Cannabidiol and naturalistic fallacy: it's natural so it's safe?

The projected market value of the UK CBD industry looks to hit £1 billion by 2025. The statistics for its safety in animals are not easily obtainable. Many owners could be, and are suspected to be, using CBD products without a veterinary prescription. Many are using CBD as a 'natural' alternative, it is important to question and explore this relatively new trend to assess if natural really does mean safe and benign, and importantly if there is enough evidence base to warrant its use in veterinary medicine.

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Cannabidiol is derived directly from the cannabis plant, a flower in the *Cannabaceae* family. Cannabis is a complex plant, with 400 chemical entities of which more than 60 are cannabinoid compounds; the major compounds being delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The discovery of these compounds has led to the further discovery of an important neurotransmitter system called the endocannabinoid system (Atakan, 2012). Gamble et al (2018) suggested that medical interest in alternative therapy has been focused on looking for more 'natural' routes, as they are believed to have less side effects or contraindications than conventional medicines.

Cannabidiol, known and marketed as CBD, is a compound that interacts with the endocannabinoid system. Until the mid-1990s the endocannabinoid system was relatively unknown, since then research into this potentially clinically useful system is advancing rapidly in humans, and animal studies are also emerging.

The projected market value of the UK CBD industry looks to hit £1 billion by 2025 (Gibbs et al, 2019). The statistics for the potential animal market are not easily obtainable. Many owners are suspected to be using CBD products without a veterinary prescription, as a 'natural' alternative to pharmaceutical products. It is important to question and explore these emerging trends to assess if 'natural' really does mean that something is safe and benign and, most importantly, to consider whether there is enough of an evidence base to warrant the use of CBD-based products in veterinary medicine.

The endocannabinoid system

Our improved understanding of the endocannabinoid system of animals, and its ubiquitous presence in nearly all animalia, has potentially opened the door to a novel approach to targeting a number of conditions such as pain, behaviour/anxiety issues and conditions of the central nervous system. However, it is important to note that studies are still in their infancy and many studies conducted have small sample sizes, meaning it is difficult to draw strong conclusions.

Endocannabinoid receptors are found throughout the bodies of all animals; anatomical locations for the CB1 receptor include the heart, blood vessels, liver, lungs, digestive system, fat and sperm cells. Studies have shown that dogs have large numbers of cannabinoid receptors in the cerebellum, brainstem and medulla oblongata. CB2 receptors have mainly been found in cells of the immune system, the spleen and tonsils (Silver, 2019).

Side effects and contraindications

There are currently no CBD-based products that have been granted a UK veterinary marketing authorisation in the UK. The Veterinary Medicines Directorate (VMD) state that CBD products for use in animals are a veterinary medication, therefore require a marketing authorisation before they can be sold or supplied in the UK. The VMD also state that as veterinary medicines, veterinary products containing CBD should be regulated as such on the basis that they fulfil the definition of a veterinary medicine in the Veterinary Medicines Regulations (VMR, 2013) by virtue of the effects they have.

Many clinicians and veterinary professionals may come across owners who are already using CBD in their animals, having read online about them. These sources of information are rarely based on any solid evidence, and are more commonly anecdotal, so can regularly contain misinformation.

It is especially important to understand the prevalence of owners using, or considering the use CBD products without a veterinary prescription, or without their veterinary surgeon's knowl-

edge, because of the possible implications for pharmacological interactions or side effects.

Owners generally appear to see CBD as a natural product and therefore assume that it is 'safe', with one study stating that a positive attitude towards the safety and efficacy of CBD was attributed to CBD being a natural product (Bhamra, 2021), but it is important to prove this is true.

Hepatic function

Results from a number of studies suggest that CBD causes changes in hepatic function. The reason for this is not yet known, and there have been no studies looking into the impact of CBD long-term. However, it could be a result of a toxicological response or adaptative response, as a return to normal alkaline phosphatase (ALP) levels was seen after treatment was ceased (Tittle, 2022). It has been suggested that the direct activation or inhibition of nuclear receptors in the liver cells by cannabinoids may result in a change of expression and activity of cytochrome P450 enzymes, which could account for some of the hepatic changes seen.

Gamble et al (2018) found that serum biochemistry showed an increase in ALP. Serum chemistry values did not differ between a placebo and CBD oil, except for ALP levels, which significantly increased over time from baseline by week 4 of CBD oil treatment; with nine of the 16 dogs showing increases over time. Increased ALP activity noted in the CBD treatment group may be an effect of the hemp extract, attributed to the induction of cytochrome P450-mediated oxidative metabolism of the liver (reported previously with prolonged exposure to cannabis). The changes in ALP levels may bring into question concerns over long-term use and hepatic health in companion animals.

In a study regarding canine epilepsy, it was seen that the CBD group had a significant increase in serum ALP activity. Two dogs in the CBD group developed ataxia and were withdrawn from the study, no other adverse behavioural effects were reported by owners (McGrath et al, 2019).

In contrast to this, in another study using higher dosages (20mg/50mg and 20mg liposomal) there were no significant alterations to cannabichromene, metabolic panel, or alanine aminotransferase/ALP values over the course of the study in any group. Gamble et al (2018) recommend that it may be prudent to monitor liver enzyme values (especially ALP) while dogs are receiving hemp products, until controlled long-term safety studies are published. The author concurs with this suggestion, owing to the nature of the current evidence and that fact that many owners will be using CBD long-term for chronic conditions, thus it is important to establish if hepatoxicity will be an issue with long-term use.

Toxicological effects

The Food Standards Agency (FSA) and the Committee on Toxicology detail several potential toxicological effects that still need to be more thoroughly investigated in companion animals. The Committee on Toxicity (2020) stated: 'Based on the available in vitro and in vivo data, CBD appears to have the following adverse effects: hepatotoxicity, immunotoxicity, reproductive toxicity, and interactions with drug metabolizing enzymes (P450), suggesting a risk to consumers. In addition, the effects on drug metabolizing enzymes following CBD exposure indicate the potential for drug interactions between CBD and pharmaceutical drugs.'

Long-term harm

Some current human and animal studies report a fairly benign safety profile, bar the hepatic changes, and some exclusions such as ataxia. In animals, the long-term 'harms' have not yet been investigated, with most studies being no longer that 12 weeks in duration. Looking at human literature could raise some questions as to areas for future study, in order to consolidate the long-term safety data for veterinary CBD products.

In a systematic review by Zeraatkar et al (2022) investigating the long-term and potentially serious harm of using medical cannabis and cannabinoids for chronic pain in humans found that adverse events are common among people living with chronic pain, but few patients experience serious adverse events.

There are differences in the prevalence and location of endocannabinoid receptors in humans and dogs, so it is not possible to directly extrapolate study data. It is important to take this into consideration for a number of reasons. Silver (2019) states that the US government conducted studies that determined that dogs have large numbers of cannabinoid receptors in the cerebellum, brainstem and medulla oblongata, which could explain the symptoms of 'static ataxia', which is a unique neurological reaction to THC in the dog. THC is a psychotropic compound, whereas CBD is not, but given the high number of receptors found in dogs, we may be able to deduce that dogs may be more susceptible to CBD than humans.

Most conditions that people are using CBD for are chronic in nature. Therefore, it needs to be noted that administration will be long-term. Many studies so far have not exceeded 4–12 weeks, so studies looking at the long-term implications are warranted.

The systematic review by Zeraatkar et al (2022) compared studies with <24 weeks and ≥24 weeks cannabis use and found more adverse events reported among studies with longer follow-up. They noted that this may be explained by increased tolerance or tachyphylaxis with prolonged exposure, requiring increases in dosage with a subsequently increased risk of adverse events. This phenomenon does not appear to have been documented in companion animal literature yet, but knowledge of optimal dose ranges for long-term use, particularly in animals with chronic conditions, would be useful.

Memory deficits

In humans, endocannabinoid system stimulation that is excessive and prolonged can lead to memory deficits. Upon cessation of prolonged endocannabinoid system stimulation, withdrawal symptoms have been seen to develop. Withdrawal symptoms in dogs have been documented following tolerisation, but impaired memory has not yet been studied in veterinary species (Silver 2019).

Interactions with P450 enzyme system

Zendulka et al (2016) stated that interactions between cannabinoid receptor ligands of both exogenous and endogenous origin and cytochrome P450 enzymes are possible between CBD and

KEY POINTS

- CBD is growing in popularity among pet owners, but it should only be prescribed by a veterinary surgeon.
- There is no CBD-containing product in the UK with veterinary marketing authorisation
- Many clients use it because they believe it to be natural and therefore safe, so it is important to educate that this may not be the case.

other compounds given.

The drug–drug interactions between cannabinoids and various drugs at the cytochrome P450 enzymes level have been reported, but their clinical relevance remains unclear. In veterinary patients, this interaction must be at the forefront of vets' minds – it is important to question owners to ascertain if they are giving a CBD -based product.

As CBD is metabolised via the P450 enzyme system, there is concern that the concurrent use of CBD with drugs that are also metabolised through that pathway may have their pharmacokinetics altered (Silver, 2019). This could alter their therapeutic value, which stresses the importance of veterinary surgeon asking clients during routine appointments if they are giving any other medicines or supplements that the veterinary surgeon is not aware of.

Conclusions

CBD is certainly an interesting compound, and may prove to be an essential tool in our kit in the future. At present, studies are still very much in their infancy and we still have much to learn. Clients should be made aware that 'natural' does not mean safe, nor effective. Patients may be receiving a CBD product obtained by their owner which may not be effectively treating or alleviating their condition, but may also be causing negative side effects and interactions with a prescribed treatment protocol. It is therefore important to ascertain if an animal is being given a CBD product, and if they are that their owners are aware of the legislative restrictions (*see the next article in this series*) and possible negative implications of doing so. CA

Conflicts of interest

The author has no conflicts of interest to declare.

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