingly, the ECS (and not the endo-opioid receptor system, triggered by endorphins) is now thought to be the system responsible for the “runner’s high” that people experience after exercise.

At this time, research has identified five endocannabinoids – the endogenous ligands for the cannabinoid receptors in the ECS. The first identified was anandamide (N-arachidonoyl ethanolamide, AEA, the “bliss molecule”) followed by 2-arachidonoylglycerol (2-AG). These molecules have been the most extensively studied and are thus far the best understood. Lesser-understood compounds are Noladin ether, Virodhamine, and NADA.

Phytocannabinoids are found in Cannabis spp. as well as other plants (such as Echinacea purpura). Phytocannabinoids bind to both CB1 and CB2 receptors in the ECS and exert similar effects to endocannabinoids. More than 80 phytocannabinoids have been discovered in Cannabis with 20 of those currently under active study. The most famous of these is tetrahydrocannabinol, also known as THC. THC is the psychoactive component of Cannabis, with modern strains of the plant being cultivated and bred to increase the psychoactive effects through higher and higher percentages in the plant. THC also has medicinal properties and is used against glaucoma, insomnia, PTSD, and anxiety disorders. Cannabidiol (CBD) is the second half of the “power couple” of cannabis. CBD is non-psychoactive and has been found to be efficacious in seizure and pain control, while also being used for its anti-inflammatory, analgesic, anxiolytic, antipsychotic, and anti-carcinogenic effects. CBD modulates the psychoactive effects of THC and helps to temper the “high” experienced. Cannabinol (CBN) is closely linked to CBD and is sometimes referred to as “CBD Lite”. It functions primarily as a sleep aid, with recent research showing some promise in its use as a topical treatment for methicillin-resistant Staphylococcus (MRSA) infections. In the UK and Canada Sativex® (nabiximol) mouth spray has been approved to treat neuropathic pain, cancer pain, spasticity, overactive bladder, and symptoms of multiple sclerosis. It is a 1:1 ratio of CBD to THC extracted from the Cannabis plant.
Synthetic cannabinoids have been developed in an effort to avoid the legal issues surrounding the use of cannabis for medical purposes and to try to isolate compounds for specific therapeutic effects. With the advent of legalization of cannabis for medical use in several states, the need for synthetic cannabinoids has lessened but they still have an important role to play in treating patients who may be reticent to buy and use cannabis, due to its stigmatization over the last 80 years. Many scientists also wish to isolate the compounds that provide specific therapeutic effects, minimizing the need for using the entire plant. The first FDA-approved synthetic cannabinoid is Marinol® (dronabinol), which is approved for the treatment of anorexia associated with weight loss in AIDS patients. Another FDA-approved synthetic cannabinoid is Cesamet (nabilone), which is approved for the treatment and prevention of nausea and vomiting associated with chemotherapy. Both dronabinol and nabilone are synthetic analogs of THC and, thus, bind to both CB1 and CB2 receptors. Nabilone is used off-label to treat chronic pain (especially associated with fibromyalgia), Parkinsonian muscle tremors, multiple sclerosis, and inflammatory bowel disease.

Synthetic cannabinoids are reported by patients to be less effective treatments compared to the use of the whole plant. This is attributed to the “entourage effect” which is not yet fully understood. For example, Cannabis contains over 100 different terpenes, which interact synergistically with phytocannabinoids and provide mediation for the ECS by modulating the psychoactive effects of THC, increasing its therapeutic index by modifying how much THC passes through the blood brain barrier. Additionally, terpenes have effects as serotonin uptake inhibitors, norepinephrine enhancers, GABA augmenters, and dopamine activity enhancers. Some of the terpenes that have been researched include caryophyllene (gastroprotective, autoimmune modulator), myrcene (sleep aid, analgesia, alleviates depression), and limonene (mood elevator, anti-fungal, anti-bacterial, anti-neoplastic). Beta-caryophyllene is anti-inflammatory molecule, found in rosemary, basil, cloves, and black pepper and is an FDA-approved additive for food products. Another component in the entourage effect is the impact of flavonoids, whose role is still not well understood.

VETERINARY MEDICAL CANNABIS USE

Although there is limited research in the United States, particularly in regards to veterinary species, many owners are using cannabinoids to treat a number of different conditions in their own pets. There are several companies providing products for the small animal market in various formulations and combinations of cannabinoids. Anecdotal reports collected by these companies show that owners are using cannabis products to treat pain, seizures, arthritis, anxiety, irritable bowel syndrome, nausea, and inappetance; these are conditions for which human patients are also using medical cannabis. Because there is little research in therapeutic uses in small animal medicine, dosing and product selection has been done on an ad hoc basis as requested by owners. Many of the companies providing medical cannabis for veterinary use have developed dosing information and are happy to consult with veterinarians and owners interested in recommending cannabis for their patients and pets. Additionally, the American Holistic Veterinary Medical Association is encouraging research into the safety, dosing, and uses of cannabis in veterinary species. To that end, they conducted an online consumer survey of owners who have used medical cannabis for their pets. According to the survey conducted by researchers at the Colorado State University Veterinary School (published Spring 2016 in the Journal of the American Holistic Veterinary Medical Association), 93% of all respondents favored the use of medical cannabis over some medications. Dog owners reported that medical cannabis helped either a moderate amount or a lot for:

- Pain relief (95%)
- Age-related changes in behavior including sleep/wake cycle disturbances, excessive vocalization and neediness, and some repetitive behaviors (93%)
- Seizures (92%)
- Inflammation (92%)
- Sleep quality (89%)
- Anxiety relief (83%)
- Nausea reduction (82%)
- Muscle spasms (79%)
- Anti-cancer activity (73%)
- GI issues (unspecified) 71%
• Noise phobias (thunderstorms, fireworks) (65%)
• Skin conditions (unspecified) (62%)

Cat owners reported beneficial effects for:

• Pain relief (100%)
• Sleep quality (96%)
• Inflammation (90%)
• Nausea reduction (86%)
• Anti-cancer activity (82%)
• Skin conditions (unspecified) 75%

The most common side effects reported in both dogs and cats were sedation and increased appetite. Most respondents reported they had not spoken with their veterinarian regarding their use of medical cannabis (43%) and that they opted to begin using medical cannabis because they thought it would work as an adjunct to therapies they were already using (50%). 89% of respondents rated medical cannabis as very safe.

In 2018, a double-blind, placebo controlled, double-crossover study (https://www.frontiersin.org/articles/10.3389/fvets.2018.00165/full) was published demonstrating safety and efficacy of a whole-plant, hemp-based CBD product (ElleVet®) for the treatment of canine osteoarthritis. This study demonstrated that a dose of 2 mg/kg of CBD provided pain relief and increased mobility, as shown by force-plate gait analysis tests performed on the study dogs.

Cannabis has been found to be useful in treating pediatric epilepsy in human patients and is beginning to be more widely used in veterinary neurology as well, taking advantage of the ECS’s down-regulatory effect on neurons. Stimulation of CB1 receptors has been found to limit cell death after damage from excitotoxic lesions and CB2 receptors provide immunomodulatory and anti-inflammatory effects by reducing the expression of inflammatory proteins. Cannabidiol (CBD) in particular has been found to provide neuroprotection during acute brain injury and ischemic events.

A double-blind, placebo controlled pilot study published in 2019 in JAVMA (https://avmajournals.avma.org/doi/abs/10.2460/javma.254.11.1301) demonstrated safety and efficacy of CBD in reduction of seizures in canine patients, though the difference between the treatment group and the placebo group was not found to be statistically significant. A full study is still enrolling subjects, and it may show that a higher dose than 2 mg/kg of CBD may be required for better seizure control in dogs.

Determination of the appropriate dose of cannabis for companion animals with different conditions has been challenging, due to the individual nature of the ECS and its response to cannabinoids, from both endogenous and exogenous sources. While we can use the published data as a guideline, most dosing is done on a case-by-case, trial-and-error basis. Because the therapeutic index of cannabis is very large, it is considered safe to experiment with different doses to determine what works best for each animal and each disease process. The recently established certification program for Veterinary Cannabis Counselors provides credentialed veterinary technicians who learn about clinical applications of cannabis in companion animals and can provide cannabis harm reduction education to clients. More information can be found at www.veterinarycannabis.org.

While cannabis therapeutics can be expensive, at least one pet insurance company (Trupanion) promises to cover medical cannabis treatment when it is “recommended” by a veterinarian. However, “recommendation” is challenging in several states, including those where cannabis and its derivatives have been legalized or decriminalized, as some Veterinary Medical Boards have barred veterinarians from even discussing the use of cannabis in their patients, while others are completely silent on the issue (see CURRENT LEGAL STATUS for more information). Those who filed claims for reimbursement with Trupanion (according to a 2015 report) reported using medical cannabis: alongside traditional treatments for cancer; to reduce seizure severity and/or frequency; to treat chronic and neuropathic pain; as an anti-
inflammatory agent; as an anti-emetic agent and appetite stimulant; and as an anxiolytic. The vast majority of Trupanion claims involving cannabis were for reimbursement for treatment of toxic ingestions, to the tune of $78,000 in suspected cannabis intoxication claims, with an average cost of $525 per claim.

CANNABIS INTOXICATION / TOXICITY

The increase in the use and acceptance of both medical and recreational cannabis has resulted in an increase of reported cases of cannabis intoxication seen in companion animals. In the first quarter of 2019, the ASPCA Animal Poison Control Center recorded a 765% increase in cannabis-related calls compared to the same time period the previous year. Pet Poison Helpline (PPH) has reported a 448% increase in calls due to cannabis intoxication between 2012 and 2018, and the actual number of cannabis toxicity cases seen in practice is undoubtedly much higher than that, as many practitioners do not feel the need to consult with a toxicologist to treat cannabis toxicity. 98% of the calls to PPH were in regards to dogs. Trupanion has also seen an increase in claims for treatment of cannabis intoxication since 2013. The top five states in which Trupanion has paid claims are California, Washington, New York, Colorado, and Florida. While cannabis intoxication is an increasingly common presentation to veterinary facilities, mortality associated with the intoxication is very low; the lethal dose in dogs is > 9 g/kg of THC ingested, with the exact dose still unknown. A 2012 study in the Journal of the Veterinary Emergency and Critical Care (JVECC) reported two deaths in a group of 125 dogs treated for cannabis intoxication in two facilities in Colorado, but the deaths could not be attributed to cannabis due to confounding from coingestions. With newer, more concentrated forms of cannabis reaching the market (i.e. vape cartridges, shatter, wax), it is reasonable to expect more severe intoxications to present at veterinary facilities.

Dribbling urine is perhaps the cardinal clinical sign that veterinary team members think of when they think of cannabis intoxication. However, the 2012 JVECC article referenced above found ataxia to be the predominant clinical sign in dogs, with 88% of cannabis intoxicated dogs presenting with ataxia. Only 47% of dogs in the study exhibited urinary incontinence. Other clinical signs included disorientation (53%), mydriasis (48%), hyperesthesia (47%), tremors or twitching (30%), and vomiting (27%). More than half the dogs (58%) were treated on an outpatient basis, showing that few patients require hospitalization for this toxicity.

Treating cannabis intoxication is made difficult by coingestions of substances that are toxic to dogs including chocolate, xylitol, macadamia nuts, or other drugs. If treating only cannabis ingestion or exposure, providing supportive care is the mainstay of treatment including fluid therapy for blood pressure support (if needed), monitoring of respiratory rate and other vital signs, and protecting patients from further harm (i.e., aspiration pneumonia if vomiting while somnolent). Activated charcoal may be used within four to six hours of ingestion and benzodiazepines are indicated if a patient is tachycardic or shows signs of excessive CNS stimulation. Intralipid emulsion (ILE) therapy has been used to treat cannabis intoxication, due to the very high lipophilicity of cannabis, but it is rarely indicated. Because the FDA does not have the power to regulate cannabis products, there may be issues of cross-contamination with pesticides, insecticides, fungicides, or fertilizers used in the cultivation of the plant, or mycotoxins present due to poor product handling and storage after harvest. When the plant is concentrated during distillation or extraction (i.e., into tinctures, butters, hashish, shatter, or other concentrated forms), these substances will also be concentrated and may exert a toxic effect. Unfortunately, it is virtually impossible to know what may be present in the ingestion.

CURRENT LEGAL STATUS (JUNE 2019)

In most jurisdictions where cannabis is legal for medicinal use, veterinarians have been excluded from the right to recommend it for their patients. Because cannabis is still classified by the DEA as a Schedule I substance, it cannot be prescribed by any practitioner – human or veterinary. In California, the Veterinary Medical Board has provided guidance advising veterinarians against recommending cannabis for their patients, and against selling hemp-based products directly from their clinic. A bill (AB 2215) passed the California legislature in 2018 that gives veterinarians the ability to discuss cannabis as a treatment for their patients; a similar bill is currently pending in New York (S8772/AB10104). While AB2215 gave California
veterinarians the ability to discuss cannabis use in their patients, it does not allow them to recommend cannabis as a therapeutic. A new bill (SB67) is pending to remedy this situation.

Most recently, the 2018 Farm Bill, which includes the 2018 Hemp Farming Act, was passed and signed into law. This Act, sponsored by Senator Mitch McConnell (R-Kentucky), fully legalized hemp (defined as *Cannabis* plants containing less than 0.3% THC) and all its derivatives. In addition, the FDA has just approved a CBD medication derived from hemp for the treatment of severe childhood seizure disorders (Epidiolex®). This approval further confuses the current legal status of CBD. The FDA has just held public hearings regarding the regulation of hemp-derived CBD products, but there is no news on the DEA’s classification of *Cannabis*. Legal experts expect to see a re-scheduling of CBD derived from hemp and/or marijuana soon.

**CONCLUSION**

While many veterinary practitioners want to see more evidence as to the efficacy of cannabis products as therapeutics, our clients are already using these substances for many different conditions in their animal companions. It behooves us as veterinary professionals to help our clients make safe choices for their pets and to educate ourselves on the potential uses of this powerful plant.

**REFERENCES**

*Available on request.*