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The Use of Medical Cannabis as Palliative Care in a Feline With Advanced Cancer

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Abbreviations

CB1	Cannabinoid type 1 receptor
CBD	Cannabidiol
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CBN	Cannabinol
CIPN	Chemotherapy-induced peripheral neuropathy
CINV	Chemotherapy-induced nausea and vomiting
THC	Delta-9-tetrahydrocannabinol
THCA	Tetrahydrocannabinolic acid
5-HT	5-hydroxytryptamine

Abstract

A 10-year-old 2.2-kg male neutered Domestic Shorthair feline presented with a history of dyspnea, coughing, and lethargy. Radiographs revealed a large mass encompassing the majority of the cranial thorax and mid-thorax. The implementation of a complex-spectrum cannabis product was well tolerated and provided resolution of cancer-related clinical signs for 6 months.

Case Report

A 10-year-old 2.2-kg male neutered Domestic Shorthair feline presented to the hospital internal medicine service for evaluation of labored breathing. According to the owner, the cat had clinical signs of moderate dyspnea, tachypnea, inappetence, coughing, difficulty climbing stairs, and lethargy for the past week but had worsened in the last few days. Prior pertinent history included mucopolysaccharidosis and toxoplasma infection. He was not receiving any medications.

On physical examination, the cat was noted to have significant skeletal abnormalities, dwarfism, severe corneal clouding, and severe arthritis with nearly absent joint flexibility. No significant abnormalities were noted on a CBC, blood chemistry panel, and urinalysis.

Thoracic radiographs were attempted but the cat developed respiratory distress, so 0.2 mg/kg of butorphanol was administered, and he was placed in an oxygen cage for 20 minutes. Once sedation was achieved, 2-view thoracic radiographs were performed and he was returned to the oxygen cage. The radiographs were reviewed by a board-certified radiologist who described an increased radiopacity involving the cranial and mid-thorax (**Figures 1a and 1b**). Two discrete structures with rounded margins were noted on the ventrodorsal view. One of the structures may have reflected the cardiac silhouette; however, a mass was considered most likely. Differential diagnoses for the thoracic mass included primary pulmonary carcinoma, lymphoma (mediastinal or pulmonary), thymoma, and ectopic thyroid carcinoma. An abdominal ultrasound was performed by a board-certified internist, and the findings were unremarkable. Due to the patient's critical condition, an ultrasound of the thoracic mass was not pursued.

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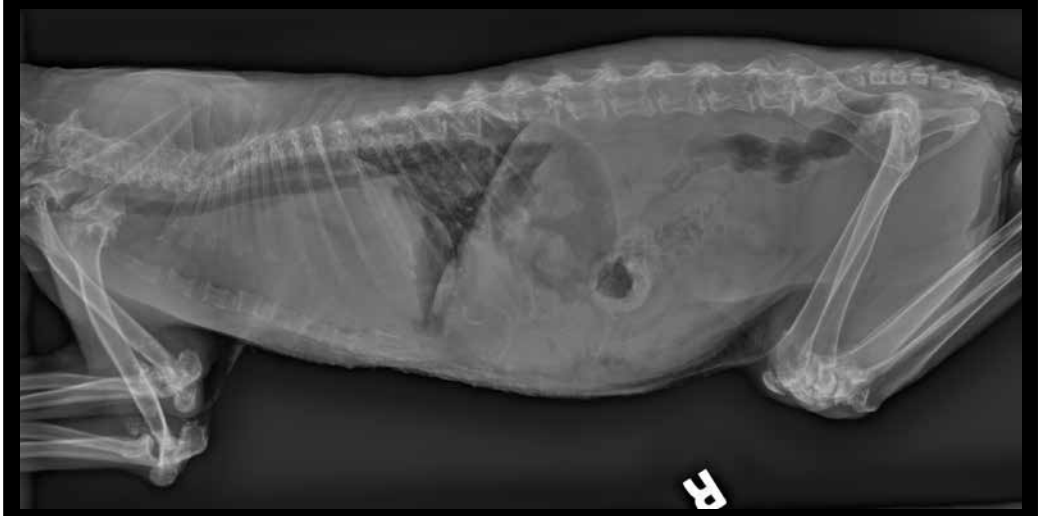
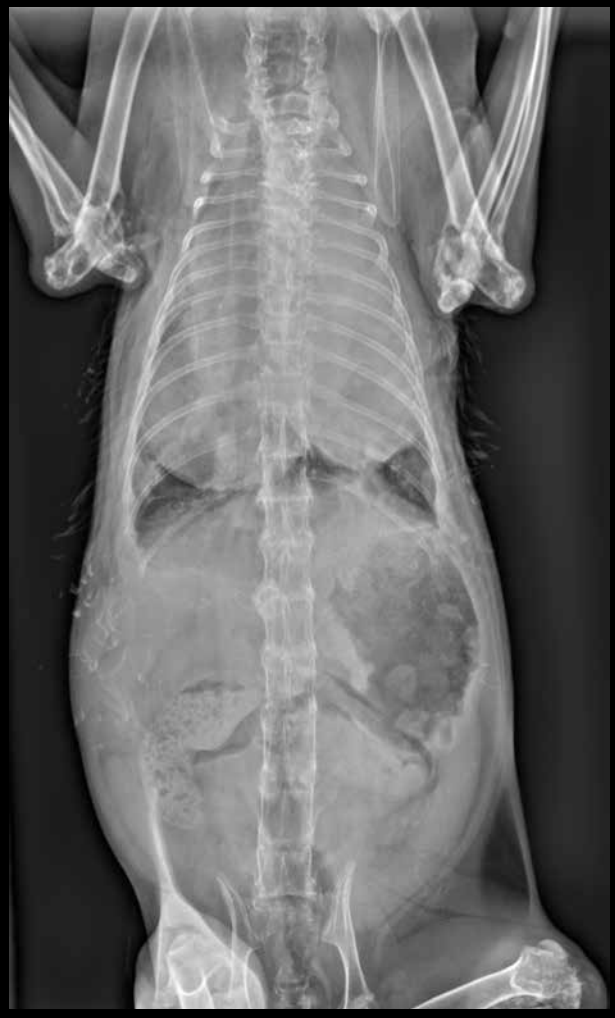
The internist and the owner discussed the options for further diagnostic tests, such as ultrasound-guided fine needle aspiration of the mass, and potential treatment options including radiation therapy, chemotherapy, and palliative care with steroids and pain medications. A grave to poor prognosis was given, with estimated survival time of days to weeks.

Figure 1a



Upon consideration of the pros and cons of each approach, the owner elected to pursue a palliative course of treatment with steroids in hopes of keeping the cat comfortable until the end. He was prescribed prednisolone (5 mg, PO, q 24 h), but after 2 doses developed progressive lethargy, became polyuric, and was having urinary accidents throughout the house. The owner discontinued prednisolone and elected to begin a complex-spectrum palliative cannabis formula intended to reduce any discomfort, promote energy and appetite, and possibly reduce dyspnea. The product was ordered online from a Los Angeles-based cannabis company with experience creating custom cannabis products for pets. The company tests each cannabis extract via a local California-licensed (Department of Cannabis Control) and ISO/IEC 17025-accredited testing lab. The lab confirmed the safety and potency of each extract that went into the custom formulation. Cannabinoid potency was confirmed using ultra high-performance liquid chromatography coupled with a diode array detector. The absence of microbials was established using real-time PCR. The absence of heavy metals, pesticides, and mycotoxins was confirmed using mass spectrometry.

Figure 1b



A palliative formulation was created with a 4:1 ratio of cannabidiol (CBD) to delta-9-tetrahydrocannabinol (THC) that also contained minor cannabinoids along with 2% beta-caryophyllene and 1% each of alpha-pinene and linalool. The starting dose of cannabinoids for this patient was 2 mg/kg (4.25 mg) of CBD, 0.42 mg/kg (0.94 mg) of THC, 0.4 mg/kg (0.9 mg) of tetrahydrocannabinolic acid (THCA), 0.23 mg/kg (0.52 mg) of cannabigerol (CBG), 0.06 mg/kg (0.14 mg) of cannabinol (CBN), and <0.1 mg cannabigerolic acid (CBGA) and other minor cannabinoids. The starting dose took into account the owner's experience with cannabis, along with the cannabis company's input on treating cats with cancer in the past. The cat initially received the oil-based tincture atop his wet food once daily.

Within 5 to 7 days of starting the cannabis product, the coughing and inappetence completely resolved and the cat developed polyphagia. At that time, as it was clear he was tolerating the initial SID doses well, the frequency was adjusted to every 12 hours along with breakfast and dinner. After 1 month of receiving the cannabis product twice daily, the owner described the cat's energy as being better than it had been for most of his life. He was able to run up and down stairs with the other animals in the household and had no clinical signs associated with the thoracic tumor. No adverse effects were reported, with the exception of polyphagia.

With the support of the pet cannabis company, the owner gradually titrated the dose by 0.05 mL every 10 to 14 days while monitoring the cat carefully for any adverse effects. Based on the titration tolerance in this patient, anecdotal evidence, and some published reports supporting the anticancer effects of THC, the owner requested a formula more concentrated in THC. This allowed the cat to receive the same small volume but an increased amount of THC.

Approximately 3 months after the initiation of cannabis treatment, the pet custom cannabis company adjusted the formulation to a 2.3:1 (CBD:THC) ratio consisting of 1.7 mg/kg CBD (3.8 mg), 0.75 mg/kg (1.65 mg) of THC, 0.55 mg/kg (1.2 mg) of THCA, 0.8 mg/kg (0.18 mg) of CBG and <0.1 mg CBN, CBGA and other minor cannabinoids. The terpenes were slightly increased to 3% beta-caryophyllene, 2% linalool, and 1.5 % alpha-pinene.

The patient tolerated the new formulation well, so the owner continued to gradually titrate the dose by 0.05 mL every 10 to 14 days over the following month. With the continued goal of steadily increasing THC exposure, at the 4-month mark the pet custom cannabis company adjusted the formula to a 1.5:1 (CBD:THC) ratio consisting of 1.5 mg/kg (3.4 mg) of CBD, 1.1 mg/kg (2.4 mg) of THC, 0.55 mg/kg (1.2 mg) of THCA, 0.8 mg/kg (0.18 mg) of CBG, and <0.1 mg CBN, CBGA and other minor cannabinoids. The terpenes were maintained at 3% beta-caryophyllene, 2% linalool, and 1.5 % alpha-pinene.

At the 5-month mark, the owner noticed that despite the cat eating approximately 1.5 times his normal amount, he appeared to have lost weight, although the owner never weighed the cat to confirm. A mobile vet visited the home and obtained blood for a CBC, chemistry panel, and T4 thyroid level. The results were unremarkable. No further diagnostics were performed.

Approximately 6 months post-diagnosis, the owner returned home and noticed the cat circling, yowling, and appearing distressed. This behavior was perceived to be related to anxiety secondary to impaired vision. The cat was confined to a small, safe place or on the owner's lap, where he stopped circling and seemed more comfortable. He continued to eat well and use the litter box normally, although the owner had to carry him to it. A veterinary examination on the next day revealed a relatively stable patient, except for apparent impaired vision. He was evaluated by a board-certified ophthalmologist who had previously examined the cat. This ophthalmologist performed a complete ophthalmic examination and measured the cat's blood pressure, which was in the normal range (exact results not available). The ophthalmologist concluded that the patient had progressive corneal opacification secondary to his mucopolysaccharidosis which resulted in complete loss of vision. No other diagnostics were performed that day.

Due to the blindness causing a decreased quality of life, the owner elected to have the pet euthanized. Even so, on the day of euthanasia the cat was still breathing normally and had an ravenous appetite.

Commentary

Cannabinoids have been used as medicine for almost 5000 years. There is evidence that the ancient Chinese, Egyptians, and Indians used cannabis for a variety of conditions including cancer, nausea, pain, and more.

Due to widespread accessibility, research, and anecdotal information on the benefits of cannabis in human medicine, pet owners are interested in utilizing cannabis for their pets. The 2 main motivations for using cannabis in cancer patients are the antitumor and palliative effects. During the last decade, numerous studies have been published suggesting that endocannabinoids, phytocannabinoids, and synthetic cannabinoids have antineoplastic properties. To date, over 100 scientific studies have been published on the anticancer effects of various cannabinoids in vitro or in laboratory animals, with most involving CBD and THC. Results from these studies suggest that cannabinoids elicit anticancer effects at several levels such as inhibiting tumor proliferation, invasion and metastasis, immune modulation, and induction of cancer cell death (1). Additional evidence suggests that cannabinoids may enhance the effects of conventional treatments like chemotherapy, targeted therapy, and radiation therapy (1-3). Pre-clinical and clinical data evaluating cannabinoids as antineoplastic agents have been identified for a variety of different cancers in various locations including brain, colorectal, liver, prostate, pancreas, thyroid, breast, bone, skin, and lung (4). In addition to cannabinoids, the phytochemicals responsible for the aroma (terpenes) and the color (flavonoids) found in *Cannabis sativa* L. have demonstrated direct anticancer activity on their own and

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may also work additively or synergistically with cannabinoids (5-7).

At this time, there are no published clinical trial data evaluating the use of cannabis in tumor-bearing dogs or cats. To date, there are 4 published canine cell culture studies on the antitumor effects of CBD. The results indicated that CBD at concentrations of 2.5 to 50 micrograms/mL reduced cell proliferation and cell viability in various neoplastic cell lines, including lymphoma, mammary carcinoma, osteosarcoma, glioma, and transitional cell carcinoma. Three of the 4 studies also demonstrated an additive or synergistic effect of CBD with certain chemotherapy agents (8-10). It is important to note that in vitro results do not always translate to clinical efficacy, and the doses required to induce cell death in vivo are often too high and not physiologically feasible. In addition, these studies evaluated the effect of CBD *isolate* on cancer cell lines. A 2018 publication demonstrated that a whole plant extract (with multiple cannabinoids) produced a more robust antitumor response in both cell culture and animal breast cancer models compared to a pure CBD isolate (11). The cannabis plant produces hundreds of other compounds with their own therapeutic potentials and the capability to induce synergy. It is therefore possible that, with a whole plant extract, the dose required to elicit a reduction in cancer proliferation and cell death may be significantly lower.

In the veterinary oncologic setting, the discussion about palliative care options for clinical signs associated with cancer or the treatment of cancer is relatively common. It is well known that cancer and chemotherapy may cause nausea and vomiting, pain, neuropathy, depression, and other debilitating symptoms (12). Current research shows that there is a potential role for medical cannabis in cancer palliation. However, the scale and quality of studies conducted to date are somewhat limited. Below is a brief review of some of the seminal articles and mechanisms of cannabis in palliative care.

Nausea and vomiting

Increasing preclinical evidence suggests that the endocannabinoid system plays a role in the regulation of both nausea and vomiting. For example, THC, via its cannabinoid type 1 receptor (CB1) agonism, reduced the emetic effects of cisplatin chemotherapy-induced emesis in a rodent model (13). CBD-induced suppression of vomiting was reversed by systemic pretreatment with a 5-HT1A antagonist, suggesting that the central antiemetic mechanism of CBD is likely mediated by the activation of 5-hydroxytryptamine (5-HT) 1A receptors (14). Another mechanism includes substance P as being a key neurotransmitter in chemotherapy-induced nausea and vomiting (CINV). Cannabinoids can modulate the release of substance P (15).

Dronabinol and nabilone are both synthetic THCs which the FDA has approved for the treatment of CINV after the failure of a trial of first-line antiemetics. A 2001 systematic review was performed to quantify the antiemetic efficacy and adverse effects of cannabis used for sickness induced by chemotherapy. Results revealed that 3 different versions of synthetic THC were more effective antiemetics than conventional antiemetics such as prochlorperazine, metoclopramide, chlorpromazine, and domperidone. Many patients in the study had a strong preference for THC over conventional antiemetics for future chemotherapy cycles. Unlike cannabis-derived THC, the synthetic THC products used in this study were more potent; therefore, the rates of side effects (both positive and negative) as well as patient withdrawal were significantly higher in the population receiving synthetic THC (16). In addition, in 2007, Meiri and colleagues randomized a small number of patients receiving emetogenic chemotherapy to dronabinol (a synthetic THC), ondansetron, both, or a placebo. Dronabinol and ondansetron were similarly effective for the treatment of CINV, with no additive antiemetic effects noted with the combination of the 2 substances (17). Duran, et al. evaluated 16 patients undergoing chemotherapy who experienced CINV despite standard antiemetic treatment. Patients were randomized to either a short titration dosing of an oromucosal cannabis-based spray containing THC and CBD (1:1 ratio), or a placebo. Those in the treatment group experienced less nausea and vomiting than those receiving placebo. Due to the small sample size, the power of the study was low. Although adverse events were more common in the treatment group (86% vs 67%), they were mostly either mild or moderate (18). The research has shown that cannabinoid therapy has antiemetic effects for only specific chemotherapies, not for all of them.

In general, a route other than oral (eg, inhalation) for cannabis delivery is advantageous when treating nausea and vomiting. However, inhalation is not an easily viable option for pets, and the author has mixed success with other non-oral routes such as intrarectal administration. A 2022 randomized crossover study evaluated the pharmacokinetics of intranasal, intrarectal, and oral administration of CBD in dogs. Despite the intranasal route resulting in faster absorption, higher plasma concentrations were achieved for the oral route. Plasma CBD concentrations after intrarectal administration were below the limit of quantification (19). This may have been due to the hydrophilic nature of the suppository

used. A previous study revealed 67% bioavailability of THC when administered rectally with suppositories in a lipophilic base (20). Cannabinoids, including CBD, have a high affinity for lipids and low water solubility (21).

CBDA, the acid precursor to CBD, is 100 times more potent than CBD in reducing CINV via its 5HT1A agonist activity, and it can work at exceedingly low doses (22). It does not have CBD's biphasic antiemetic effect, which may allow for a wider therapeutic window, and it has also been shown to potentiate the effect of the 5-HT3 receptor antagonist, ondansetron (22-24).

Appetite stimulation

Endocannabinoids regulate eating behavior via several pathways in the brain and the periphery including the hypothalamus and the limbic system as well as the intestinal tract (25). These pathways regulate peptides associated with appetite regulation, including ghrelin, leptin, and melanocortins (25). Medical cannabis, THC specifically, has been shown to increase appetite in humans and laboratory animals, but most of the research is for noncancerous conditions (such as AIDS-related anorexia). Overall, the studies assessing the effects of cannabis or THC on appetite in cancer patients have been equivocal. A Phase 2 study demonstrated that low doses of THC were effective in improving appetite in 72% of patients with advanced cancer (26). Several other publications, however, demonstrated that cannabis-derived products were no more effective as appetite stimulants than was a placebo. Over the past 20 or more years, 6 randomized controlled trials have evaluated the impact of cannabinoids on appetite-related outcomes in oncology patients in comparison with a control group or placebo. There is no definitive evidence that cannabinoids improve appetite, food intake, weight, or appetite-related quality of life in cancer patients. In the author's experience, less than 20% of veterinary cancer patients receiving cannabis appear to experience appetite stimulation.

Cancer-related pain

The etiology of cancer-related pain is complex and not well understood. There is evidence that cannabis can affect both the sensation and perception of pain (15). A large survey study indicated that over 50% of human cancer patients have pain (27). The incidence and severity of pain associated with various cancer types in animals has not been well documented. Similar to humans, pain associated with cancer has varying degrees of severity and is dependent on multiple factors such as location, type of cancer, duration, and presence of inflammation.

Research is promising for cannabis to relieve acute pain from various sources, including cancer. Preclinical studies have demonstrated that cannabinoid receptor agonists can reduce cancer-related pain (28). Two review articles demonstrated that cannabis can alleviate chronic and neuropathic pain in advanced cancer patients (29, 30). A large observational study of cancer patients using cannabis over 6 months demonstrated a decreased number of patients with severe pain and decreased opioid use, whereas the number of patients reporting good quality of life increased (31). The ability to reduce pharmaceutical pain medication when cannabis is used concomitantly is not a new finding in either human or veterinary medicine (32, 33). A 2020 pilot study evaluating a complex spectrum hemp-derived CBD product in dogs with osteoarthritis concluded that 21 of 23 dogs that received CBD treatment were able to either discontinue or reduce their dosage of gabapentin (34). Interestingly, cannabinoids directly target the opioid system as well as work with opioids to modulate both cannabinoid and opioid pathways (35-37).

A 2018 study by Bar-Lev Schleider and colleagues reported that 52.9% of patients with advanced cancer reported a pain level of 8 to 10 on a 10-point scale at baseline, and only 4.6% reported that intensity of pain after 6 months of cannabis treatment. It was concluded that cannabis appears to be a safe and effective palliative treatment for patients with cancer pain (38). A previous multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating the efficacy, safety, and tolerability of 1:1 THC:CBD extract and THC extract in patients with intractable cancer-related pain revealed that the THC:CBD extract was efficacious for the relief of pain in patients with advanced cancer pain which was not fully relieved by strong opioids. Interestingly, there was no significant change in the THC group. There was, however, a decrease in the use of strong opioids observed within both treatment groups (39). A subsequent study by the same author showed that the long-term use of 1:1 THC:CBD oral spray was generally well tolerated, with no evidence of loss of effect for the relief of cancer-related pain. Furthermore, patients who kept using the product did not seek to increase their dose of cannabis or other pain-relieving medication over time, suggesting that the adjuvant use of cannabinoids in cancer-related pain could provide useful benefit (40). Cannabis may be a promising adjunct or an alternative to opioids and other analgesics for cancer-related pain in the future, though more data is needed.

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious dose-limiting adverse effect associated with several

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commonly used chemotherapeutic agents including taxanes, platinum agents, and vinca alkaloids. In veterinary medicine, this particular side effect is rarely seen secondary to chemotherapy but is still possible, especially secondary to vinca alkaloid therapy. The preclinical data on this subject have shown that CBD prevents the development of paclitaxel-induced mechanical sensitivity in mice and that its clinical use may be enhanced by co-administration of low doses of THC (41, 42). The mechanism for CBD in this case appears to relate to the serotonin receptor 5-HT1A, similar to its antiemetic mechanism.

Most studies evaluating the efficacy of cannabis on CIPN are preclinical in nature; however, a recent paper indicated a statistically significant protective effect against the development of CIPN in patients who received cannabis prior to oxaliplatin chemotherapy (43).

A recent case series suggests that topical cannabinoids may be helpful for patients with CIPN (44). The application of topical cannabis for cancer or cancer-related pain is a reasonable treatment option in pets, as the author has found high owner compliance and essentially absent side effect profiles with this approach. Caution should be taken to monitor patients for licking or ingestion of topical products (especially ones containing THC) and for signs of skin irritation, particularly when utilizing products that contain terpenes or inactive ingredients that may act as irritants or allergens.

Despite limited randomized clinical trials in humans, cannabis shows promise as an antitumor agent as well as the ability to improve clinical signs associated with cancer and its treatments. Several cannabinoids and terpenes offer a more natural approach to enhancing direct or indirect cytotoxicity and improving quality of life. Recent changes in the social climate and the legalization of cannabis will hopefully facilitate an increase in the number of high-quality studies performed. These studies will be essential in order to identify and confirm which compounds (cannabinoids, terpenes, flavonoids) and doses provide superior antitumor and palliative effects. It is time to move beyond in vitro studies and conduct clinical trials in tumor-bearing companion animals. Despite the large number of pharmacokinetic, pharmacodynamic, and safety data (including long term safety) in dogs, similar studies need to be conducted in tumor-bearing

animals to establish baseline values and safety in that particular population. As previously mentioned, in vitro results do not always translate in vivo. Specifically, the targeted tissues may not require the same concentrations that have been established to elicit cell death in vitro, organs may absorb different levels of cannabinoids than what is found in plasma, and the use of a complex spectrum product may require significantly lower doses than isolates. A polypharmacy approach should be considered when developing clinical trials that use cannabinoids as adjuncts to established cancer therapies, with the potential of improved efficacy and reduced side effects.

This case report illustrates the principles that underlie combination pharmacology, specifically the integration of specific cannabinoids and terpenes to provide additive or superadditive effects. *Additive effect* describes the combination of 2 drugs or compounds that equals the sum of the expected effects of both drugs acting independently. It is critical to recognize that combining 2 or more drugs (or compounds) may be associated with reduced efficacy or greater side effects, known as a *subadditive effect*. *Superadditive* (sometimes referred to as synergistic) effect refers to the combined result of 2 or more drugs or compounds being greater than the sum of their individual effects.

Cannabis, similar to many alternative treatments, requires a personalized approach. Products and doses should be selected based on multiple patient factors including the presence of comorbidities, breed, age, potential for drug interactions, pet and client tolerability for side effects, and ultimate goals (palliative vs definitive intent).

In the case described in this report, the cat had no known contraindications or possible drug interactions, and the owner was seeking palliation and to reduce inflammation and pain associated with her pet's osteoarthritis and skeletal deformities. The cat's formula included CBD specifically for its potential antitumor, anti-inflammatory, and antiemetic activity (3, 45, 46). The THC was included for its potential antitumor, analgesic, appetite stimulatory, bronchodilatory, and antiemetic properties (3, 27, 29, 47). The terpenes beta-caryophyllene, alpha-pinene, and linalool were intentionally added for their potential anti-inflammatory, bronchodilatory, and calming effects respectively, as well as for their potential antitumor effects (3, 48-51).

Per the author's clinical experience, the rapid response (within 1 week of starting the cannabis product) is fairly typical in most palliative-intent cancer cases. Here, the argument could be made that the cat's initial clinical improvement may have resulted from the 2 doses of prednisolone, especially if his diagnosis was lymphoma or lymphocyte-rich thymoma. However, it is incredibly unlikely that it would take more than a week for prednisolone, an intermediate-acting steroid with a half-life of 12 to 36 hours, to provide a clinical response. Also, prednisolone would not likely maintain clinical improvement for almost 6 months.

This case demonstrates the importance of gradual titration to find the individual pet's optimal therapeutic dose (providing maximal benefit without causing side effects). As the cat was slowly titrated to higher doses (while also reducing the overall CBD:THC ratio), tolerance to the negative effects of THC developed. This allowed an increase in the THC dose from 0.42 mg/kg to 1.1 mg/kg. As the owner had experience with cannabis, the cat was monitored closely for side effects including constitutional (lethargy), neurologic (ataxia, dysphoria), GI (vomiting, diarrhea), and behavioral (mood or vocalization) changes.

Without a definitive diagnosis, it is difficult to confirm how much longer the cat lived compared to the expected survival time or if a measurable objective response was achieved (follow up radiographs were not performed). This cat, however, with the help of cannabis, enjoyed a significantly improved quality of life that provided comfort for 6 months.

Clinical evidence in populations with cancer is beginning to emerge to support the use of cannabis for treating CINV, loss of appetite, pain, and peripheral neuropathy. There are also data from other disease conditions that suggest that cannabis could potentially alleviate anxiety, depression, fatigue, and sleep disorders. Improving the quality of life of the veterinary cancer patient should be a top priority. Although the field is in the nascent stages of development, cannabis may play an important role in the management of clinical signs in this population. It is important to discuss the potential benefits and adverse effects of cannabis and to provide guidance to pet owners regarding appropriate starting doses, titration, and product selection.

Cannabis has multifaceted potential therapeutic benefits that appear to outweigh its risks (when dosed appropriately) in many cases. There remains a need for high-quality, randomized, placebo-controlled trials in tumor-bearing companion animals to properly elucidate safety and efficacy as well as to optimize cannabis preparations and doses in both the definitive and palliative intent settings. This case is a good example of how cannabis provided palliative support to a cat with a diagnosis of advanced-stage cancer.

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