Narrative review:
cannabinoids in veterinary medicine

Executive summary

The purpose of this analysis was to better understand the safety, efficacy and pharmacokinetics of cannabinoids in veterinary populations. In the past 2 years there has been a high volume of quality cannabinoid research in veterinary medicine. Results from placebo-controlled interventional studies and preclinical controlled studies are included here.

All cannabinoid types were included however the most common cannabinoid investigated was cannabidiol either as an isolate or as the dominant isoform.

To our knowledge (as of 31st May 2021) there have been 9 interventional studies in canine populations exploring safety (6 studies) and efficacy endpoints (7 studies). Four studies investigated both safety and efficacy-related endpoints. These studies are summarised in Table 1, Table 2 and Table 3 below. Indications explored in these populations were osteoarthritis, epilepsy and anxiety - the only justified clinical applications of cannabis in veterinary medicine according to a recent systematic review by Hazzah et al., 2020 and confirmed by the present narrative review.

There have been 2 interventional studies in feline populations all of which explored safety and pharmacokinetics endpoints. There have been no studies of efficacy in feline populations and as such, all reports of cannabinoid efficacy in cats remain anecdotal. The growing number of safety and pharmacokinetics studies in felines will inform efficacy studies in the future. Equine cannabinoid research would benefit from bioequivalence studies exploring cannabinoid effects in conditions known to improve in humans and canines.

There have been 2 interventional studies in equine populations, both of which measured efficacy through effects on wound healing and movement reactivity. While there was nil effect on wound healing potentially owing to a low dose explored, movement reactivity was altered following cannabidiol dosing. Similarly to feline research, equine cannabinoid research would benefit from bioequivalence studies based on promising results in human and canine populations.

While the tables below summarise clinical studies performed, the review explores other aspects of veterinary medicine where anecdotal evidence exists and veterinary practitioners have expressed interest in exploring. These are the endocannabinoid system, broad anti-inflammatory effects, novel formulation opportunities, respiratory disease, gastrointestinal and endocrine disease, cognitive and neurological disease, and neoplasia. Further study in these areas is warranted.

Review

The endocannabinoid system, cannabinoids and veterinary medicine

The endocannabinoid system (ECS) plays a neuromodulatory role in many physiological and pathophysiological processes - broadly, the role is homeostatic. The ECS is often either up-regulated or down-regulated in disease states. Through their actions on the endocannabinoid system, cannabis and its constituents are increasingly being recognized as bona fide pharmacologic agents which boast significant therapeutic potential. Importantly, the cannabis plant does not consist of a single therapeutic agent but rather a heterogeneous blend of a multitude of compounds with distinct pharmacological uses. For example, cannabidiol (CBD), the major non tetrahydrocannabinol (THC) constituent of cannabis, can exert numerous biological effects through several different receptors and signaling pathways, including anti-inflammatory effects in both acute and chronic conditions. A useful detailed exploration of the endocannabinoid system in the context of veterinary medicine was published by Hazzah et al., 2020.

The most common and scientifically justified clinical applications of cannabis in veterinary medicine to date are analgesia for osteoarthritis and anticonvulsant activity for epilepsy in canines (Table 1). There are no clinical studies monitoring disease states in felines, however the safety and pharmacokinetics studies completed to date lay the groundwork for further research (Table 2). There have been two clinical studies monitoring cannabinoids for disease states in equine populations at doses unlikely to be effective based on canine and human research (Table 3).

Broad anti-inflammatory effects and novel formulations

CBD exerts robust and quantifiable anti-inflammatory effects in experimental and clinical paradigms. CBD has been shown on multiple occasions to significantly decrease pain, increased mobility and reduced levels of inflammatory cytokines IL-6 and TNF-a in a dose-dependent fashion in canines diagnosed with arthritis (Table 1). Osteoarthritis aside, inflammation forms the basis for many diseases that animals present with in the veterinary context, including asthma, inflammatory bowel diseases, anxiety, diabetes, epilepsy and cancer. Tangential preclinical evidence for therapeutic effects in these domains warrants further investigation in a clinical study context.

Novel formulations of CBD have been shown in the context of pain to improve CBD innate poor bioavailability, insights which can broadly be applied to other areas of veterinary medicine. CBD ordinarily has poor bioavailability that can be improved with formulations that improve water solubility, such as a liposomal formulation. Liposomal CBD (20 mg/day) was shown to be as effective as the highest dose of non liposomal CBD (50 mg/day) in improving pain outcomes using a proprietary product developed by Medterra. This formulation could see promise in equine medicine where the effective doses are multiple fold higher than required for canines and felines.

Table 1. Veterinary studies in canine populations

Efficacy outcomes		
Authors	**N, indication**	**Results**
Gamble et al., 2018	N=14, osteoarthritis	CBD oral oil 2 mg/kg twice daily for 4 weeks decreased pain and increased activity compared to PLB. Owner and vet-assessment.
Brioschi et al., 2020	N=21, osteoarthritis	CBD oral transmucosal 2 mg/kg twice daily for 12 weeks decreased pain and mobility. Owner assessment.
Mejia et al., 2021	N=23, osteoarthritis	CBD oral oil (dose unspecified) daily for 6 weeks did not affect movement when measured objectively via accelerometry and clinical metrology.
Kogan et al., 2020	N=37, osteoarthritis	Full spectrum 13:1 CBD:THC oral oil 0.25 mg/kg (over 90 days) improved (vet-reported) pain and mobility. Enabled reduction in gabapentin dose in over half of cohort. A subset of these (¼ of cohort) ceased gabapentin altogether.
McGrath et al., 2019	N=26, epilepsy	CBD oral 2.5 mg/kg twice daily for 12 weeks (in addition to anticonvulsants) reduced seizure frequency by 33% compared to anticonvulsants alone
Morris et al., 2020	N=16, anxiety	CBD oral 1.4 mg/kg daily for 7 days did not improve anxiety endpoints in the canine population.
Corsetti et al., 2021	N=24, aggression	CBD oral oil 0.5 mg/kg daily for 45 days appeared to reduce aggressive behaviour, however the reduction in aggression was not statistically significant.
Safety outcomes		
Authors	**N, indication**	**Results**
Gamble et al., 2018	N=14, osteoarthritis	CBD oral oil 2 mg/kg twice daily for 4 weeks did not result in any owner-reported side effects. Clinical tests suggestive of liver damage (ALP). PK half life of 4.2 hours.
Deabold et al., 2019	N=8, healthy	CBD oral chews 2 mg/kg twice daily for 12 weeks appeared safe based on CBD and biochemistry values.

Brioschi et al., 2020	N=21, osteoarthritis	CBD oral transmucosal 2 mg/kg twice daily for 12 weeks with no severe side effects. Cell count and serum chemistry were not performed.
Mejia et al., 2021	N=23, osteoarthritis	CBD oral oil (dose unspecified) daily for 6 weeks. Clinical tests suggestive of liver damage (ALP) in n=14 canines. Vomiting in n=2 canines.
Chicoine et al., 2020	N=13, healthy	Oral CBD dominant formulation (1:20 THC:CBD) of 2, 5, 10 mg/kg delivered as a single dose resulted in neurological symptoms (hyperesthesia or proprioceptive deficits) in ⅝ dogs treated with 10 mg/kg. These symptoms were rare in the medium and low dose groups.
McGrath et al., 2019	N=26, epilepsy	CBD oral 2.5 mg/kg twice daily for 12 weeks (in addition to anticonvulsants). Clinical tests suggestive of liver damage (ALP). No adverse effects were reported by owners.

PLB, placebo; ALP, alkaline phosphatase enzyme; PK, pharmacokinetics

Respiratory disease

To date, there have been no canine or feline studies conducted in asthma. The attenuating effect of CBD on pro-inflammatory cytokines mentioned above in the context of inflammatory pain may be extrapolated into the context of pulmonary inflammatory disorders such as asthma. It is hypothesised that CBD regulates oxidative stress and lipopolysaccharide (LPS) induced inflammatory responses in macrophages, epithelial cells, and fibroblasts - all of which are implicated in the disease processes of pulmonary inflammation. In human bronchial cells, CBD differentially regulated basal pro-inflammatory response and attenuated both LPS-induced cytokine release and NF-κB activity in monocytes, similar to dexamethasone - a common medication for asthma and pulmonary disorders.

Interestingly, while CBD and dexamethasone treatments both reduced inflammation when treated individually, they showed antagonistic effects when used in combination. This is preliminary evidence to suggest that CBD may override the anti-inflammatory potential of steroids when dosed simultaneously - an important clinical consideration. Certainly further targeted studies in the area are warranted.

Gastrointestinal and endocrine disease

To date there have been no studies in vet populations to explore gastrointestinal disorders - however the preclinical results in cell and rodent models described are promising. The gastrointestinal effects of cannabinoids are mixed - adverse events and gut-specific anti-inflammatory action are both observed.

Gastrointestinal effects of cannabinoids in clinical veterinary populations have predominantly presented as adverse events. For example, mild adverse events after CBD dosing mainly manifest as

gastrointestinal including nausea, vomiting and diarrhea. Gastrointestinal effects are less common but still somewhat prevalent with THC containing/THC dominant formulations. While they are mild and transient, the incidence of gastrointestinal adverse events in human and veterinary populations makes it seem counterintuitive that cannabinoids could have therapeutic effects.

Inflammatory bowel diseases are caused by unbridled inflammation, and in a human cell model of inflammatory bowel disease, cannabidiol was shown to reduce inflammation and permeability through interacting with inflammatory cytokine pathways and intestinal tight junction proteins, respectively. Therapeutic action at these targets is important for ensuring the patient can optimally absorb nutrients from their diets. Results from this study present further evidence that the gut is dependent centrally on endocannabinoid tone for the immune response and barrier function.

While there are no studies looking into cannabinoids for diabetes control in canine and feline populations, the area has been explored in murine models with promising results. Experimental cannabidiol treatment reduced early pancreatic inflammation in type 1 diabetes based on quantification of microscopic levels of circulating inflammatory markers (Lehmann et al., 2016).

Table 2. Veterinary studies in feline populations

Efficacy outcomes		
N/A		
Safety outcomes		
Authors	**N, indication**	**Results**
Kulpa et al., 2021	N=20, healthy	Titration up to 30.5 mg/kg CBD and 41.5 mg/kg THC were achieved over 6-7 weeks starting from 2.8 and 3.8 mg/kg respectively. All side effects were mild and transient. Side effects of lethargy, hypothermia and ataxia were common in the THC group. No toxicity concerns from clinical chemistry.
Deabold et al., 2019	N=8, healthy	CBD oral chews 2 mg/kg twice daily for 12 weeks appeared safe based on CBD and biochemistry values. Adverse events of excessive licking and head-shaking in ¼ to ⅓ of cats. Less prevalent adverse events were pacing, chewing, gagging and vomiting. Nil cats experienced loose stool.

PLB, placebo;

Cognitive and neurological dysfunction

Cognitive dysfunction refers to deficits in attention, verbal and nonverbal learning, short-term and working memory, problem solving, processing speed, motor functioning, and visual and auditory processing. Anxious and aggressive phenotypes may be associated with cognitive dysfunction - for

example the owner of an anxious dog may notice poor attention and poor working memory. Addressing underlying anxiety would in turn yield improvements in cognitive domains. The anxiety and aggression studies in canine populations above provide preliminary evidence for a role for cannabinoids in cognitive dysfunction - noting that the dose required to elicit an effect may be above 1.4 mg/kg, as this dose was not seen to be effective in the study tabulated above (Table 1).

Canine anxiety, and noise aversion are some of the most common reasons that pet owners seek information on and administer CBD to their pets. One study addressed that anxious canines can be triggered by loud noises, noting that strong medications to cope with this trigger (such as benzodiazepines, given to humans for anxiety) are not sustainable due to side effects. Human studies into the effects of cannabidiol on anxiety also in part arose from concern regarding side effects of first like anxiolytic therapies. These studies have to date been balanced towards efficacy results within an approximate dose range of 5 -10 mg/kg (in a 60 kg adult).

The potential anxiolytic effects of CBD have been attributed to several mechanisms, including its activation of 5-HT1A receptors and its ability to indirectly activate cannabinoid receptors by inhibiting the metabolism of the endocannabinoid anandamide. CBD effects on cortisol have been speculated, however the results from the anxiety study tabulated above suggest an alternative mechanism may be responsible for therapeutic effect at the dose administered.

Promising results in canine epilepsy studies (Table 1) may be extrapolated to feline populations, however cannabinoids are yet to be explored in feline epilepsy (Table 2). Studies in this specific population is warranted, as there is evidence to suggest that felines respond to cannabinoids in a divergent way to dogs. For example, felines appear to tolerate higher levels of THC than canines before experiencing adverse effects and toxicity. While the toxic limit for THC in dogs is known, observed to cause seizures at and above 3 grams per kilogram body weight, the toxic in cats has not been characterised.

Table 3. Veterinary studies in equine populations

Efficacy outcomes		
Authors	**N, indication**	**Results**
Drager et al., 2020	N=24, healthy (reactivity, movement)	CBD oil 50 mg daily for 6 weeks (~0.13 mg/kg in 400kg adult horses) reduced reactivity scores and horses spent more time in stance phase.
McIver et al., 2020	N=6, superficial wound	1% CBD in manuka honey topical application for 42 days did not show CBD to be effective compared to placebo.
Safety outcomes		
N/A		

PLB, placebo;

Neoplasia

No clinical studies in canines or felines to date have treated or induced neoplasia, a process of cellular proliferation leading to benign and malignant tumors, however murine models of cannabinoids in neoplasia can be used to form the basis for our understanding of effects in veterinary populations.

Inflammation is implicated in cancer genesis and proliferation. Cannabidiol has been shown to exhibit similar anti-inflammatory effects in neoplastic processes to those explored above in pain. Studies suggest cannabidiol could potentially be considered as an anti-colon cancer medicine as it exerts an inhibitory effect on angiogenesis, tumor growth, and metastasis through reducing VEGF gene expression, decreasing cytokines, and increasing antioxidant enzyme activities (Honarmand et al., 2019).

As mentioned the effects of cannabinoids can be quite distinct. There is some preclinical evidence that CBD and THC may have divergent anti-tumor effects. For example, one study showed that the treatment of brain cancer and lung cancer cell lines treated with THC led to increased cell proliferation. This study suggests in cancer therapy, it is very important to consider the risk of acceleration of tumor growth due to the concentration-dependent proliferative potential of cannabinoids (Honarmand et al., 2019).