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Medical Marijuana - What Every Veterinarian Needs to Know

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Background Information

Cannabis sativa L., more popularly known as: marijuana, Mary Jane, pot, weed, ganja, bhang, reefer, dope, grass, *Cannabis*, etc. has been a part of human history since before the written word. Archeological and anthropological evidence supports the fact that *Cannabis* was cultivated by humans since the beginnings of agriculture more than 10,000 years ago. During the Neolithic period ancient peoples used every part of the plant: the stems and stalks for fiber for cordage and cloth; the seeds which are high in protein and omega 3 fatty acids, for nourishment, and the roots, leaves and flowers for medicinal and ritual applications.

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

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

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

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

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

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

Useful and accurate websites to check for this information include:

1. **NORML**:
   http://norml.org/states (http://norml.org/states)
2. **PRO-CON**:
   http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881
   (http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881)
3. **GOVERNING**:
   www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html
   (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 "bipartisan" legislation pending in congress to reschedule *Cannabis* to a more "legal" DEA scheduling such as Schedule II or hopefully, lower schedules such as III or IV. Recently a federal judge ruled against a civil suit to reschedule *Cannabis*, saying that it was up to a higher court or congress to change the law. Things are moving forward, (although too slowly for many who have urgent medical needs for this emerging therapy) with regards to a more consistent federal legal stance relative to individual states' legislation allowing the legal medical or recreational use of *Cannabis*.

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

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

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

Table 1. Major and minor cannabinoids

Δ-9-tetrahydrocannabinol (Δ-9 THC)	Analgesic (reduces pain), antiinflammatory, antioxidant, bronchodilatory, improves symptoms of Alzheimer's disease, benefit duodenal ulcers, muscle relaxant, anti-itch, cholestatic jaundice.
Δ-9 tetrahydrocannabinolic acid (Δ-9 THCA)	THCA is the acidic or carboxylated form of THC. It is the predominant cannabinoid in psychoactive strains. It is non-psychotropic until activated or decarboxylated, smoked or cooked at temperatures greater than 245°F. Also has medicinal benefits, similar but also separate and different than THC.
Δ-9 tetrahydrocannabivarin (Δ-9 THCV)	Antiinflammatory, anticonvulsant, analgesic properties, antioxidant, neuroprotective in model of Parkinson's in one study, improved glucose tolerance and insulin sensitivity *in vivo*
Δ-8 tetrahydrocannabinol (Δ-8 THC)	Stable in air, much less psychotropic than Δ-9 THC; at low doses, Δ-8 THC (0.001 mg/kg PO was found to induce appetite stimulation without psychotropic effects.)
Δ-8 tetrahydrocannabinolic acid (Δ-8 THCA)	The carboxylated (acidic) form of Δ-8 THC.
Cannabidiol (CBD)	Antianxiety, anticonvulsant, Parkinson's disease, Huntington's disease, psychosis, MS, Alzheimer's, cytotoxic for breast cancer, effective against MRSA, reduces oily skin, treatment of addiction.
Cannabidiolic acid (CBDA)	Acidic form of CBD, carboxylated form of CBD. Has medicinal properties but not well studied at this point in time.
Cannabichromene (CBC)	Antiinflammatory, analgesic, antifungal, antidepressant, Anandamide reuptake inhibitor.
Cannabigerol (CBG)	Antifungal, GABA uptake inhibitor (calming), antidepressant, analgesic, antiinflammatory, reduces scales in psoriasis, effective against MRSA.
Cannabidivarin (CBDV)	Anticonvulsant
Cannabinol (CBN)	Sedative, effective versus MERSA, helps with burns, reduces scales in psoriasis, helps with breast cancer. May be a degradation product of THC or CBD.

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

The US FDA considers terpenes and terpenoids to be generally recognized as safe (GRAS), as they are flavor and fragrance components common to human and pet diets. Cannabinoids, terpenes and terpenoids are all produced in the same glandular structure on the *Cannabis* plant, the trichome, from the same chemical precursor, geranyl pyrophosphate. Hops (*Humulus lupus*) is a member of the same Cannabaceae family as *Cannabis*, and they share many of the same terpenes and terpenoids such as β-myrcene, β-pinone, humulone, and β-caryophyllene. Cannabinoids are virtually odorless, emitting only a slight pitch-pine scent.

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

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

The Endocannabinoid System and Cannabinoid Receptors

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

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

The CB1 Receptor

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

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

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

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

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

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

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

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

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

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

Cannabis Research in Dogs

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

Tolerance to the "behavioral" effects of THC in the dog developed after daily injections were given. McMillan found that a dose of 2 mg/kg IV produced marked static ataxia, evidenced by "swaying movements, hypersensitivity to moving objects and a prance-like foot placement." However, some dogs in this study group developed tolerance rapidly after the first administration of 2 mg/kg of THC. Subsequent injections continued to increase the degree of tolerance to THC in this study group. The magnitude of tolerance developed in these canine studies was in excess of 100 fold.[9]

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

CB2 Receptors

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

Non-CB Receptor-Dependent Activity

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

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

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

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

Potential Clinical Applications for *Cannabis* (Boothe 2015)

1. Pain, inflammation and immunomodulation:

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

2. Epilepsy:
   a. CBD attenuates seizures in experimental models of epilepsy in animals.
   b. THCV inhibits CB1 receptor activity resulting some anticonvulsant activity.
3. Anxiolytic:
   a. CBD exerts benzodiazepam-independent activity, postulated to be via post-synaptic 5-HT1A receptors.
4. Neuroprotection:
   a. CBD acts as an antioxidant and as such has been suggested for Alzheimer's, Parkinson's and Huntington's diseases.
5. Antiemesis:
   a. CBD in animal models has been found to be effective for the control of vomiting that is unresponsive to 5-HT-3 agonists such as metoclopramide or ondansetron.
6. Diabetes mellitus:
   a. CBD inhibits development of diabetes in experimental models of diabetes in mice. Reduction of pancreatic inflammation and antioxidant effects are credited with this benefit.
7. Bone formation:
   a. Cannabinoids stimulate the stem cells responsible for fracture healing and bone formation, as well as reducing bone loss by controlling bone reabsorption.
8. Cancer:
   a. Many of the cannabinoids have antiapoptotic effects and reduce neoplastic proliferation in selected tumor cell lines.
   b. Anecdotal reports from both human and veterinary patients indicate the potential for complete remission and possibly even cure of a number of different neoplastic diseases.
9. Antimicrobial:
   a. Both CBC and CBG have potent antibacterial effects including against MERSA (MIC of 0.5–2 mcg/ml).

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

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

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

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

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

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

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Speaker Information

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Cannabis and Cancer

Wild West Veterinary Conference 2016
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Objectives

1. Provide scientific evidence that cannabinoids have an anti-neoplastic effect.
2. Explain what has been determined scientifically to be the anti-neoplastic effects of cannabis.
3. Discuss other benefits of cannabis to the cancer patient.
4. Describe how to use cannabis to improve a cancer patient's outcome.

Introduction

In 1974, researchers at the Medical College of Virginia, funded by the NIH to find evidence that marijuana damages the immune system, instead discovered that THC slowed the growth of three different types of cancer in mice: Lung, breast, and viral leukemia.[1] This first-ever *in vivo* study found that THC slowed the growth of lung cancers, breast cancers and virus-induced leukemia in mice, as well as increasing survival times by 36%. This study was suppressed by the DEA. In 1976 President Gerald Ford put an end to all public cannabis research, giving exclusive rights to the major pharmaceutical companies to develop synthetic forms of THC.

In 1983 the Reagan/Bush administration tried to get American universities to destroy all 1966–1976 cannabis research work, including compendiums in libraries, and large amounts of information have since disappeared, according to Jack Herer in his book, "The Emperor Wears No Clothes."[2]

It took nearly 30 years before the next *in vivo* study documented the benefit of cannabis for cancer. This study experimentally-induced brain cancer in 45 rats. Tumor growth was confirmed with MRIs. Three cohorts of 15 subjects each were created. One group received no treatment and were the controls. A second group of 15 received THC by injection. The third group of 15 were injected with a synthetic THC compound (Win-55,212-2). THC or synthetic THC were administered after 15 days of tumor growth.

Untreated rats died within 12–18 days after glioma cell inoculation. THC-treated rats survived significantly longer than the control group. Three rats in this group died by days 16–19. Nine of the THC-treated rats survived up to 19–35 days. The tumor was eradicated in 3 of the treated rats. Similar results were seen with the synthetic THC molecule.

The authors remark in the study: "...MRI analysis of ...tumor-free rats showed no sign of damage related to necrosis, edema, infection, or trauma...We also examined other potential side effects of cannabinoid administration. In both tumor-free and tumor-bearing rats, cannabinoid administration induced no substantial change in behavioral parameters such as motor coordination or physical activity. Food and water intake were unaffected during and after cannabinoid delivery... General hematological profiles of cannabinoid-treated rats were normal."[3]

Mechanisms of Anti-Neoplastic Effects of Cannabinoids

The Endocannabinoid System and Cancer

Our understanding of how the endocannabinoid system plays a role in cancer pathophysiology is still under development. From existing studies, there are some conflicting data. For instance, we know that cannabinoid receptors and their endogenous ligands (Anandamide and 2-AG) are generally up-regulated in tumor tissue as compared to non-tumor tissue. In fact, some studies have found the expression levels of cannabinoid receptors, endocannabinoids and endocannabinoid-metabolizing enzymes associated with tumor aggressiveness. This implies that the endocannabinoid system may be pro-tumorigenic.

Some studies support this theory. For instance, in mouse models of cancer, the genetic ablation of CB1 and CB2 receptors reduces ultraviolet light-induced skin carcinogenesis. Further, it has been found that CB2 receptor (found mainly in the immune system) over-expression enhances predisposition to leukemia following leukemia virus infection.[4]

On the other many more studies support that the pharmacological activation of cannabinoid receptors reduces tumor growth. Upregulated endocannabinoid-degrading enzymes have been observed in aggressive human tumors and cancer cell lines, indicating that endocannabinoid signaling can also have a tumor suppressive role.

For instance, when CB1 receptors have been deleted in a genetic mouse model of colon cancer, it was found that tumor growth was increased. Precancerous lesions in the mouse colon, induced by the chemical azoxymethane, could be reduced with increases in endocannabinoid levels. With less expression of an endocannabinoid degrading enzyme monoacylglycerol (its reduction allows prolonged elevated serum levels of endocannabinoids), tumor growth was reduced in xenografted mice.

More studies are needed to further define the precise signaling mechanisms that regulate cannabinoid induced cell death or cell proliferation. This information will help to clarify the role the endocannabinoid system plays in tumorigenesis and tumor suppression.

Cannabinoids and Cancer

That being said, since the late 1990s quite a few studies have shown that the various cannabinoids have an anti-tumor effect in a wide variety of experimental models of cancer. These studies have found that regardless of the role the endocannabinoid system plays in tumor initiation or tumor suppression, that the pharmacological stimulation of CB receptors is mostly anti-tumorigenic.

Multiple cannabinoids have been shown to have this activity, including: THC; The endocannabinoids, 2-AG and anandamide; synthetic cannabinoid receptor (with equal affinity for both CB1 and CB2) agonists such as WIN 55,212-2 and HU-210; (with higher affinity for CB1) agonists such as methanamide; (with higher affinity for CB2) agonists such as JWH-133). From these studies looking at the direct pharmacological effect of the cannabinoid agonists on the course of tumor progression, several anti-neoplastic mechanisms of action have been determined for cannabinoids. These anti-neoplastic actions are in addition to the already well-established anti-inflammatory activity of cannabinoids. Inflammation is considered one of the primary triggers for the induction of neoplasia.

Induction of Cancer Cell Death and Anti-Proliferative Effects

THC and other cannabinoids induce apoptosis through CB1 and CB2 stimulation of the *de novo* synthesis of the pro-apoptotic sphingolipid ceramide. THC acutely upregulates the expression of the stress-regulated protein P8 (AKA NUPR1) which is a transcription regulator and implicated in the control of tumorigenesis and tumor progression, and it does by targeting endoplasmic reticulum (ER) stress-related transcription factors ATF4 and CHOP (AKA DDIT3) and others.

ER stress response is a complex intercellular signaling pathway that becomes activated in response to Ca^{+} depletion, oxidative injury, a high fat diet, hypoglycemia, viral infections and exposure to certain anti-cancer agents. ER stress is designed to lessen the protein load on the ER by shutting down protein translation and gene transcription. This can result in autophagy, which is another cause for cancer cell death in with an entirely different cascade of events as compared to the cascade of events causing apoptosis.

In addition to inducing cancer cell death through autophagy or apoptosis, cannabinoids also have been found to have an anti-proliferative effect by inducing cell cycle arrest. The effect of cannabinoids on hormone-dependent tumors may be due, in part, to their interference with activation of growth factor receptors. L arginine, or CBD, is a cannabinoid that does not bind to CB1 or CB2 receptors yet uses many alternate pathways to influence the endocannabinoid system. CBD has been observed to promote the apoptotic death of cancer cells, independent of CB1 and CB2 receptors. Its mechanism of action, which has not been completely worked out, promotes the production of reactive oxidative species in cancer cells.

Inhibition of Angiogenesis, Tissue Invasion, and Metastasis

Cannabinoids block the activation of the vascular endothelial growth factor (VEGF) pathway, which is known to induce angiogenesis. It has been found that cannabinoids down regulate the VEGFR (receptor) pathway by reducing production of VEGF via pharmacological blockade of ceramide biosynthesis. Through this mechanism VEGFR activation is decreased due to the reduced amount of its ligand, VEGF that is available to bind to VEGFR and activate it through the VEGF/VEGFR signaling cascade. Activation of the CB receptors in vascular endothelial tissue inhibits proliferation and migration, and induces apoptosis. Thus, cannabinoid activity results in a more normalized tumor vasculature with smaller and/or fewer vessels that are less "leaky", therefore less likely to result in metastasis.

Cannabinoids have been found to reduce the formation of distant tumor masses, and inhibit adhesion, migration, and the invasiveness of glioma, breast, lung, and cervical cancers grown in tissue culture. Cannabinoids modulate extracellular proteases (MMP2) and their inhibitors (TIMP1).

Additionally, it has been found that although cannabinoids have a potent effect on most neoplastic tissue, normal cells are unaffected, and in some cases, even favored by the cannabinoid therapeutics.

Clinical Use of Cannabinoids in Cancer Patients

Treatment of immunocompetent rats for 2 years with high doses of THC (50 mg/kg/d) decreased the incidence of several types of tumors and increased the overall survival of these laboratory animals.

In a pilot phase one clinical study, 9 patients with actively growing recurrent glioblastoma and had previously failed standard therapy underwent intracranial THC administration. In this study, several patients responded to the cannabinoids with decreased tumor growth rate as evaluated by MRI imaging. Additionally, it was determined from two of these patients that the molecular mechanism of cannabinoid anti-tumor activity involves *in vivo*, the same mechanisms as determined *in vitro*. (P8 upregulation, stimulation of autophagy and apoptosis, inhibition of cell proliferation, decreased VEGF signaling, and MMP2 down-regulation.

The most effective approach to the use of cannabinoids in the cancer patient involves the combination of THC with CBD, usually in a 1:1 ratio. This combination enhances anticancer activity compared with THC alone and helps to reduce the dose of THC that is needed to inhibit tumor growth. The use of CBD also reduces the unwanted side-effects of THC, such as convulsions, discoordination, and psychotic effects, and in the dog, static ataxia.

Several studies have found that the use of cannabinoids concurrently with two chemotherapeutic agents will enhance their cytotoxicity. Temozolomide combined with cannabinoids exerts a strong anti-tumor effect on glioma xenografts in mice, with no observed toxicity in these mice. Gemcitabine combined with cannabinoids synergistically reduces the viability of pancreatic cancer cells. Anandamide (an endocannabinoid) and HU-210 (a synthetic CB1 and CB2 agonists have been found to enhance the anticancer activity of paclitaxel and 5-fluoracil respectively.

Use of Cannabinoids in the Veterinary Cancer Patient

For the veterinary cancer patient, legal constraints to the use of THC must be accounted for in a reasonable and safe fashion. Veterinarians cannot prescribe or dispense THC. However, pet owners will come to a veterinarian asking for help using cannabinoids to treat their pet's cancer. The veterinarian should explain the risks and the problems with the current legal landscape. The vet should explain that they cannot legally recommend or prescribe these schedule one controlled substances. If the owner persists, then the veterinarian can give advice that will help to create a successful outcome free of unwanted side effects.

In terms of the type of cannabis to use, it is recommended to use cannabis that has a nearly equal ratio of THC to CBD. Initially the client should be instructed to dose based on the THC content, using guidelines previously described by this author, so as to prevent adverse side-effects to the THC, and so as to induce tolerance over a week. At that point in time, the pet owner should be informed to gradually escalate the dosage each week to the point just before their pet becomes "loopy", which is a subjective perception that the THC is having a psychotropic effect on their pet.

There has been a lot written about Rick Simpson oil, or Phoenix tears which is a distilled extract of cannabinoids in a resin form. This oil is in use by many cancer patients with a good deal of success. It is very concentrated, and thus quite strong. Dosing is usually recommended as being the size of a grain of rice or two, but in general is not specifically laid out based on milligrams of formula and body weight of the patient.

The oil itself though is not necessary for cannabis to have an anti-neoplastic effect. The cannabinoids can be extracted through the use of coconut oil or alcohol very efficiently without distillation. The efficacy of the cannabinoids is due to their being present in the extract in adequate amounts, not on the actual type of extract. Even loose herb in capsules can be effective as an anti-neoplastic agent as long as the patient gets enough THC and CBDs, as well as the minor cannabinoids and the terpenes.

In summary, there is sufficient evidence to support the use of cannabinoids for veterinary patients with cancer in general, although specific tumor types may be more or less resistant to their beneficial effects. The biggest problem to date is the legal landscape, since cannabinoids have been shown to be quite safe. Cannabinoids can be use concurrently with chemotherapy, since some of their mechanisms of action work well with chemotherapeutics. Inducing tolerance to the adverse effects of THC in the dog, and then gradually escalating the dosage will need to be done prior to dosing specifically for the cancer. Determining the effective dosage for an individual patient and tumor type will improve outcomes, and is work that still needs to be done.

Cannabinoids can induce autophagy, apoptosis, cell cycle arrest, reduce angiogenesis, tissue invasion, and metastasis, without affecting normal cells. This makes the use of cannabinoids for cancer very attractive to both the practitioner and the pet owner.

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Scientific Report

CONSUMERS' PERCEPTIONS OF HEMP PRODUCTS FOR ANIMALS

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ABBREVIATION
CBD — cannabidiol
CBDA — cannabidiolic acid
THC — delta-9 tetrahydrocannabinol
THCA — tetrahydrocannabinolic acid

Abstract

This study was designed to determine which hemp products pet owners are purchasing, reasons for their purchases, and the perceived value of these products on pets' health. An anonymous online survey was given to pet owners who buy products from an online hemp company. Total responses were 632, of which 58.8% indicated they currently use a hemp product for their dog. Most dog owners (77.6%) indicated they use the product for an illness or condition diagnosed by a veterinarian, with the most common conditions including seizures, cancer, anxiety and arthritis. Fewer participants indicated they currently use hemp products for their cat (11.93%), with 81.8% indicating they use the product for a veterinarian-diagnosed illness or condition, most commonly cancer, anxiety and arthritis. The results of this study provide support for the growing number of anecdotal stories and offer guidance to researchers seeking to perform clinical studies on hemp in terms of its putative effectiveness and possible adverse outcomes. The information from this survey can serve as the basis for controlled clinical trials in areas including pain management, behavioral interventions for sleep disorders and anxiety for dogs, and pain management, inflammation reduction, and improvement in sleep patterns for cats.

Introduction

The term "cannabis" refers to plants belonging to the genus Cannabis as well as those products designed for therapeutic applications (1). Cannabinoids can be administered in a variety of methods including orally, sublingually, or topically and either extracted naturally from the plant or manufactured synthetically (2).

Both hemp and marijuana originate from the *Cannabis sativa* plant. As such, both contain an array of plant-based chemicals called "cannabinoids," including the 2 main cannabinoids, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). THCA, when dried or heated, converts to the psychoactive cannabinoid, delta-9 tetrahydrocannabinol (THC). Similarly, decarboxylation of CBDA yields cannabidiol (CBD). The main differences between hemp and marijuana are the ratio of THC to CBD, the amount of fiber in the stalks, and the production of seeds for oil (3). By definition, "industrial hemp," the hemp of commerce which can be used for medicinal purposes, food, or fiber content, contains high levels of CBD and less than 0.3% THC on a dry matter basis. By comparison, tests of some modern strains of marijuana reveal levels of THC greater than 20% and much

lower levels of CBD (4). While many people differentiate THC as "psychoactive" and CBD as "non-psychoactive," CBD does affect the nervous system; however, it does not cause the typical "high" associated with THC (5).

Some countries have legalized medicinal-grade cannabis. In the United States, 23 states and Washington, DC have introduced laws to permit the medical use of cannabis (6). A recent meta-analysis that included 79 randomized human clinical trials (6462 participants) found moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity; and low-quality evidence suggesting that cannabinoids are associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome (1). When assessing adverse effects, cannabinoids were associated with an increased risk of short-term adverse effects including asthenia, balance problems, confusion, dizziness, disorientation, diarrhea, euphoria, drowsiness, dry mouth, fatigue, hallucination, nausea, somnolence, and vomiting (1, 7). Additionally, The National Institutes of Health, as of 2015, has updated its website (http://www.drugabuse.gov/publications/drugfacts/marijuana-medicine) to include information about the positive effects of cannabis on cancer, reporting, among other benefits, that it has been found to kill cancer cells without harming healthy cells (7).

In the United States, cannabis is a controlled substance and has been classified as a Schedule I agent (a drug with increased potential for abuse and no known medical use) by federal law. This makes the use, sale, and possession of cannabis (marijuana) illegal. Its status as a Schedule I drug has imposed strict limitations on clinical research, severely hampering the ability of clinicians to inform patients and clients about its benefits and risks from an evidence-informed perspective. This has resulted in patients having to adopt a trial-and-error method to determine which, if any, cannabinoids can help alleviate their symptoms or benefit their conditions. It is for these reasons that numerous physician and health care organizations, including the American Medical Association, American Public Health Association, and National Association for Public Health Policy, are urging the federal government to reschedule marijuana, thereby easing research restrictions, to permit more cannabinoid-based research (8, 9).

In addition to a lack of research, the field also suffers from a lack of oversight and control. For both medical and recreational use, a "buyer beware market" currently exists for cannabis products. As the use of cannabis has expanded, a variety of edible products for oral consumption has been developed with current estimates noting that 16%–26% of patients using medical cannabis consume edible products (10, 11). Even though oral consumption eliminates the harmful by-products of smoking, lack of adequate control over dose titration can result in overdosing or underdosing, highlighting the importance of accurate product labeling (12).

Independent analyses have found that medicinal marijuana food products designated for human consumption, such as candies, brownies and teas, often are not labeled correctly. One study, for example, evaluated the contents of 75 products from 47 different brands purchased at marijuana dispensaries in San Francisco, Los Angeles, and Seattle, for their content of THC and cannabinoids. Their analysis uncovered widespread discrepancy between the actual amount of THC and cannabinoids from what was printed on the products' labels. Among the products analyzed, only 17% were accurately labeled; 23% of the products contained more of these compounds than listed; and 60% contained less than stated (12).

A growing number of states has gone beyond legalizing medical cannabis and made recreational cannabis legal as well. Colorado, Washington, Oregon, Alaska, and the District of Columbia all have legalized medical cannabis; and another 11 states, all of which have decriminalized possession of small amounts of marijuana, are expected to approve similar ballot initiatives between now and mid-November of 2016 (13). Perhaps tellingly, the market for legal cannabis has been identified as one of the fastest-growing industries in the United States, with a market growth of 74% in 2014, to $2.7 billion, up from $1.5 billion, in 2013 (14).

Given the expanding interest in both medical and recreational cannabis, it is perhaps unsurprising that this interest has expanded to include consideration of its potential benefits for companion animals (15). Biscuits, edibles, and capsules containing non-psychoactive cannabinoid compounds (e.g., CBD) have become available and are being marketed to pet owners with several companies in California, Oregon, and Washington rising to fill this need (16–19). Anecdotal reports from pet owners indicate that some find cannabis products helpful for pain, arthritis, seizures, anxiety, and inappetence in both dogs and cats.

Another study summarized by the AVMA reported that pet owners are using cannabis to treat behavior-based disorders such as separation anxiety and noise phobia, in addition to problems affecting the body and mind such as irritable bowel syndrome, and management of pain, nausea, and seizures (20). Many caregivers report positive outcomes. Consequently, interest in cannabis as a therapeutic agent for animals is spreading, and veterinarians are fielding more requests from their clients about whether cannabis might help their pets (8, 21).

However, just as in human medicine, there is little research-based information available to provide analysis and guidance about the use of medical cannabis for animals. Restrictions on cannabis research for veterinary patients have, until recently, imposed nearly insurmountable barriers on clinical investigations of the medical applications of hemp and medical marijuana. Lacking rigorous scientific evidence, veterinarians cannot determine safe dosages and THC/CBD ratios of medical marijuana for dogs, cats, and other animals. As is true for physicians, veterinarians are left relying on anecdotal reports, trial and error reports from clients, and companies' claims (22).

The few studies that have been published on cannabis in non-humans have mainly focused on toxicity (23, 24). Marijuana exposure in pets, as reported to the American Society for the Prevention of Cruelty to Animal's Poison Control Hotline, is becoming more frequent. Since 2009, calls reporting marijuana exposure have risen by 50%. It is unknown if this increase is truly due to an increase in the number of animals that are exposed to marijuana or because of the recent legalization of medical marijuana in many states, making people more likely to admit that their animal has ingested a marijuana product. Most reported cases of cannabis poisoning in pets are from the ingestion of marijuana edibles (e.g., brownies, cookies, etc.) that contain THC (25).

In response to the burgeoning interest of medical cannabis for animals, the American Veterinary Medical Association, while not yet articulating an official position on the issue, has instead urged veterinarians to make treatment decisions using sound clinical judgment and current medical information in compliance with federal, state, and local laws and regulations (20). The American Holistic Veterinary Medical Association is currently the only veterinary organization that officially encourages researching the safety, dosing, and uses of cannabis in animals (26). In response to the present lack of scientific research and regulation oversight, most veterinarians suggest that pet owners use caution when giving any cannabis product.

In addition to the paucity of reliable information on the safety, dosage, and effectiveness of cannabis, there is the ambiguity as to its legal status. While there are no Federal Drug Administration approved marijuana products for use in animals, the legality surrounding the recommendation by veterinarians of hemp products for medicinal use in animals can be confusing. While some people cite The United States Court of Appeal for the Ninth Circuit in *Hemp Industries Assn., v. Drug Enforcement Admin.*, 357 F.3d 1012 (9th Cir. 2004), that recognized that "non-psychoactive hemp [that] is derived from the 'mature stalks' or is 'oil and cake made from the seeds' of the Cannabis plant, ...fits within the plainly stated exception to the CSA definition of marijuana" as rationale that hemp is legal, others point to state statutes that govern industrial hemp to argue that the legal status depends on individual state's laws (27). Therefore, it is suggested that veterinarians and pet owners should check with their individual state to determine if they are able to prescribe or purchase hemp for their patients and pets (22). That said, however, with respect to hemp products, the Farm Bill of 2013, signed into law in 2014, does make allowances for academic research on industrial hemp if state statutes also allow for such research to occur. Colorado is 1 state that has passed statutes allowing for hemp research under particular conditions and restrictions.

This study was designed to survey consumers who have experience with hemp use for their pets. The findings should 1) assist academic researchers in determining which conditions have raised the most interest for therapeutic hemp among consumers and 2) identify promising directions for clinical research. The study explores which products (e.g., capsules, liquid, chews, etc.) pet owners are purchasing, reasons for their purchases, and their perceived value of these products on their pets' health.

Materials and Methods

An online anonymous survey (a) was made available from January 25, 2015, to February 25, 2015, via a link on a commercial website for a company that specializes in hemp products for animals. The survey was originally piloted by faculty at Colorado State University for assessment of

ambiguity, and/or potentially missing or inappropriate response options. Descriptive statistics and frequency distribution (reported in percentages) were performed using commercially available software (b). Because not all questions were answered by all participants, the totals for each question vary. Reported percentages for each individual question are based on total responses for that question. It should be noted that the data were collected from visitors to 1 animal hemp product company and therefore, due to potential biases, care should be taken before generalizing the results to other hemp products.

Results

A total of 632 people responded. Out of those who reported gender (n=495), 83.2% indicated they were female, and the majority of participants were between 51-60 years of age. Only 74 (14.8%) were 35 years of age or younger. When asked about education (n=495), most reported having some college (176, 35.56%) or a 4-year degree (25.66%). When asked to report what state they live in, the largest percentages were California (109, 21.8%), and Washington (59, 11.8%). The survey questions asked pet owners if they had used specific hemp products for either their dog(s) or cat(s). If they responded that they had used hemp products, they were asked several questions about their product choices and their perception of the effects that the product had on their pet. Questions pertained to the amount of time they had been giving the product, reasons for discontinuation of the product (if applicable), reasons they chose the product, and their perception of the product's impact on specific health issues. Additional questions asked how they had heard about the product, how their veterinarian responded (if told) to the fact that they were using hemp for their animal, and consumers' views about the product's safety as well as its comparison to other forms of treatment.

Usage for Dogs

Out of 631 respondents answering this question, 371 (58.8%) indicated they currently use a hemp product for their dog; 86 (13.6%) indicated they did use, but no longer use, a product; 104 (16.5%) have a dog but have not tried a product; and 70 (11.1%) indicated they do not have a dog (**Table 1**). For those who answered why they had discontinued usage (n=88), 18 (20.45%) reported it was because the product was too expensive; 15 (17.05%) reported it was not effective; and 4 (4.55%) said it was due to negative side effects. The remaining 59 (67.1%) replied "other." The "other" responses were predominately related to the death of the animal or the fact that the medical issue had been resolved. Most people (77.6% of 313 responses) indicated they use the product for an illness or condition diagnosed by a veterinarian with the most common conditions including seizures, cancer, anxiety and arthritis.

Table 1: Usage of product for dogs (n=631)
Out of 631 survey respondents answering this question, the percent and number of respondents choosing a specific answer are indicated.

Yes, currently using	58.8% 371
Yes, but not using any longer	13.6% 86
No, I have a dog, but have not tried any dog canna-pet products	16.5% 104
I don't have a dog	11.1% 70

Usage for Cats

The number of people (from 570 respondents) who indicated they currently use a hemp product for their cat was 68 (11.93%); 36 (6.32%) reported they used it in the past; 154 (27.02%) reported having a cat but have not tried any cat hemp products; and 312 (54.74%) indicated they do not have a cat (**Table 2**). For those who answered why they had discontinued usage (n=36), 4 (11.11%) reported it was because the product was too expensive; 7 (19.44%) reported it was not effective; and none reported negative side effects. The remaining 25 (69.4%) replied "other." Most of the "other" responses were due to the death of the cat or an inability to administer the medication. When asked if they were using the product for an illness or condition diagnosed by a veterinarian, most people (81.8% of 55 responses) indicated that they were, with the most common conditions reported being cancer, anxiety, and arthritis.

Table 2: Usage of product for cats (n=570)
Out of 570 survey respondents answering this question, the percent and number of respondents choosing a specific answer are indicated.

Yes, currently using	11.93% 68
Yes, but not using any longer	6.32% 36
No, I have a cat, but have not tried any cat canna-pet products	27.02% 154
I don't have a cat	54.74% 312

Perceived Impact of Product

Participants were asked to indicate how helpful the products they had been giving their dog were in relieving a multitude of signs and ailments (**Table 3**). Dog owners reported that the hemp products were moderately or very helpful in numerous areas. The areas felt to be positively impacted by the products were relief from pain (reported by 64.3% as helping moderately or a great deal); helping with sleep (reported by 50.5% as helping moderately or a great deal); and relieving anxiety (reported by 49.3% as helping moderately or a great deal). When queried about side effects, those reported most frequently included sedation (with a moderate or significant effect reported by 22.0%) and over-active appetite (reported as having moderate or significant effect by 15.9%) (**Table 4**).

Table 3: Perceived Impact of Product on Symptom Reduction in Dog(s).

The percentage and number of respondents who answered this question by indicating the type of response observed in their dog after using a hemp product

Perceived Product Impact on Survey Respondents	Did not help at all	Helped a little	Helped moderate amount	Helped a great deal	N/A or don't know	n = number of respondents selecting impact statement
Provided pain relief	1.35% 4	2.02% 6	25.93% 77	38.38% 114	33.00% 98	299
Aided with sleep	2.47% 7	3.89% 11	18.73% 53	31.80% 90	43.11% 122	283
Helped relieve anxiety	3.55% 10	6.38% 18	21.28% 60	28.01% 79	40.78% 115	282
Provided nervous system support	1.41% 4	1.77% 5	14.84% 42	26.15% 74	55.83% 158	283
Reduced inflammation	1.85% 5	1.85% 5	17.34% 47	24.72% 67	54.24% 147	271
Reduced seizures or convulsions	1.44% 4	1.08% 3	10.11% 28	19.13% 53	68.59% 190	278
Reduced vomiting and nausea	2.59% 7	1.48% 4	4.81% 13	14.07% 38	77.78% 210	272
Helped suppress muscle spasms	2.27% 6	2.27% 6	4.92% 13	11.74% 31	79.17% 209	265
Helped with digestive tract problems	2.65% 7	4.55% 12	5.68% 15	11.74% 31	75.38% 199	264
Helped with thunderstorm or fireworks phobia	3.00% 8	4.12% 11	5.99% 16	7.12% 19	80.52% 215	269
Inhibited cell growth in tumors/cancer cells	2.60% 7	1.12% 3	4.46% 12	5.58% 15	86.62% 233	270
Helped with skin conditions	3.77% 10	4.15% 11	7.17% 19	5.66% 15	79.25% 210	265
Killed or slowed bacteria growth	2.97% 8	1.49% 4	1.49% 4	1.86% 5	92.57% 249	270
Helped with fungal infection	2.63% 7	1.50% 4	0.38% 1	1.50% 4	94.36% 251	267
Reduced risk of artery blockage	1.53% 4	–	0.76% 2	1.53% 4	96.56% 253	263
Reduced blood sugar levels	1.50% 4	–	–	–	98.50% 263	267
Promoted bone growth	1.15% 3	–	–	–	98.85% 257	260

Table 4: Perceived Side-effects of Product on Dog(s).

The percentage and number of respondents who answered this question by indicating the type of side-effect observed in their dog after using a hemp product

Perceived Product Side-effects on Survey Respondents	No Affect	Minimal Effect	Moderate Effect	Significant effect	N/A or don't know	n = number of respondents selecting impact statement
Over-active appetite	42.03% 124	15.59% 46	10.85% 32	5.08% 15	27.46% 81	298
Lack of energy	46.42% 136	16.72% 49	6.83% 20	4.10% 12	26.62% 78	295
Panic reactions	50.17% 147	3.41% 10	7.17% 21	4.10% 12	35.15% 103	293
Panic reactions	39.12% 115	13.61% 40	5.10% 15	2.72% 8	39.80% 117	295
Dry mouth, excessive drinking	34.67% 104	24.67% 74	19.67% 59	2.33% 7	20.00% 60	304
Sedation	1.44% 4	1.08% 3	10.11% 28	19.13% 53	68.59% 190	278
Nausea	51.03% 149	2.74% 8	3.08% 9	1.71% 5	41.78% 122	293
Vomiting	53.24% 156	3.07% 9	2.05% 6	1.71% 5	40.27% 118	294
Increase seizures	55.52% 161	1.72% 5	1.03% 3	0.69% 2	41.38% 120	291
Impaired mental functioning	51.03% 149	3.77% 11	2.05% 6	0.68% 2	42.81% 125	293
Dry or red eyes	51.37% 150	3.08% 9	1.37% 4	0.34% 1	44.18% 129	293
Dizziness	48.79% 141	3.46% 10	1.04% 3	0.35% 1	46.71% 135	290
Rapid heartbeat	43.64% 127	2.75% 8	1.03% 3	–	52.92% 154	292
High blood pressure	38.97% 113	1.03% 3	–	–	60.00% 174	290

For cats, the areas felt to be positively impacted by the products were relief from pain (reported by 66.0% as helping moderately or a great deal); reduction of inflammation (reported by 56.3% as helping moderately or a great deal); and help with sleep (reported by 44.0% as helping moderately or a great deal) (**Table 5**). When asked to report on side-effects, the ones reported most frequently were sedation (with a moderate or significant effect reported by 19.2%) and over-active appetite (reported as having moderate or significant effect by 16.0%) (**Table 6**).

How Purchasers Learned of Products

When asked how they learned about hemp products (n=557), most reported hearing about them from the Internet (284, 50.99%), followed by a friend (90, 16.16%) or their veterinarian (80, 14.36%). When respondents were

Table 5: Perceived Impact of Product on Symptom Reduction in Cat(s)

The percentage and number of respondents who answered the question by indicating the type of response they experienced in cat after using hemp product

Provided pain relief	—	—	32.08% 17	33.96% 18	35.85% 19	54
Provided nervous system support	—	—	10.00% 5	16.00% 8	74.00% 37	50
Killed or slowed bacteria growth	—	2.00% 1	4.00% 2	2.00% 1	92.00% 46	50
Reduced blood sugar levels	—	—	6.00% 3	—	94.00% 47	50
Reduced vomiting and nausea	—	5.77% 3	13.46% 7	21.15% 11	59.62% 31	52
Helped with fungal infection	—	—	2.08% 1	2.08% 1	95.83% 46	48
Reduced seizures or convulsions	2.00% 1	—	2.00% 1	4.00% 2	92.00% 46	50
Reduced inflammation	—	6.25% 3	27.08% 13	29.17% 14	39.58% 19	49
Aided with sleep	2.00% 1	—	18.00% 9	26.00% 13	54.00% 27	50
Reduced risk of artery blockage	—	—	4.26% 2	4.26% 2	91.49% 43	47
Inhibited cell growth in tumors/ cancer cells	2.13% 1	—	4.26% 2	4.26% 2	89.36% 42	47
Helped with skin conditions	—	6.25% 3	10.42% 5	8.33% 4	75.00% 36	48
Helped with thunderstorm or fireworks phobia	—	—	—	2.04% 1	97.96% 48	49
Helped suppress muscle spasms	—	4.08% 2	—	2.04% 1	93.88% 46	49
Helped relieve anxiety	2.04% 1	6.12% 3	18.37% 9	18.37% 9	55.10% 27	49
Helped with digestive tract problems	—	6.12% 3	12.24% 6	14.29% 7	67.35% 33	49
Promoted bone growth	—	—	2.08% 1	—	97.92% 47	48

Table 6: Perceived Side-effects of Product on Cat(s)

The percentage and number of respondents who answered the question by indicating the type of side effects experienced in their cat after using hemp product

Sedation	17.31% 9	32.69% 17	15.38% 8	3.85% 2	30.77% 16	52
Lack of energy	36.73% 18	14.29% 7	10.20% 5	2.04% 1	38.78% 19	50
Over-active appetite	32.00% 16	14.00% 7	16.00% 8	—	38.00% 19	50
Increase seizures	32.65% 16	—	—	—	67.35% 33	49
Rapid heartbeat	26.00% 13	2.00% 1	2.00% 1	—	70.00% 35	50
High blood pressure	20.41% 10	2.04% 1	—	—	77.55% 38	49
Dry mouth, excessive drinking	28.57% 14	14.29% 7	4.08% 2	2.04% 1	51.02% 25	49
Nausea	36.00% 18	6.00% 3	2.00% 1	6.00% 3	50.00% 25	50
Vomiting	40.00% 20	8.00% 4	4.00% 2	6.00% 3	42.00% 21	50
Dry or red eyes	40.82% 20	—	2.04% 1	—	57.14% 28	49
Impaired mental functioning	40.82% 20	4.08% 2	2.04% 1	—	53.06% 26	49
Dizziness	38.78% 19	—	—	2.04% 1	61.22% 30	50
Panic reactions	37.50% 18	6.25% 3	4.17% 2	2.08% 1	52.08% 25	49

asked if they had spoken to their veterinarian about the products (n=558), 274 (49.1%) reported that they had, with most indicating their veterinarian had responded positively (169, 61.7%); only 21 (7.7%) reported their veterinarian had responded negatively; and 84 (30.7%) said their veterinarian did not express an opinion. The number who did not tell their veterinarian was 192 (34.4%), and 47 (8.4%) indicated they had not visited a veterinarian since they began using a hemp product (**Table 7**).

Table 7: Veterinarians' Reactions to Discussion of Product (n=558)
Out of 558 survey respondents answering this question, the percent and number of respondents choosing a specific answer are indicated.

Yes and s/he responded positively about using this product	30.29% 169
Yes and s/he responded negatively about using this product	3.76% 21
Yes and s/he did not express an opinion on using this product for my pet	15.05% 84
No I have not spoken to my veterinarian about using this product	34.41% 192
I have not visited a veterinarian since using this product	8.42% 47
Other	8.06% 45

Product safety

Of the participants who indicated their view about product safety (n=492), 88.8% rated the products as very safe. When asked to compare the products with human hemp-based products (n=500), most (315, 63.00%) indicated they did not know which was safer. The remaining responses, with the exclusion of 2 responses, reported feeling the products were as safe as or safer than human hemp based products. Most respondents felt it was very important to have an independent laboratory analysis conducted to determine the actual content of CBD in each item (394, 78.5%), (n=502). Only 19 (3.8%) of the total 502 respondents reported this was not important.

Product compared to other treatments

When asked to compare the hemp product they used most recently with other forms of animal medication or therapy (n=461), only 34 (7.37%) reported feeling the hemp product did not work as well as other forms of treatment. The number who felt the product worked better than any, most, or some other treatments was 288 (62.48%), and 139 (12.15%) reported the product worked as well as most or some other treatments (**Table 8**).

Table 8: Product Comparison to Other Medications or Therapies (n=461)
Out of 461 survey respondents answering this question, the percent and number of respondents choosing a specific answer are indicated.

This product works better than ANY treatments/medications	19.31% 89
This product works better than MOST other treatments/medications	24.73% 114
This product works better than SOME treatments/medications	18.44% 85
This products works as well as SOME other treatments/medications	20.82% 96
This products works as well as MOST other treatments/medications	9.33% 43
This product does not work as well as MANY other treatments/medications	2.82% 13
This product does not work as well as ANY treatments/medications	2.60% 12
This product does not work as well as MOST other treatments/medications	1.95% 9

Reasons for using product

Lastly, respondents were asked how important several reasons were in their decision to use any hemp products. The most commonly endorsed reasons included liking the idea that the products came from natural sources (rated as moderately or extremely important by 85.1%); thought this product would work as an adjunct to other therapies (rated as moderately or extremely important by 81.1%); the cost of the product (rated as moderately or extremely important by 70.4%); and preferring hemp products to conventional medicine (deemed as moderately or extremely important by 68.8%) (**Table 9**).

Table 9: Reasons for Using Product
The percentage and number of respondents who answered this question by indicating the reason they have used hemp product(s) on their pet.

Reason for Using Hemp Products (Respondents)	Not at all Important (percent, number)	Slightly Important (percent, number)	Moderately Important (percent, number)	Extremely Important (percent, number)	n=number of respondents to each question
I prefer hemp products to conventional medicine	17.31% 85	14.46% 71	30.35% 149	38.49% 189	494
I don't like to support major pharmaceutical companies	33.54% 165	16.46% 81	17.48% 86	32.93% 162	494
I like the idea that this product comes from "natural" sources	7.27% 36	8.08% 40	24.65% 122	60.40% 299	497
The cost of this product is right for me	13.87% 67	16.98% 82	35.61% 172	34.78% 168	489
I thought this product would work as an adjunct to other therapies	11.07% 54	7.99% 39	31.15% 152	50.00% 244	489

Discussion

This is the first study of its kind to systematically investigate the reasons why an increasing number of owners use hemp for their small animals. This study analyzed the feedback of customers from 1 company that specifically produces hemp-based products for animals (28).

The results from this study provide information about why pet owners purchase hemp products and their impressions of the results they have seen. The majority of survey respondents indicated they currently use a hemp product for their dogs, with far fewer reporting they purchased the products for their cats. Dog owners reported that the hemp products were moderately or very helpful in numerous areas. The reported positive impact was highest for relief from pain (64.3%), followed by helping with sleep (reported by 50.5%), and relief from anxiety (49.3%). The most frequently reported side effects were sedation (22.0%) and over-active appetite (15.9%). For cats, the areas felt to be most positively impacted by the products were relief from pain (66.0%), reduction of inflammation (56.3%), and help with sleep (44.0%). The most common side effects for cats were sedation (19.2%) and over-active appetite (16.0%). Side effects were rarely mentioned as a reason for discontinuing a product. For dogs, the most common reason to discontinue a product was expense, followed by ineffectiveness. For cats, the most common reason was ineffectiveness, followed by expense.

When asked to compare hemp products to other forms of medication or therapy, most owners felt the hemp products work better than other treatments with only 7% reporting feeling they do not work as well. The most common reasons for choosing to use hemp products included a positive feeling about the fact that the products come from natural sources, and that the products could be used as an adjunct to other therapies. Furthermore, nearly 90% indicated that they thought hemp products were "very safe," though they would prefer verification on the contents, especially that of CBD, the active major constituent.

The fact that owners turned to hemp for the treatment of medical conditions may suggest that, similar to human medicine, many are not satisfied with more conventional modes of care. In our survey we found that most respondents were well-educated and that the treatment worked better or at least as well as other approaches. Although the potential of a placebo effect cannot be ignored, these results do suggest a large number of pet owners felt hemp products helped their pets for numerous ailments with minimal side effects. These results lend additional support to the anecdotal stories currently circulating about the use of hemp products for animals (29).

It is important to avoid interpreting these results as an endorsement for the efficacy of any THC or CPD product in veterinary medicine. Limitations of this study are the potential bias of gathering owners' opinions based on their own observations, the lack of placebo or control group, the lack of assessment of an owner's ability to accurately and objectively report changes in their pet's medical condition, and the anecdotal nature of the survey responses. Nevertheless, the survey does point out that some pet owners are viewing marijuana based products for their pets favorably, emphasizing the need for veterinarians to be informed about these opinions and need for objective, placebo controlled clinical trials.

In addition to providing some support for the growing number of anecdotal stories, these results give guidance to researchers seeking to perform clinical studies on hemp in terms of its putative effectiveness and possible adverse outcomes. We have identified the positive outcomes most commonly observed by consumers. The next step to determine the viability of hemp use therapeutically would be carefully controlled clinical trials. Potential areas of research would include pain management and behavioral interventions for sleep and anxiety for dogs, and pain management, inflammation reduction, and improvement in sleep patterns for cats.

Finally, in terms of safety, independent laboratory analysis of product contents and purity was deemed highly desirable. It is suggested that the field would benefit from studies analyzing the actual content of available products, including amounts of active ingredients; impact of non-active ingredients/additives; stability in the products administered; batch-to-batch variability; and potential contamination with pesticides, fungicides, and herbicides.

In conclusion, the use of cannabis products for animals warrants the attention of veterinarians and researchers. Indeed, it is suggested that both the promises and perils of medical marijuana for animals point to the need for science-based education, regulation, and research;

and veterinarians should be key players in the efforts surrounding the creation of well-designed, controlled clinical trials looking at this emerging area of animal treatment (22).

FOOTNOTES

a. Survey Monkey,

b. IBM SPSS Statistical software, version 21

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