

Equine Research on the Short-Term Effects of Cannabidiol for the Treatment of Chronic Pain and/or Anxiety

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Abstract— Cannabidiol (CBD) is one of the major non-psychoactive cannabinoids produced by *Cannabis sativa L.* Hemp is classified as a *Cannabis* varietal because it has less than 0.3% tetrahydrocannabinol (THC) – the psychoactive component found in *Cannabis*. Recent studies have shown that CBD has good tolerability and a wide range of reported health benefits. The purpose of this study was to measure the effects of CBD increase movement and promote calmness in horses. CBD was studied in horses after the administration of two oral doses (50 mg each) each day over a two-week timeframe. Forty-one horses were studied across the United States and participants were obtained through relationships with horse shelters, rescues, farms with retired show and race horses, and general pleasure horse farms. In all of the cases, the horses were evaluated and determined, at the outset, to have impaired movement & presentation and/or demonstrated common vices of anxiety like cribbing, pacing or reluctance to load to trailers or gates.

INTRODUCTION

Routine nonsteroidal anti-inflammatory drug (NSAID) treatments, phenylbutazone and Banamine® (flunixin meglumine), may not provide adequate relief of chronic pain due to diagnosis like musculoskeletal injuries or osteoarthritis and might have potential side effects that preclude its use, particularly in geriatric patients with certain comorbidities, such as gastrointestinal ulceration, especially of the stomach and large colon or (more rare) kidney damage or bleeding disorders. Reactions to allergies have also been reported.

Clinical studies in horses have shown that oral meloxicam has fewer negative effects on the permeability of the gastric mucosa than phenylbutazone (D’Arcy-Moskwa et al, 2012) and that oral meloxicam was not associated with the same reduction in blood albumin concentration that was seen following 13 days’ administration of phenylbutazone (Noble et al, 2012). There are also differences in the anti-inflammatory effects of the available NSAIDs, as demonstrated in recent studies of experimentally-induced acute synovitis in the horse. Oral administration of meloxicam significantly reduced inflammatory mediators such as substance P and

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matrix metalloproteinase activity within synovial fluid (de Grauw et al, 2009), while no reduction in these mediators was observed in horses treated with phenylbutazone (de Grauw et al, 2014). These studies also showed that meloxicam reduced inflammation induced cartilage catabolism, which phenylbutazone did not. This suggests that meloxicam is a good choice for the treatment of acute inflammatory orthopedic conditions. Few studies comparing the analgesic efficacy of the available NSAID products have been published in horses. In a recent blinded study of 77 horses with chronic lameness, meloxicam was shown to have equivalent analgesic efficacy to phenylbutazone (Olsen et al, 2016). It also appears that analgesic efficacy may depend on the inciting cause of orthopedic pain, with meloxicam demonstrating superior efficacy to phenylbutazone in a model of acute synovitis, but not in a model of mechanical lameness (Banse et al, 2017).

The endocannabinoid receptor system is known to play a role in pain modulation and attenuation of inflammation (5–7). Cannabinoid receptors (CB1 and CB2) are widely distributed throughout the central and peripheral nervous system (8–10) and are also present in the synovium (11). However, the psychotropic effects of certain cannabinoids prevent extensive research into their use as single agents for pain relief (5, 12). The cannabinoids are a group of as many as 110 different compounds that possess complex polypharmacology that may or may not act through the CB receptors. One cannabinoid, cannabidiol (CBD), may actually be an allosteric non-competitive antagonist of CB receptors (13). In lower vertebrates, CBD is reported to have immunomodulatory (14), anti-hyperalgesic (15, 16), antinociceptive (17, 18), and anti-inflammatory actions (5, 19), making it a potential therapeutic option in equines with chronic pain or osteoarthritis (OA). Currently there are few companies distributing nutraceutical derivatives of industrial hemp, rich in cannabinoids for animals, yet little scientific research regarding safe and effective oral dosing has been done.

"Horses are able to ‘cover’ their pain due to the presence of a built-in pain suppression response that mammals have, which is called ‘stress-induced analgesia,’ or SIA," explains Ann Wagner, DVM, MSc, Dipl. ACVP, ACVA, a professor in anesthesia at Colorado State University’s (CSU) College of Veterinary Medicine & Biomedical Sciences. "Essentially, SIA explains how a racehorse that suffers a serious leg injury during a race can keep galloping despite the jockey’s efforts to pull it up."

Nora Matthews, DVM, Dipl. ACVA, a professor of anesthesia at Texas A&M University’s College of Veterinary Medicine, adds, "The pain scales we have are designed for specific types of pain such as orthopedic pain or colic, but the equine industry needs a pain scale that can provide a good assessment of all types of pain."

Wagner encourages owners to take the time to assess their horses’ behavior daily and be aware of the more subtle signs of pain. These can include lameness; restlessness; head-lowering; teeth-grinding; flaring of nostrils; sweating; rigid posture; head turning toward the flank; kicking at the abdomen; reluctance to be handled; flight behaviors; and aggression. Other signs of chronic pain are weight loss; shifts in social behavior such as allodynia (e.g., a horse that normally enjoys being petted now shows aversion being groomed or petted); changes in eating, drinking, and sleeping patterns; and decreased response to stimuli.

Current Treatment Options

Matthews presented a comprehensive review of pain-relieving drugs at the 2009 American Association of Equine Practitioners (AAEP) Annual Convention. In her presentation she described currently available drugs for managing horses' pain, including non-steroidal anti-inflammatory drugs (NSAIDs); opioids such as morphine or butorphanol; α -2 adrenergic agonists (e.g., xylazine); dissociative drugs such as ketamine; and local anesthetics such as lidocaine.

While some of these drugs are extremely important for providing "balanced anesthesia" in horses before, during, and after surgery, most of them simply are not useful for managing chronic pain, largely because they are not available in easy-to-administer oral formulations and possess numerous side effects

"We need more options for treating chronic pain in horses," says Matthews. "New formulations of existing drugs, such as oral drugs that owners can give to their horses or transdermal patches, and long-lasting formulations are needed."

Non-steroidal anti-inflammatories are considered the mainstay for chronic pain management and include such staples as phenylbutazone (Bute), firocoxib (Equioxx), and the topical product 1% diclofenac sodium (Surpass). Two other non-NSAID drugs that might be suitable for managing pain in specific cases (upon the advice of a veterinarian) are gabapentin and tramadol. Gabapentin is an anticonvulsant drug (generally used to treat neuropathic pain in humans and small animals) that can also be used to treat neuropathic pain caused by an injury or disease affecting the equine nervous system. The second drug, tramadol, is a narcotic-like pain reliever related to codeine. Although it has been used successfully in humans to treat moderate to severe pain, such as back pain, studies on the efficacy of tramadol in horses have yielded conflicting results.

Matthews notes, "Further study is needed regarding effectiveness, dosing, and the availability of (each) drug after oral administration, how these drugs are metabolized, and potential side effects."

Alternative Pain Treatment Options

Pain has a large negative impact on the horse's health and well being. It is important to find safe treatments to alleviate the animal's pain to minimize discomfort but also to accelerate the healing process. Unfortunately, even with the use of pharmaceutical drugs, some horses' pain cannot be adequately controlled. In these cases some veterinarians might consider alternative therapies.

"There are a large number of alternative therapies available for horses that are used as adjuncts to more traditional regimens to help control chronic pain," relays Muir.

The list of complementary and alternative therapies is extensive and includes massage, hydrotherapy, chiropractic, static magnets, nutritional supplements, prolotherapy (repeated injections of an irritant solution, such as hypertonic glucose, with a goal of reducing pain), extracorporeal shock wave therapy, and acupuncture, among many others. However, not all modalities have been properly studied, so currently researchers and veterinarians cannot make any firm recommendations on treatments and whether they work. Of the available alternative therapies, acupuncture is commonly used in equine practice to help manage chronic pain caused by musculoskeletal pain due to lameness in the feet or back.

One study presented at the 1997 AAEP Annual Convention assessed using acupuncture on pain caused by special lameness-inducing shoes in five horses. Researchers from California State Polytechnic University's Department of Animal and Veterinary Sciences judged pain based on heart rate, which has previously been shown to be a reliable indicator of pain in the horse. When the shoes were manipulated to induce pain and lameness, the horses' heart rates increased. The heart rates were subsequently measured every 15 seconds during and after acupuncture treatment, and a significant decrease in heart rate was noted in four of the five horses. Based on this study, the authors concluded, "there is evidence to suggest that acupuncture has merit as an alternative source of therapy in the alleviation of equine pain."

A second study conducted by researchers at the University of Pennsylvania (also presented at the 1997 AAEP Convention) evaluated acupuncture use for treating horses with chronic back pain. To test their theory that it would be useful for this purpose, the researchers performed various forms of acupuncture (i.e., laser stimulation, traditional dry needling, or injection of saline with or without methylprednisolone acetate) on 350 horses with back pain. Each horse received one weekly treatment for eight weeks. In total, 263 (75%) horses responded positively and were able to perform at an acceptable level following treatment, prompting the researchers to conclude that "acupuncture may be a useful form of treatment for chronic back pain in horses."

Both studies' authors did indicate, however, that more research in this field would be beneficial.

Researchers also have studied the effects of chiropractic and manipulation on conditions such as back pain. At the 2010 AAEP Convention, Kevin Haussler, DVM, DC, PhD, of CSU, presented results from his and colleagues' research suggesting spinal manipulation poses notable pain relief for horses with chronic neck and back pain (Oke, 2018).

To explore whether CBD can be used as a dietary supplement to support joint health and possibly alleviate pain or anxiety, a foundation study was designed to measure health benefits. The objectives of this study were to determine whether a single concentration dose of CBD would demonstrate improvements in movement, lessening of perceived pain (see below) and whether there was a decrease in anxiety scores in selected animal participants. Short-term safety was also measured through reporting any adverse events to the dosing regimen. Our underlying hypotheses were that appropriate dosing of CBD-rich hemp oil tablets would safely diminish perceived pain and increase activity in horses with chronic pain and/or calming for anxieties.

PROCEDURES FOR STUDY

Participant Selection

Forty-one (41) horses with clinical evidence of osteoarthritis or other chronic pain as a result of musculoskeletal injuries were selected. The majority of patients enrolled were not currently receiving treatment for their osteoarthritis or injuries. Participating horses received the cannabidiol product at an approximate dose of 1 mg CBD/10 kg of body weight, with a select group receiving 1 mg CBD/5 kg of body weight, twice daily for 2 consecutive weeks. Horse owners or care givers were asked to use a specifically designed inventory questionnaire to assess pain in the animals receiving CBD. This questionnaire is extremely important to the study to evaluate the horse's response to the dietary supplement and whether the base line condition is improved through the dosing regimen. Owners and/or care givers were asked to evaluate the patient one week prior to administering the CBD to establish a baseline for observation and one week following discontinuation of the product. An on-line survey link was provided for the caregiver to collect the data each week.

Study Duration Details

Participation in this study required that horse owners administer the test product twice daily to their horse for two consecutive weeks. During the trial period, other medications or therapies were discontinued to more accurately assess the effects of the test product. Since this study is observational and relies on the systemized feedback from pet owners, no other clinical procedures were performed on any patient during the study period.

Survey Summary

1. Establishing baseline:

a. Using the Colorado State Comfort Assessment, please score the horse's worst pain over the prior seven days before starting the treatment.

b. Using the Colorado State Comfort Assessment, please score the horse's average pain over the seven days prior to starting the treatment.

c. Please assess the animal using the 1-10 scale below

i. General activity

ii. Enjoyment of life

iii. Ability to walk

iv. Ability to trot

2. Begin dosing with Panacea Pets Equine Product as indicated with product shipment. Assess animals twice weekly:

a. Using the Colorado State University Comfort Assessment, please score the horse's worst pain (1-4) over the prior seven days before starting the treatment.

b. Using the Colorado State University Comfort Assessment, please score the horse's average pain over the seven days prior to starting the treatment.

c. Please assess the animal using the 1-4 scale below

i. General activity

ii. Enjoyment of life

iii. Ability to walk

iv. Ability to trot

d. Report on ease of administering the tablets

i. Did the horse freely take the tablets?

ii. Did the horse need for the tablets to be mixed with feed to take?

iii. Did the owner/care giver have to force administer the tablets?

e. Report on ANY observed adverse events or other observed changes in horse behavior as a free form document.

3. In week 2, repeat video documentation of horse activity and behavior using as similar to the baseline video.

4. *One week following the discontinuation of dosing repeat online assessment:*

a. Using the Colorado State University Comfort Assessment, please score the horse's worst pain over the prior seven days before starting the treatment.

b. Using the Colorado State University Comfort Assessment, please score the horse's average pain over the seven days prior to starting the treatment.

c. Please assess the animal using the 1-10 scale below:

i. General activity

ii. Enjoyment of life

iii. Ability to walk

iv. Ability to trot

v. Ability to saddle and ride

vi. Ability to load into a transport

RESULTS

The results obtained from the two week evaluation included details about each participant along with the condition being evaluated. Additionally, included is the aggregation of score data including the pre-study condition score derived using the CSU Pain Evaluation technique. Also presented are the complete Start and Finish Scores for the study period for all 41 horses.

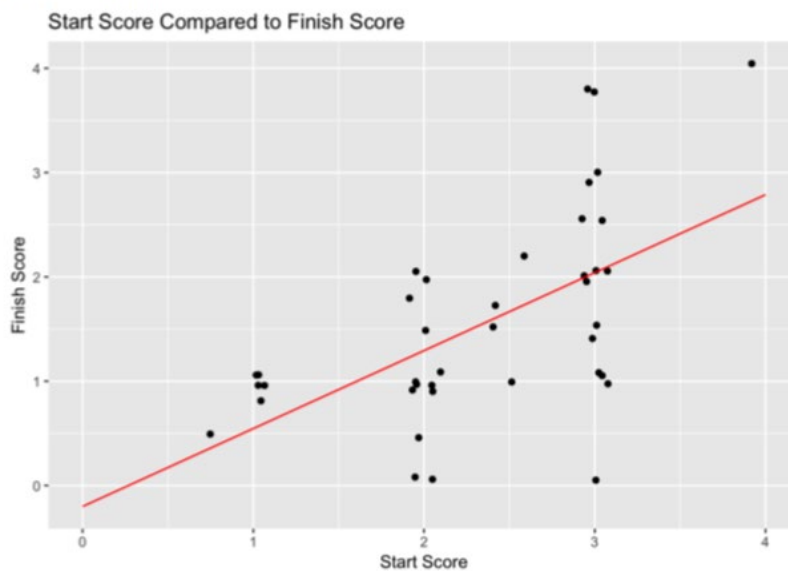
| Breed | Weight | Height | Age | Health | Condition | Start | Finish | Improvement | Gender |
|------------------|-----------|--------|-----|--------|-----------|-------|--------|-------------|--------|
| Warmblood | 1501-2000 | 17.1 | 17 | | Pain | 3 | 2 | 1 | M |
| Other | <1000 | 14.3 | 4 | 6 | Anxiety | 4 | 4 | 0 | M |
| Paint | 1001-1500 | 15.1 | 21 | 2 | Pain | 3 | 2.5 | 0.5 | F |
| Thoroughbred | 1001-1500 | 17.3 | 8 | 3 | Pain | 3 | 3 | 0 | M |
| Warmblood | 1001-1500 | 15.3 | 16 | 2 | Pain | 2 | 1 | 1 | F |
| Other | <1000 | 10 | 20 | 2 | Pain | 2 | 1 | 1 | M |
| Quarter Horse | 1001-1500 | 15.1 | 21 | 2 | Pain | 2 | 1 | 1 | M |
| Other | <1000 | 14.3 | 29 | 2 | Pain | 2 | 1.75 | 0.25 | F |
| Quarter Horse | 1001-1500 | 16.1 | 10 | 2 | Pain | 2 | 1 | 1 | M |
| Thoroughbred | 1001-1500 | 16.1 | 11 | 2 | Pain | 2 | 1.5 | 0.5 | M |
| Other | <1000 | 14.2 | 12 | 3 | Pain | 3 | 1.5 | 1.5 | F |
| Other | <1000 | 14 | 10 | 2 | Anxiety | 2 | 0 | 2 | F |
| Thoroughbred | 1501-2000 | 17 | 10 | 3 | Pain | 3 | 1 | 2 | M |
| Warmblood | 1501-2000 | 17 | 10 | 3 | Pain | 3 | 1 | 2 | M |
| Other | 1001-1500 | 15.2 | 17 | 2 | Pain | 2.5 | 1 | 1.5 | M |
| Thoroughbred | 1001-1500 | 16.3 | 4 | 2 | Pain | 2 | 1 | 1 | F |
| Tennessee Walker | <1000 | 14.2 | 20 | 3 | Pain | 3 | 1.5 | 1.5 | M |
| Other | <1000 | 15.1 | 15 | 2 | Pain | 2 | 0.5 | 1.5 | M |
| Thoroughbred | 1001-1500 | 17.2 | 8 | 5 | Anxiety | 2 | 0 | 2 | M |
| Thoroughbred | 1001-1500 | 17h | 10 | | Pain | 3 | 2 | 1 | M |
| Quarter Horse | <1000 | 15.2 | 15 | | Anxiety | | | | F |
| Quarter Horse | <1000 | 14.2 | 8 | | Pain | 3 | 0 | 3 | M |
| Thoroughbred | 1001-1500 | 16.2 | 5 | | Anxiety | 2 | 2 | 0 | M |
| Thoroughbred | <1000 | 16.1 | 14 | | Pain | 3 | 2 | 1 | F |
| Other | <1000 | 13.2 | 8 | | Anxiety | 3 | 3.75 | -0.75 | F |
| Other | <1000 | 14h | 17 | | Anxiety | 3 | 3 | 0 | F |
| Thoroughbred | 1001-1500 | 16.2h | 14 | | Pain | 3 | 3.75 | -0.75 | M |
| Thoroughbred | <1000 | 15.2h | 13 | | Pain | 3 | 1 | 2 | M |
| Arabian | <1000 | 15.1 | 10 | | Pain | 3 | 2 | 1 | M |
| Other | <1000 | 13.3 | 12 | 2 | Pain | 2 | 1 | 1 | F |
| Thoroughbred | 1001-1500 | 15 | 14 | .75 | Pain | 0.75 | 0.5 | 0.25 | M |
| Paint | 1001-1500 | 14.3 | 16 | 2.5 | Pain | 2.5 | 1.5 | 1 | F |
| Paint | 1001-1500 | 14 | 16 | 1 | Pain | 1 | 0.75 | 0.25 | F |
| Quarter Horse | 1001-1500 | 15 | 3 | | Pain | 1 | 1 | 0 | F |
| Miniature | <1000 | 42 in | 18 | | Pain | 2 | 2 | 0 | F |
| Thoroughbred | 1001-1500 | 16.1 | 8 | | Anxiety | 1 | 1 | 0 | M |
| Thoroughbred | 1001-1500 | 15.3 | 6 | | Anxiety | 1 | 1 | 0 | M |
| Other | 1001-1500 | 15.0 | 10 | 2 | Anxiety | 1 | 1 | 0 | M |
| Thoroughbred | 1001-1500 | | ? | | Pain | 2.5 | 2.25 | 0.25 | F |
| Thoroughbred | 1001-1500 | | ? | | Pain | 2.5 | 1.75 | 0.75 | M |
| Thoroughbred | <1000 | 16.2 | 5 | | Pain | 3 | 2.5 | 0.5 | M |
| Total Scores | | | | | | 93.8 | 62 | 31.75 | |

Statistical Results

| Totals | Counts | Percent |
|------------------|--------|---------|
| Data Reported | 41 | |
| Horses Improved | 29 | 71% |
| Horses Remained | 10 | 24% |
| Horses Regressed | 2 | 5% |
| By Condition | | |
| Anxiety Horses | 9 | |
| Horses Improved | 2 | 22% |
| Horses Remained | 6 | 67% |
| Horses Regressed | 1 | 11% |
| Pain Horses | 32 | |
| Horses Improved | 27 | 84% |
| Horses Remained | 4 | 13% |
| Horses Regressed | 1 | 3% |

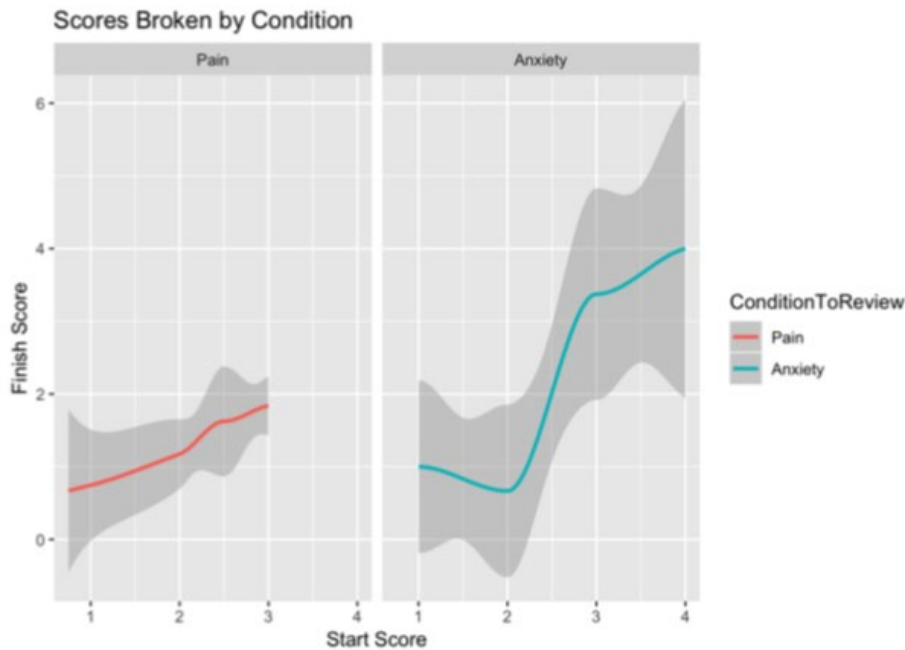
OVERALL EVIDENCE OF CONDITION IMPROVEMENT IN BOTH CATEGORIES

SPSSRawData.xlsx



Overall, a 1 point increase in the start score results in, on average, a 0.75 point increase in the Finish score. (The red line is the average.)

For each condition, there is a positive correlation between between the start score and the finish score. Lessening of perceived pain appeared to improve over the two week study period on a moderate basis. The ability of CBD to provide a calming effects appeared to be much stronger in the horses that responded to the treatment. The following charts are identified as Chart 2.1 – Pain and Chart 2.2 – Anxiety.



For each condition, there is a positive correlation between between the start score and the finish score. Pain is more constant. Anxiety is stronger.

CONCLUSIONS AND EVIDENCE-BASED RECOMMENDATIONS

This report attempted to find evidence for a causal relationship between use of CBD and pain management and anxiety support in horses. Based on the data gathered in this study, we made the following conclusions: 1) There is significant evidence of an association of CBD with an improvement in health and a reduction of pain observed in horses, $P < 0.01$ (Chart 2.1 - Pain). Interestingly, there appeared to be a continual improvement in pain response through the course of the study. CBD demonstrates a trend towards improvement in the anxiety score, but did not demonstrate statistical significance for improvement across all participants at the dose utilized in this study. Interestingly, in those animals that did respond to CBD treatment, the anxiety score improved. In those animals that demonstrated lower anxiety, the effect was more profound, with an improvement by 3 units, $P < 0.001$.

Outcome Critical Appraisal and Conclusion

Author's conclusion for pain management: Although the treatment protocol for the control group is not clear, there is a statistically significant improvement in the CBD treatment groups. This strength of conclusions in this study would be increased by increasing the control group, incorporating a cross-over design, adding various dosing groups, and including plasma CBD measurements for

stronger correlation with “drug” levels and improved health. It would also be beneficial to extend the study for a 4 week period to see if perceived linear improvements persist.

Author’s conclusion: the slightly improved anxiety scores in this study merits further exploration. Increasing the number of study animals is needed to obtain higher powered statistical results. The addition of higher CBD dosing groups and specific anxiety conditions may strengthen the initial findings reported in this paper. As with the pain management arm of the study, adding in a cross-over design is needed to better characterize the calming effect potentially provided by CBD . Additionally, the treatment protocol for the control group (historic control) is not clear.

IMPLICATIONS FOR FURTHER RESEARCH

Given that this study demonstrates CBD has a positive effect on pain management in horses further studies are suggested that incorporate dose-range finding as well as pharmacokinetics to better correlate plasma CBD levels with health improvements. Next studies should also incorporate a double blind cross-over design to further demonstrate efficacy of CBD in alleviating various conditions. Further, it would be of interest to study CBD as appropriate supplements providing benefits for horse athletes, i.e horses competing in races or in rodeo events. The potential of CBD as safe dietary supplement supporting joint and muscle health in horse athletes may be important due to the limited alternatives to manage pain in competing animals due to drug testing prohibitions.

The anxiolytic effects of CBD seem less clear where the small sample size did not reach significant improvements across the group. Implementing similar suggestions as with the pain management study for an improved study are warranted. Increasing the number of study subjects and adding more objective measures of anxiety allow stronger conclusions to be attained. Note also that there may be a higher dose needed for anxiolytic effects compared to pain responses.

AUTHORS

James (Jamie) Baumgartner was appointed President of Panacea Life Sciences in 2017. Jamie has had a lifelong passion for bringing novel treatments to patients in need. Jamie holds a Bachelor of Science in Biochemistry from the UC, Davis and a Ph.D. in Biochemistry and Pharmacology from Washington State University. He is an innovative business leader who combines his acute business acumen with his broad scientific excellence. His expertise in drug discovery and development has led to him assisting over 700 biotechnology and pharmaceutical companies reach unparalleled levels of success, especially in the area of advancing projects to IND filing. He adds over 25 years of drug discovery experience to Panacea Life and reinforces the company’s commitment to its foundation in scientific research and development in the healthcare and biotech industries.

Lawrence (Larry) Dukes was appointed national Equine Consultant of Panacea Life Sciences in 2018. Larry has been involved in technology, predictive analytics and research in several industries including competitive sports including the equine world. He holds a BA in Business

Administration from Loyola University – Maryland and a MAS in Information Technology from Johns Hopkins University. He has held extensive leadership position including President and CEO of several successful businesses in the health, finance and sports industries. He is author of a book and authored a patent in these industries.

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