DO YOUR HOMEWORK
With cannabis products becoming more accessible, veterinary professionals must understand their applications and safety to address client questions.

NUTRITION & INTEGRATIVE MEDICINE

Cannabis Products in Small Animal Medicine

***Trina Hazzah**, DVM, DACVIM (Oncology), CVCH, Green Nile, Inc., Los Angeles, Calif.*
***Gary Richter**, MS, DVM, Holistic Veterinary Care, Oakland, Calif.*

In recent years, cannabis products for pets have inundated the market. Pet owners can purchase hemp extracts at local pet stores and online marketplaces, and for those living in states with medical or recreational cannabis laws, products high in Δ-9-tetrahydrocannabinol (THC, the main psychoactive constituent of cannabis) intended for use in pets are often sold in cannabis dispensaries. The widespread accessibility of cannabis products presents veterinary professionals with a unique opportunity to guide pet owners toward safer products and fulfill our mission of helping patients live longer and better lives. To do so, we must answer 3 questions: Is it safe? Is it effective? Is it legal?

SAFETY

Determination of the safety of any specific cannabis product frequently relies on the due diligence of veterinarians or pet owners. Today's marketplace is flooded with products, and it is critical that consumers and veterinarians understand how to evaluate product safety. When we, as medical practitioners, consider any therapeutic product for our patients, safety is our most important determination.

When it comes to cannabis, one main misconception affects both practitioners and pet owners: that THC is toxic for dogs. Dogs have a larger number of CB1 receptors in the brain than other animals, including humans,[1] which renders dogs more susceptible to potential THC intoxication. However, when dosed appropriately, THC is not "toxic" for dogs; rather, it can be an essential component of formulations for the treatment of conditions such as extreme pain (e.g., bone, neuropathic), certain cancers, loss of appetite, and more. However, severe overdoses can lead to THC intoxication, which can be serious and require medical intervention. In dogs, potential side effects associated with high doses of THC include hypersalivation, depression, mydriasis, urinary incontinence, hypothermia, static ataxia (standing rigidly, rocking back and forth as if trying to move but cannot), and tachycardia or bradycardia (dose-dependent).[2-3] In cats, overdose signs include lethargy, hypothermia, ataxia, protrusion of the nictitating membrane, and vocalization.[4] Treatment of THC overdose in animals is largely supportive. Those that exhibit severe clinical signs and are unable to eat or drink may require hospitalization and IV fluid support.

For dogs, there is no evidence of death directly caused by systemic THC exposure of up to 3000 mg/kg PO.[5] Although uncommon, fatalities occur from pneumonia and septicemia when highly intoxicated animals vomit

and aspirate the vomitus. Severe THC toxicity is less concerning with regard to over-the-counter products with low THC content (<0.3% THC by dry weight at time of harvest) or when dosing is guided by a cannabis-knowledgeable veterinarian.

Pharmacokinetics

Studies of the pharmacokinetics, dosing, and safety of multiple types of cannabis products have found that short-term use of these formulations are safe for dogs and cats. In dogs and cats, cannabidiol (CBD) at high doses can lead to elevated liver enzymes, occasional sedation, and transient gastrointestinal upset.[2,3,6-8] On the basis of these studies, as well as the large number of dogs and cats receiving cannabis products (mostly hemp-derived) in real life without negative effects, cannabinoid-based products seem to be well tolerated as long as they are made with quality cannabis, tested for purity, and dosed appropriately. Because the pharmacokinetics of CBD seem to vary between dogs and cats, dosing may differ by species. Information regarding the effects of long-term use of CBD products in pets requires more research.

Product Selection

Products appropriate for human medical patients are not necessarily safe for animals. The contamination testing limits that are appropriate for humans may differ dramatically from those that are safe for animals. In addition, products from the human cannabis market that are used for animals should be carefully evaluated to avoid extra additives, coloring, or sweeteners. Clients should be carefully counseled to avoid products with known toxins (e.g., xylitol, chocolate, raisins).

Before choosing a product, research the company and the manufacturing process. Look for products from brands that are transparent about their testing policies and procedures and how they source their ingredients. Consider products that are formulated by or endorsed by veterinarians with cannabis knowledge and experience.

Also look for a certificate of analysis (CoA), an evaluation of a cannabis product that provides an objective measurement of its contents. Ideally, a CoA should come from a third-party laboratory that meets ISO/IEC (International Organization for Standardization/International Electrotechnical Commission) standard 17025. A comprehensive CoA will report not only which cannabinoids are present (e.g., CBD, THC, CBG [cannabigerol]) but also levels of pesticides, fungicides, molds, heavy metals, and other potentially problematic substances. Each batch/lot number of a product should have a unique CoA. Many products now have a QR code on the label that will link to the product CoA. Avoid buying any product that does not have a batch/lot-specific CoA.

Despite the high demand for cannabis-based pet products, they are neither regulated nor approved by the U.S. Food and Drug Administration. A 2020 evaluation of 29 over-the-counter commercial pet CBD products found that only 2 products did not provide the CBD or total cannabinoid concentration on their packaging or website and 22 could provide a CoA from a third-party laboratory.[9] Only 10 of the 29 products were found to contain within 10% of the total cannabinoid concentrations claimed on their label. Heavy metal contamination was found in 4 products; the most prevalent contaminant was lead (found in 3 products).

An easy way to identify a safe cannabis product is to look for evidence that the product company has a certification indicating that it has successfully passed a comprehensive third-party audit by a certifying body. This type of process, which is separate from a CoA, generally includes stringent evaluation of processes involved in manufacturing, safety, appropriate labeling, and adverse events reporting. Third-party certification should be overseen by an accreditation body, which creates confidence that the certifying body is impartial and without conflicts. A private, product-neutral company that provides certification through assessing animal supplements for both safety and accuracy in labeling/advertising is the National Animal Supplement Council (nasc.cc).

CLINICAL EFFICACY

According to an anonymous online survey study conducted in Canada in 2019, the 3 main reasons that pet owners added cannabis to their pet's treatment regimen were pain, inflammation, and anxiety. Owners also perceived these preparations to be as effective as or more effective than conventional medications.[10] A subsequent U.S.-based online survey study concluded that human patients and dog owners reported similar motivations for using cannabis products to treat chronic pain; the most popular reasons were that cannabis products are natural, preferred over

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conventional medication, and a good treatment option for pain. Similar proportions of human patients (86%) and dog owners (82%) reported that use of cannabis products fulfilled their expectations. Qualitative data revealed that expectations were met by reduced pain, increased relaxation, and improved sleep and overall wellbeing of the pet.[11]

Pain

A handful of peer-reviewed published studies have evaluated the efficacy of CBD products (including full-spectrum hemp-derived isolates and transdermal products) for pain management in dogs with osteoarthritis. All but one demonstrated reduced pain, increased mobility, and improved quality of life.[12-16] Because all product formulations differ, it is difficult to confirm if one type of formulation works better for osteoarthritis or if osteoarthritis treatment requires a personalized medicine approach. It also seems that clinical benefit is more likely with lower doses of full-spectrum products than with isolate products, which is similar to what practitioners are seeing clinically. Full spectrum refers to an extract that contains all of the naturally occurring components of the cannabis plant being used (i.e., multiple cannabinoids [including THC], terpenes, and flavonoids). By contrast, isolate refers to a purified product containing only a single component (e.g., CBD).

Inflammation

In vitro and preclinical studies have established multiple mechanisms behind the anti-inflammatory activity of cannabinoids. However, no in vivo clinical trials in companion animals have evaluated the effects of cannabinoids on specific inflammatory markers. One study, which used a canine ex vivo inflammatory model, demonstrated anti-inflammatory and immunomodulating properties of CBD directly in dogs' immune cells (i.e., reduced expression of interleukin-6, tumor necrosis factor α, nuclear factor-κB, and cyclooxygenase-2).[17]

Anxiety

Despite anxiety being one of the top 2 reasons why pets receive cannabis, peer-reviewed veterinary research that describes the efficacy of cannabinoids as an anxiolytic agent in companion animals is sparse. Only 2 studies evaluating the effect of CBD on anxiety in dogs have been published.[18,19] The first study found no anxiolytic effect or reduced cortisol when dogs were exposed to the sound of fireworks; however, the study design did not account for the half-life of CBD in dogs and it was given too far in advance (4 to 6 hours) of fireworks exposure.[18] The second study demonstrated that CBD reduced shelter dog aggression toward humans; however, compared with the placebo group, the difference was not statistically significant.[19] Potential causes of negative results in both studies are limited product chemical profile and lower doses of CBD (especially critical if the products were CBD isolates).

Other Potential Uses

Seizures: Since the first plant-derived cannabinoid medicine, Epidiolex, was approved for treatment of severe forms of epileptic seizures in children, pet owners have been wanting to use cannabis to relieve seizures in their pets. One study found elevated concentrations of anandamide (N-arachidonoylethanolamine [AEA]) in the cerebrospinal fluid of epileptic dogs.[20] A subsequent clinical trial that evaluated dogs with refractory idiopathic epilepsy demonstrated an association between CBD receipt and significant (median 33%) reduction in seizure frequency in some, but not all, dogs compared with the placebo group.[21] Of note, a negative correlation was found between seizure frequency and CBD plasma concentrations.

Cancer: Cannabinoids may play a role in treating cancer in veterinary patients. When cannabis is used to treat cancer, the 2 main objectives are definitive (direct antitumor activity) or palliative (i.e., improved quality of life through reduced pain, gastrointestinal signs, and anxiety). More than 100 studies have evaluated the

antitumor activity of cannabinoids, but most were in vitro and preclinical work. Three recent (and 1 unpublished) studies indicated that CBD, as a single agent and with standard chemotherapies, can reduce cell viability and induce apoptosis for multiple canine cancer cell cultures.[22-24] Whether these results are translatable in vivo remains unknown.

Pruritus: Two clinical studies recently evaluated the use of cannabinoids in dogs with atopic dermatitis. The first, a retrospective case series of 8 dogs with atopic dermatitis, demonstrated decreased pruritic behavior after CBD (without THC) was given twice daily; it was well tolerated by all dogs over a wide dose range (0.14 to 1.4 mg/kg/day).[25] A subsequent prospective, randomized, double-blinded, placebo-controlled study involving 32 dogs demonstrated no change in skin lesions or inflammatory markers but a significant reduction in pruritus (based on visual analog scale score) in dogs receiving 2 mg/kg q12h of a CBD/CBDA (cannabidiolic acid, a CBD precursor) dominant hemp extract.[26]

LEGALITY

Although the question of cannabis product legality is not specifically a medical concern, it is critical for veterinarians to understand what we can, and cannot, do and say. As ubiquitous and versatile as cannabis products may be for veterinary patients, veterinarians must be aware of their state and local laws and be certain to practice within the bounds set forth by their governing agency. Legal questions concerning veterinarians and cannabis concern either high-THC or low-THC (hemp-derived) cannabis products.

High-THC Cannabis

Cannabis extracts containing more than 0.3% THC are still federally illegal, although 37 states have laws legalizing these products for medicinal and/or recreational use. The ability to "discuss" or "recommend" high-THC cannabis products has been largely unaddressed by most state regulators and veterinary boards. Veterinary boards in some states, such as Colorado, have stated that veterinarians have an obligation to completely educate companion animal owners with regard to the potential risks and benefits of marijuana products in animals, as long as they are acting within the bounds of a valid veterinarian–client–patient relationship. California, by comparison, initially forbade veterinarians to talk about the medical use of cannabis in any form; however, through legislation, veterinarians are now able to "discuss" the use of cannabis for patients, and a currently pending bill would allow California veterinarians to "recommend" high-THC cannabis. As interest in products with higher THC content grows, more legislatures and veterinary boards are likely to address these policy issues.

Low-THC Cannabis

Hemp-derived cannabis is considered federally legal, although technically its distribution and sale are not. Despite this technicality, hemp extracts are widely available in retail stores, online marketplaces, and in some veterinary hospitals. The ability to recommend these products varies by state. In 2021, Nevada became the first state to pass legislation allowing veterinarians to "recommend" and "administer" hemp-derived CBD products. Many other states have no official policy position regarding hemp and hemp extracts in veterinary medicine.

State and Federal Laws

State and federal laws are continually changing, and many people believe that the federal government will eventually legalize all forms of cannabis for medical, and possibly recreational, use. Until then, policy discussions and recommendations will continue to come from the American Veterinary Medical Association, the American Association of Veterinary State Boards, state veterinary boards, and legislators. The Veterinary Cannabis Society (vcs.pet) was formed as a 501(c)(3) nonprofit to, in part, provide expert guidance to veterinarians, industry professionals, and regulators on how to safely use, produce, and regulate cannabis for animals and is a good resource for veterinary professionals, pet owners, and industry members. Practitioners interested in learning more about the specific regulations in their state should contact their state veterinary board or their state veterinary medical association. TVP

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Trina Hazzah

Dr. Hazzah is a board-certified integrative veterinary oncologist who has been using cannabis for her patients for more than 7 years. She has performed cannabis-related clinical research, cannabis formulation work, published a review in *Cannabis in Veterinary Medicine*, and co-authored multiple cannabis-related textbooks. She is also the president and co-founder of the Veterinary Cannabis Society, as well as the founder of Green Nile, Inc., a cannabis consulting service.

Gary Richter

Dr. Richter is a graduate of the University of Florida College of Veterinary Medicine and is certified in acupuncture, chiropractic, and Western herbology. His book on integrative medicine, *The Ultimate Pet Health Guide*, was released in 2017. In addition to full-time practice, Dr. Richter is a vocal advocate for the safe use of medical cannabis for animals. He is also the past president of the American College of Veterinary Botanical Medicine and co-president and a founding member of the Veterinary Cannabis Society, a nonprofit society dedicated to education and advocacy in support of the use of medical cannabis for veterinary patients.

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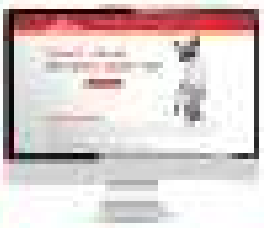

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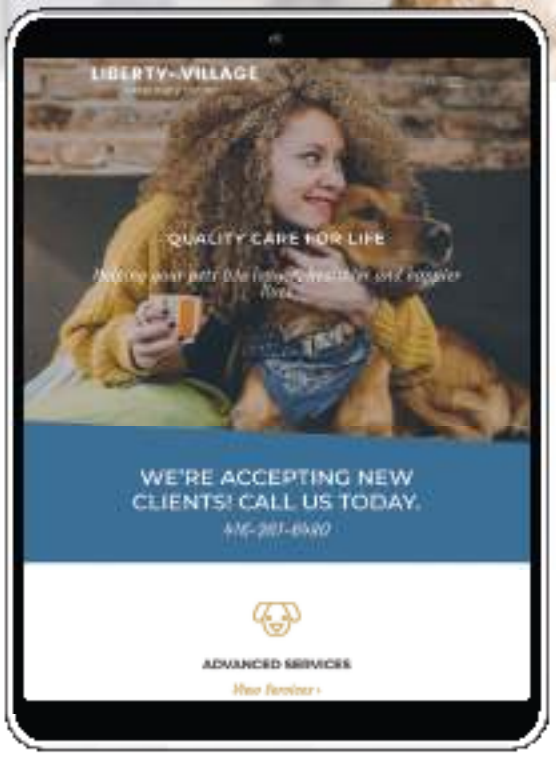

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