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INCREASED VISIBILITY

CBD products marketed for pets can be bought in stores or online in many states, elevating the importance of veterinary professionals being educated on the subject.

INTEGRATIVE MEDICINE

Emergence of the CBD Pet Market and the Role of Veterinary Nurses

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At the end of 2020, the global pet market for cannabidiol (CBD) was \$125 million (**FIGURE 1**). This market is expected to grow by almost 59% each year from 2021 to 2028. The driving forces behind this boom are the perceived benefits of CBD products and pet owners' preference for natural supplements.¹ Despite public opinion that CBD is a safe and effective treatment for various ailments, the lack of scientific clarity on the safety, dosage, and efficacy of CBD renders continued research in companion animals critical.² As the number of products containing CBD grows, so does interest from pet owners seeking guidance in purchasing and using these products for their pets. Popular formulations of CBD products for pets (e.g., chewable treats, tinctures) are available in stores and online. The ability to purchase these products is quite easy and does not require the approval of a veterinarian.

More often than not, pet owners are purchasing CBD products and administering them on their own, which can become problematic when new products enter the market of an unregulated industry. As of November 2019, the Food and Drug Administration had issued warning letters to 15 companies for violating the Federal Food, Drug, and Cosmetic Act.¹ The violations include but are not limited to illegally selling CBD products, using adulterated animal food items, and making unauthorized claims for drugs/dietary supplements;^{1,3} consequences include fines, label changes or ceased production, and even incarceration. The costs of cannabis products range wildly, from as low as \$20 to as high as \$200,

depending on the manufacturer and formulation. The cost of these products does not always correlate with the quality of the product.

To help our clients, veterinary professionals need to be armed with accurate medical information and data. We need to understand the pharmacokinetics of CBD products within companion animals as well as the legal landscape surrounding their use.

BRIEF HISTORY OF CANNABIS AND ITS LEGAL STATUS

Cannabis is a plant in the family Cannabaceae

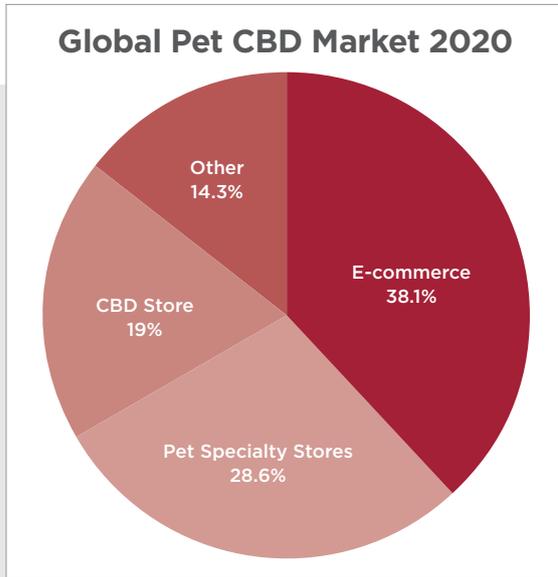


FIGURE 1. Cannabidiol (CBD) products are readily available to pet owners via a number of sources, often without veterinarian approval.¹

(a member of the hop family), associated with fibrous hemp and psychoactive chemicals. It has been grown for its medicinal and industrial use for more than 12000 years. It is believed that the cannabis plant was first discovered in central Asia and around the 17th century traveled westward.⁴

Until the late 1900s, hemp was a staple of the United States and was used for manufacturing rope, sails, clothing, and medicine.⁴ In 1906, the number of pharmaceutical restrictions grew, as did the villainization of cannabis. Soon farmers no longer grew hemp, pharmacies refused to stock cannabis products, and selling cannabis came with harsh punishments, such as imprisonment.⁵

The Controlled Substance Act of 1970 labeled cannabis as a Schedule I drug. The Schedule I classification described cannabis as having no medical use and potentially being associated with abuse and potential

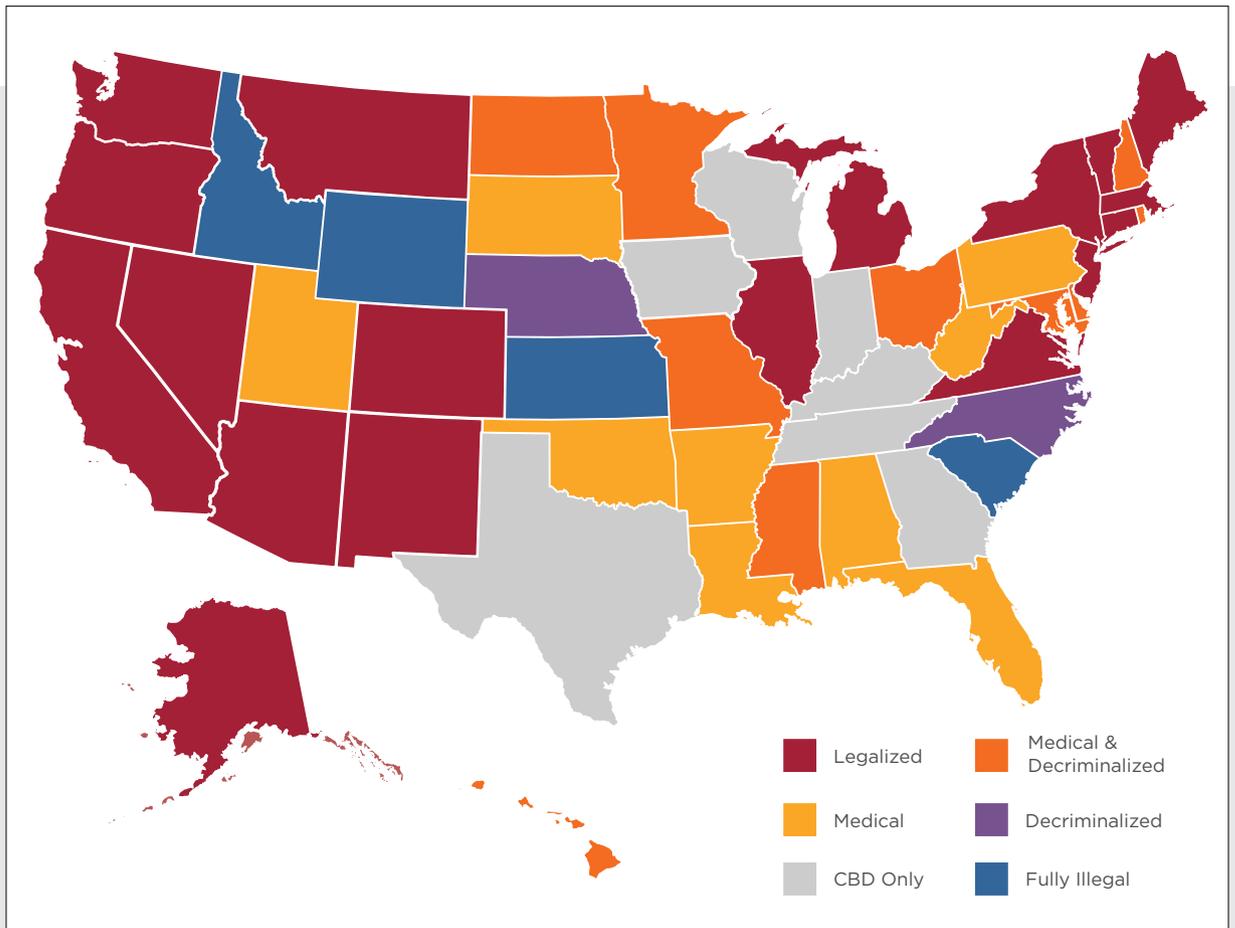


FIGURE 2. Marijuana legality, by U.S. state.⁷

psychologic and physical dependency. This act grouped all cannabis products together, completely outlawing medical or recreational use of cannabis products.⁵

The Agriculture Improvement Act of 2018 (2018 Farm Bill) once again authorized production of hemp in the United States. This Act removed hemp and hemp seeds from the Drug Enforcement Administration schedule of controlled substances, allowing farmers to grow hemp legally.⁶ The 2018 Farm Bill not only declassified hemp from Schedule I but arbitrarily defined hemp as containing less than 0.3% Δ -9-tetrahydrocannabinol (THC) at time of dry harvest and marijuana as a product containing more than 0.3% THC at time of dry harvest.⁶ The removal of hemp from Schedule I created a pathway for universities and companies to legally gain access to hemp for studies and production.

At the time of publication, 18 states have decriminalized and legalized the selling/use of marijuana and hemp for medicinal and recreational purposes, while the remaining states have varying definitions of what is legal or illegal.⁷ **FIGURE 2** offers a snapshot of the status across the United States, but it is strongly advised that veterinary nurses verify the most updated information for the legal status of cannabis in their state.

THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is considered one of the largest neurotransmitter systems within the body and works with other systems to promote homeostasis.⁸ The ECS was discovered by Dr. Raphael Mechoulam in 1964.⁸ During this time, Mechoulam and his team also discovered that within the cannabis plant were the psychoactive phytocannabinoid THC and the nonpsychoactive phytocannabinoid CBD.^{4,8} The discovery of these 2 compounds prompted Mechoulam and his team to dig deeper and identify 2 receptors—cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2)—and the endogenous cannabinoids anandamide and 2-arachidonoylglycerol (2-AG).⁸ Recent studies have found these receptors in several other vertebrate species in addition to humans and in invertebrate species as primitive as the hydra.⁹

The 3 main components of the ECS are cannabinoid receptors, cannabinoids (endogenous/exogenous), and the enzymes responsible for synthesis and degradation of cannabinoids.¹⁰ Endogenous cannabinoids are made on demand by the body, and exogenous cannabinoids



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are derived from plants (phytocannabinoids) or synthetically made in a laboratory. Whether made on demand by the body or supplemented, all cannabinoids exert an effect on the ECS.

Also involved with promoting homeostasis are the central nervous system and the immunomodulatory system.^{8,10} CB1 receptors are primarily located within the central nervous system and interact with the endogenous cannabinoid anandamide and the exogenous cannabinoid THC.¹¹ CB2 receptors are located on peripheral tissues and immune cells and interact with the endogenous cannabinoid 2-AG and the exogenous cannabinoid CBD.¹¹ After a cannabinoid interacts with a receptor, an enzyme is released and begins the process of degrading the cannabinoid. The enzyme fatty acid amide hydrolase degrades the endocannabinoid anandamide, and the enzyme monoacylglycerol lipase degrades the endocannabinoid 2-AG.¹⁰ Contrary to traditional nerve pathways, information from the ECS can flow backward/upstream in a process known as retrograde inhibition.⁸ By sending a signal upstream, the ECS allows cells to cease firing or “time-out”; this action enables the body to protect the nervous system from hyperactivity.⁸ After a signal is sent from a presynaptic neuron and crosses the synaptic gap to a postsynaptic neuron, an endocannabinoid is released and sent backward/upstream, across the synaptic gap to its corresponding receptor on the presynaptic neuron. After the cannabinoid interacts with the receptor, its corresponding enzyme begins to degrade the cannabinoid, completing the retrograde feedback loop (**FIGURE 3**).

The cyclical flow of the ECS, like many other organ systems, can be flawed and can need medical intervention. In 2001, Dr. Ethan Russo proposed the concept of clinical endocannabinoid deficiency in humans. His study proposed that the ECS tone (overall



state of the ECS) can become unbalanced and no longer function optimally as a result of genetic predisposition or metabolism.¹³ Russo believes that patients with a clinical endocannabinoid deficiency suffered from chronic illnesses such as fibromyalgia, irritable bowel syndrome, and migraines. Through study, he was able to see improvement in patients who supported their ECS with cannabinoids.¹³ This study presents another avenue for investigation in the veterinary world. Anecdotally, veterinary professionals could infer that our patients may be experiencing similar illnesses resulting from an endocannabinoid deficiency. More studies are needed to provide factual evidence of this condition in veterinary patients.

CURRENT RESEARCH

Growth of the CBD pet market is largely attributed to public perception of the supposed health benefits of CBD, including analgesic, antioxidant, anti-inflammatory, apoptosis, and anti-anxiety effects.² The current bank of veterinary-specific studies regarding cannabis in animals is limited. Studies that have been performed are relatively small, and some are funded by corporations in the CBD pet market. Many of the concepts and current applications of cannabis in veterinary medicine are anecdotal (from human

studies) or gleaned from clinical experience; they include antiseizure activity, osteoarthritis pain relief, and decreased noise aversion.

Antiseizure Activity

During 2016 to 2017, Dr. Stephanie McGrath at Colorado State University College of Veterinary Medicine and Biomedical Sciences performed a small clinical trial to determine whether a CBD-rich oil could help control epileptic seizures in dogs. She found that 89% of dogs that received the CBD-rich oil in addition to existing antiepileptic treatments experienced fewer seizures compared with dogs in the placebo group.¹⁴ She is pursuing a double-blinded crossover clinical trial examining the effects of CBD oil treatment on epilepsy. Her goal is to enroll 60 dogs to determine the efficacy of higher versus lower dosages of CBD, safety margins of CBD, and whether CBD will have any inhibitory actions against other medications used long term.¹⁵

Osteoarthritis Effects

In 2018, Cornell University College of Veterinary Medicine performed a small short-term clinical trial to assess the pharmacokinetics, safety, and analgesic

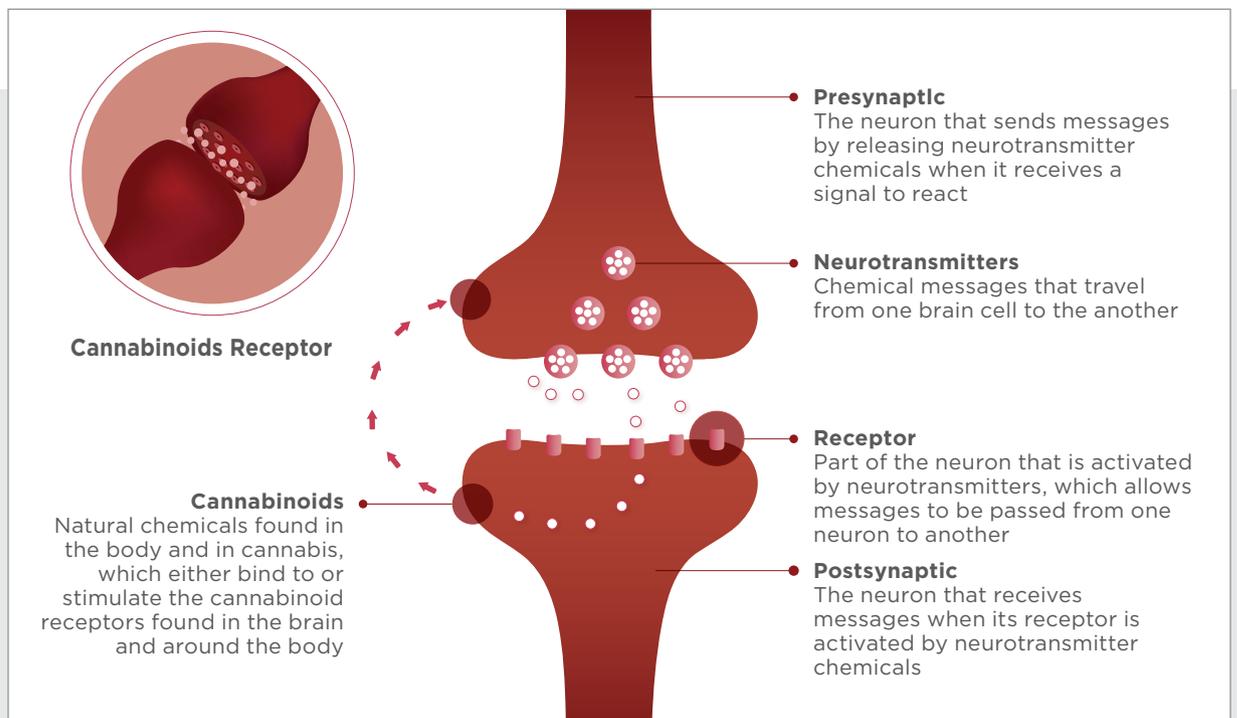


FIGURE 3. The endocannabinoid system.¹²

efficacy of oral CBD when used to treat osteoarthritis in dogs. The study showed a decrease in assessed pain during CBD treatment.¹⁶ Overall, owners of the study dogs did not perceive any side effects, although some dogs experienced increased liver enzymes. It is unclear whether the increase resulted from administration of the CBD oil in conjunction with cytochrome P450-mediated metabolism or from the product itself. The study report recommends monitoring liver values until further long-term safety studies are performed.¹⁶

Noise-Aversion Effects

Noise aversion is one of the most common fearful behaviors in dogs; behavioral responses vary considerably (e.g., from mild panting and hiding to destructiveness, self-trauma, and extreme behaviors). An estimated 40% to 50% of dogs demonstrate at least one fearful behavior in response to noise. One study assessed the effects of feeding a hemp-based CBD treat on induced noise aversion in dogs.² Before this study, CBD had been shown to reduce anxious behaviors in mouse, rat, and human models, but little to no literature described its effect on canine behavior. In this study, 16 dogs were divided evenly into 2 groups: 1 group received the CBD treat along with a dose of trazodone and the other group received placebo. All study dogs were allowed 2 hours of daily exercise before the aversive noise stimulus was introduced.² Throughout the trial, the study group was given a CBD treat 4 to 6 hours before exposure to the aversive stimulus, followed by a dose of trazodone approximately 2 to 4 hours before exposure. The results of the study did not provide strong support for the anxiolytic effect of CBD in dogs. Concurrent administration of trazodone during the trial made it hard to glean concrete information on anxiolytic effects of CBD treatment alone. The cytochrome P450 inhibitory effect of CBD may have reduced the anxiolytic effects of the trazodone, thereby limiting any relief for the dogs during noise exposure.²

Absorption and Pharmacokinetics of CBD

CBD products are absorbed to varying degrees, depending on the formulation and the species of the animal. A small study performed in 2019 documented absorption and pharmacokinetics of a CBD-rich hemp-based oil in healthy dogs and cats.¹⁷ This study found the hemp-based CBD oil to be relatively safe for use in healthy dogs and cats. The study also noted that

Short-term use of CBD products may increase liver enzymes, inhibit other medications, and potentially lead to side effects (e.g., inhibitory cytochrome P450, gastrointestinal effects, salivation, ataxia).



cats seemed to absorb the CBD oil better than the dogs. A few of the side effects noted were unpalatability and increased liver enzyme levels in dogs and cats. Short-term use of CBD products may increase liver enzymes, inhibit other medications, and potentially lead to side effects (e.g., inhibitory cytochrome P450, gastrointestinal effects, salivation, ataxia).

The studies described here are just a few examples of the research performed and published to date. More studies of the short-term and long-term effects of CBD in companion animals are needed and continue to be performed as the pet market for CBD grows.

ROLE OF THE VETERINARY COMMUNITY

Legislation regarding the ruling of *Conant v. Walters* permits medical practitioners in human medicine to discuss the pros and cons of cannabis therapy with their patients and to issue a written recommendation. However, these same physicians are not permitted to prescribe or dispense marijuana to a patient.¹

Many states are beginning to address the failure to include veterinarians in this law. Over the past 4 years in California, veterinarians, pet owners, and stakeholders in the cannabis industry have advocated for veterinarians' rights to discuss and recommend cannabis for their patients. In 2019, first-of-its-kind legislation was passed in California, advocating to provide similar legal parameters for veterinarians as their physician counterparts, thereby creating a legal pathway for cannabis recommendation.¹⁸

Through harm-reduction education, veterinary professionals can provide clients with baseline



information about cannabis products for companion animals. It is strongly advised to discuss the medical history of the patient, current medication, and the intended use of a cannabis product. Research whether the product is safe for consumption by requesting a certificate of analysis from the company. If the company does not supply you with this information, the product must be deemed unsafe. Any product for consumption must be free of toxins, solvents, and metals and must show proof of cannabinoids within the product. A product label may say “full spectrum” but contain CBD only, whereas another product label may say “CBD only” but contain other cannabinoids.

One way you can become active in the cannabis community is to learn more about cannabis medicine. Some resources available to the veterinary community are provided by the Veterinary Cannabis Society (veterinarycannabissociety.org) and the Veterinary Cannabis Education and Consulting group (veterinarycannabis.org). A pet owner, veterinary nurse, or veterinarian can become a member of the Veterinary Cannabis Society and gain access to the published articles and media sources created by many leaders in this field of study.

If you are a veterinary nurse who wants to become certified as a Veterinary Cannabis Counselor, you can apply for certification through Veterinary Cannabis Education and Consulting. You can become the point person for cannabis information in your clinic or you can refer cases.

Despite passage of the bill in California permitting veterinarians to discuss cannabis with their clients, veterinary nurses are advised to check in with their local veterinary medical board and review the laws in their state. As the legal landscape continues to change, the veterinary community should continue to search for new studies as they become available, remain active in protecting their patients from harm, and provide continued guidance and education.¹⁸ **TVN**

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