

# The Use of ElleVet Sciences Calm and Comfort Acute Strength CBD+CBDA Chews for Anxiety Inducing Events in Dogs

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## Summary

Anxiety in dogs is a significant health issue and a primary reason for veterinary and behavior specialist visits. Phytocannabinoids, such as CBD, are thought to be an effective means of addressing anxiety in dogs, but there is a lack of evidence to support this, aside from a myriad of anecdotal reports of success. However, there is a need for a treatment that can effectively mitigate anxiety and phobias in dogs. Untreated, anxiety creates chronic stress, with the associated health and human-animal bond issues. With prolonged stress, there is an increase in cortisol production and a depression of the catecholamine system, which in turn affects the immune system and is a contributor to stress related diseases such as GI diseases, dermatological issues, respiratory and cardiac issues as well as significant behavioral problems<sup>1</sup>. ElleVet Sciences, the leader in cannabinoid research in companion animals, developed a CBD+CBDA (the native acid form of CBD found in plants naturally) acute strength soft chew designed to address anxiety and phobias in canines without side effects, often observed with other pharmaceuticals. This novel product was the subject of a pilot study to evaluate canine response to anxiety producing events after treatment with the chews and to determine the efficacy and safety of the novel product based on client outcome measures.

## Introduction

According to the AVMA, 20-40% of dogs referred to a behavior specialist are referred for anxiety related issues<sup>2</sup>. A June 2016 Harris online poll of pet owners suggests that 44% of dogs have noise aversion related anxiety<sup>3</sup>.

Tynes (2014)<sup>4</sup> defines stress as “any chemical, physical or emotional force that interferes with an organism’s homeostasis”. Tynes further defines phobias as “persistent and excessive fears of certain things or situations that usually are out of proportion to the actual threat that they present<sup>5</sup>”. Fear is a normal reaction to perceived danger.

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<sup>1</sup> Overall K.L. Karen Overall on the Effects of Fear on Veterinary Patients. [(accessed on 21 December 2016)];2014 Available online: <http://veterinarynews.dvm360.com/facing-fear-head-tips-veterinarians-create-more-behavior-centered-practice>.

<sup>2</sup> <https://www.avma.org/javma-news/2017-07-01/dogs-overdrive>

<sup>3</sup> <https://www.zoetisus.com/news-and-media/recent-consumer-research-indicates-more-than-40-percent-of-dog-owners-say-their-dogs-suffer-from-noise-aversion.aspx>

<sup>4</sup> Tynes V.V. The Physiologic Effects of Fear. [(accessed on 21 December 2016)];2014 Available online: <http://veterinarymedicine.dvm360.com/physiologic-effects-fear>

<sup>5</sup> von Bernhardi R., Bernhardi L.E., Eugenin J. (2017) What Is Neural Plasticity? In: von Bernhardi R., Eugenin J., Muller K. (eds) The Plastic Brain. Advances in Experimental Medicine and Biology, vol 1015. Springer. Available online: <https://www.ncbi.nlm.nih.gov/pubmed/29080018>

Anxiety, on the other hand, is the anticipation of future danger, and a persistence of anxiety has a deleterious effect on the dog's overall wellbeing. Noise phobias, most notably thunderstorms and fireworks, can cause an extremely fearful reaction in a dog, resulting in immediate physiological response, which then can increase in severity with each future experience. Separation anxiety, a widespread canine response to being left alone, is a significant cause of chronic anxiety and stress, and can manifest in behavioral problems such as property destruction and self harm.

Separation and noise phobias are the most commonly reported anxiety issues. However, anxiety can result from many other fear-producing events such as veterinary visits, kennel stays, grooming, car rides or stranger anxiety. While behavior modification and removal of triggers is the ideal way to resolve anxiety, there are limitations, particularly with separation, where it may not be possible to remove the trigger, and noise phobias, where the stress level is so high that behavior modification without medical intervention is difficult. One of the biggest concerns with relying primarily on behavior modification techniques is the unrealistic time commitment by owners to carry out the tasks necessary and where the synergistic use of pharmacologic interventions becomes useful, particularly when triggers can be anticipated.

Traditional pharmaceutical interventions have their limitations, including potential toxic or untoward side effects including sedation, neurologic ataxia, and personality changes. In addition, there are many pet owners who have negative perceptions and reservations regarding the use of pharmaceuticals. Treatment with ElleVet's extra strength CBD+CBDA is a potential solution meeting a need for quick and short acting intervention that has few to no side effects that are often associated with pharmaceutical products.

## **Background**

ElleVet Sciences is the first company to conduct a successful clinical trial on dogs with osteoarthritis using their CBD+CBDA product. The study, conducted in collaboration with Cornell University College of Veterinary Medicine, has shown approximately an 80% efficacy rate in reducing pain in canine OA. During this study a personal observation of the primary investigator was that dogs appeared less anxious during veterinary manipulation providing us cursory information to pursue use of ElleVet as an anxiolytic agent. ElleVet is committed to evidence-based products and has multiple clinical trials ongoing as well as a published long-term safety study on the use of CBD+CBDA for dogs and cats. ElleVet is the leader in scientific research in the field of cannabinoids as a treatment for companion animals.

The endocannabinoid system, or ECS, is one of the largest receptor systems in the mammalian body and is responsible for maintaining homeostasis in the body. The ECS is comprised of endogenous cannabinoids (endocannabinoids or eCBs), cannabinoid receptors (CB1 and CB2), and enzymes responsible for the synthesis and degradation of endocannabinoids. Endocannabinoids are distinguished from other neuromodulators in that they are produced “on-demand,” rather than synthesized in advance and stored, and respond on demand to events or stimuli<sup>6</sup>. The eCBs plays a vital role in maintaining homeostasis in several organs and systems, including the brain and the Central Nervous System (CNS). As stress is a force that alters an organism’s homeostasis, examining the effect of CBD on anxiety and stress is a reasonable investigation. Stress resilience is related to a healthy ECS, and along with healthy habits, the use of cannabinoids can contribute to the robustness of this system. Most interestingly is that CBD itself does not act directly on the ECS, but rather inhibits the degradation of the body’s own naturally produced ligand to the ECS system; in essence, giving it a boost. Further, the eCBs are thought to be important in cognitive functions such as the extinction of aversive memory, which supports CBD as a potential mediator of strong fear reactions as seen in dogs with noise phobias. The ECS is responsible for processing stress and the associated memories, as well as the physical response such as the fight or flight response or post traumatic stress (PTSD) response, which involves neuroendocrine release. Impaired fear extinction is a symptom of anxiety disorders and continued exposure to the stimuli can elicit traumatic memories and flashbacks from a deficit in the neural mechanism involved in fear extinction.

A study on rats with induced PTSD response indicates that administration of the CB/CB2 cannabinoid receptor agonist normalizes behavioral and neuroendocrine abnormalities resulting from prior stress exposure. The study further suggested that the administration of the cannabinoid receptor agonist within 24 hours of the stressful event was necessary to prevent the stress induced disruption<sup>7</sup>. Although CBD is not a direct agonist to the CB receptors it causes a heightening of natural ligands to be formed in the nervous system accentuating natural tone of the ECS system. Fear extinction, or the ability to rewire the neural pathways to tone down the heightened fear response with the administration of CBD prior to a trigger event, is a potentially highly effective means of addressing noise phobia in dogs. Furthermore, CBD appears to stimulate neuroplasticity, or the brain’s ability to reorganize itself with new neural connections,

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<sup>6</sup> Neural Dev. 2018 Jun 1;13(1):9. doi: 10.1186/s13064-018-0105-x. Homeostatic plasticity in neural development. Available online: <https://www.ncbi.nlm.nih.gov/pubmed/29855353>

<sup>7</sup> Cannabinoid Modulation of Midbrain Urocortin 1 Neurons During Acute and Chronic Stress. N. M. Derks O. Pintér W. Zuure C. Ledent M. Watanabe C. S. Molnár Y. Wei E. W. Roubos S. Wu E. Hrabovszky D. Zelena T. Kozicz. Available online: <https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2826.2012.02355.x>

helping to explain the positive effects of CBD on both anxiety and depressive disorders in animals.

## **Study**

This pilot study is the first to objectively evaluate the success of minimizing anxiety in dogs using a cannabinoid product. In this study, 24 dogs with owner reported anxiety in their animals were enrolled in the study. While it can be challenging to measure behavioral changes in dogs objectively, the dog owner's assessment remains paramount. Pet owners were given questionnaires that included questions on time until effect, duration of effects, how readily the dog took the chew, as well as specific questions on the type of response seen.

The pet owners in the trial were interested in using a CBD-rich product as an option before considering pharmaceutical options and were compliant with recording data. The dogs were varying ages and sexes. All dogs were deemed healthy within a year of starting this short trial through veterinary examination results aside from some geriatric conditions. Dogs were allowed to remain on preventative medication such as flea and tick products and non-steroidal anti-inflammatories, but no anxiety medications were permitted. The pet owners were provided with ElleVet's Calm and Comfort chew and directed to administer the dose appropriate to their dog's weight. The target dose was 4 mg/kg and was given to the dog at least 120 minutes before the onset of the trigger. The owners were not instructed to give the chew with or without food.

## **Results**

The results of the study showed that 83% (20/24) dogs responded positively and had decreased stress or anxiety-related behaviors when given ElleVet Calm and Comfort. 17% (4/24) reported no effect. 41% (10/24) owners reported an effect in 60 minutes, 25% reported an effect in 120 minutes, 20.83% saw an effect in 15 minutes, and 12.5% reported an effect in 30 minutes. 60% of pet owners reported the effects lasting 1-6 hours, and 40% reported effects lasting 7-12 hours. Timing of onset appeared to peak at the 60 minute time point, with 75% of dogs responding in an hour or less, dosing between 1-2 hours prior to the trigger event is likely to be optimal. No dogs vomited within an hour of taking the chew. However, four dogs had a single vomiting episode more than an hour after ingestion. These dogs took the chew on an empty stomach, indicating that it may be advisable to dose with a small meal. Previous ElleVet studies have shown increased bioavailability when given CBD+CBDA products with food, further supporting this indication.

Follow up to this study included providing 64 dogs the same Calm and Comfort 3mg/kg dose with food. Out of the 64 dogs, none experienced vomiting or GI upset. Palatability for the Calm and Comfort chew was 91%, with 58/64 dogs readily accepting the chew.

## **Conclusion**

Anxiety in dogs is prevalent and an issue of significant concern for pet owners. Separation, loud noises, car rides, veterinary visits, kenneling, and grooming, as well as strangers coming into their space, are common triggers of stress and anxiety in dogs. Treatment of anxiety in dogs with the use of cannabinoids has gained popularity and has reported anecdotal success. However, there is a lack of scientific data in this area of veterinary medicine, and a gap in the treatment options to successfully address anxiety in dogs. ElleVet Sciences developed an anxiety product, Calm and Comfort and conducted a successful pilot study on dogs with anxiety. The findings of this study, with an 83% positive response, demonstrate that ElleVet Calm and Comfort CBD+CBDA soft chews are a highly effective and safe product to address the need for an easy to administer, palatable, short acting anxiety product for dogs. The 91% palatability and the lack of side effects when given with food, indicate that the Calm and Comfort soft chew is safe and easy for pet owners to administer. These results suggest that the product could be a significant alternative to pharmaceutical treatments and can not only alleviate short term stress response, but may also reduce the long-term psychological effects of chronic stress. Based on the success of this pilot study, ElleVet is launching the Calm and Comfort CBD+CBDA soft chew as well as undertaking a further long term anxiety study.