The Wonderful World of Cannabinoids in Small Animal Practice!

Dr Joseph Wakshlag
DVM, PhD, DACVSMR, DACVIM (nutrition)
CVMO– ElleVet Sciences

ElleVet SCIENCES

1

#trending

ElleVet SCIENCES

2

Endocannabinoid system (ECS)

- Largely eluded scientists until mid-1990s
- Legal and regulatory issues surrounding cannabis and associated molecules made research difficult
- 2018 Farm Bill → explosion of interest, products, and research

ElleVet SCIENCES

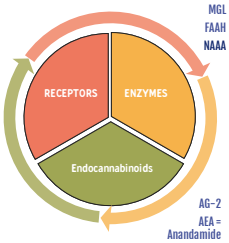
3

The Endocannabinoid System (ECS)

- Thought to be the largest and probably oldest receptors system in the body
- Present in every animal but insects
- Internal regulatory system
  - Restores homeostasis following a cellular stressor
  - Communicates with all other systems in the body, notably the CNS and the PNS
  - Autocrine, paracrine and neurological and neuromuscular REGULATION functions such as:

✓ Pain Perception ✓ Inflammation ✓ Sleep
✓ Immune response ✓ Appetite ✓ Emotions

CB1
CB2
TRPV1
GPR55
PPAR
GLY-R



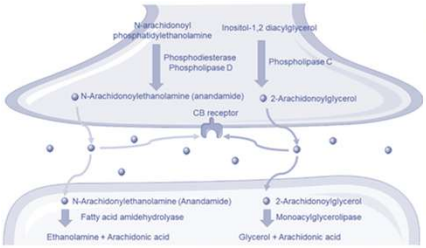
MGL
FAAH
NAAA

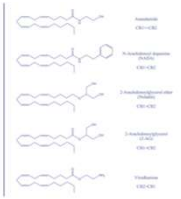
AG-2
AEA = Anandamide
Others

ElleVet SCIENCES

4

Endocannabinoids and CB Receptors



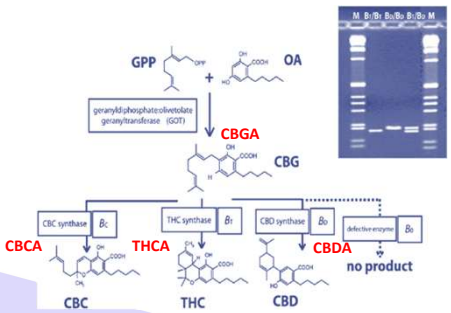


ElleVet SCIENCES

Maayah et al, BAA –molecular basis of dz, 2020

5

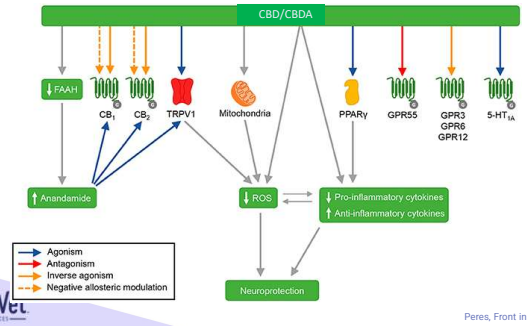
The biosynthetic pathways of hemp



ElleVet SCIENCES

6

The endocannabinoidome!



Peres, Front in Pharm, 2019

7

Cannabis vs Hemp vs Marijuana: What's the difference?

Cannabis/Hemp – Legal to distribute	Marijuana/Cannabis
• Cannabis Sativa • Industrial hemp • Grown for its tall, sturdy stalks • Paper, textiles, biodegradable plastics, health food, fuel • Low THC level < 0.3%	• Cannabis Sativa (Cannabis Indica) • Recreational and medical drug • Restricted substance • Leaves and flowering portions of the plants • High THC level > 0.3%

8

Use of Hemp CBD Product in Veterinary Clinics

- Hemp CBD is not a controlled substance federally or in any state
- VMBs regulate veterinarians—not AVMA or other VMAs
- AAVSB recommends that veterinarians who use hemp CBD use products that:
  - Have a COA by an independent 3rd party lab
  - Tested for safety
  - Tested for accuracy of the label
  - Efficacy tested products preferred

AAVSB

AAVSB GUIDANCE DOCUMENT
FOR CBD USE ON COMPANION ANIMALS

9

Allowed without FDA Approval – A Nutraceutical

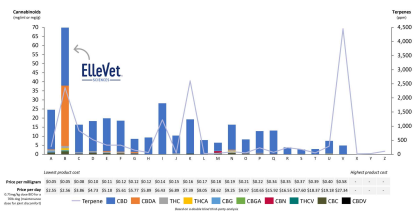
DASUQUIN ADVANCED
JOINT HEALTH SUPPLEMENT

10

A Confusing Market

11

Not all products are the same



12

Heavy Metal Contamination

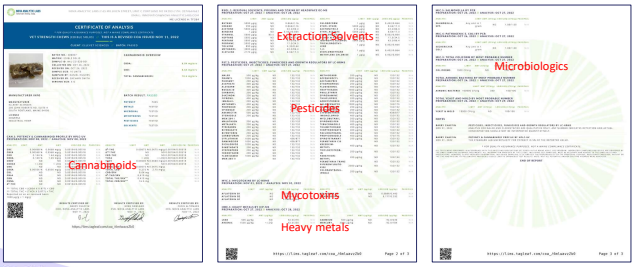
- 4 of 29 products were contaminated
- Hemp is often used for bioremediation of soil
- Increased uptake of mineral from soil
- Must ask for COA on final product
- Oils and other ingredients can be contaminated

ElleVet SCIENCES

13

13

COA – from a certified 17025 laboratory

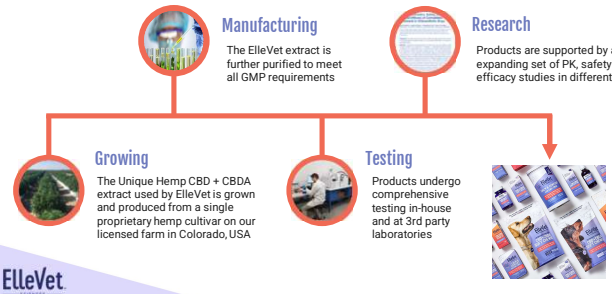


ElleVet SCIENCES

14

14

ElleVet – from Farm to Customer



ElleVet SCIENCES

15

15

Pharmacovigilance beyond QC, literature monitoring/production…

Adverse event and product complaint management –NASC…..

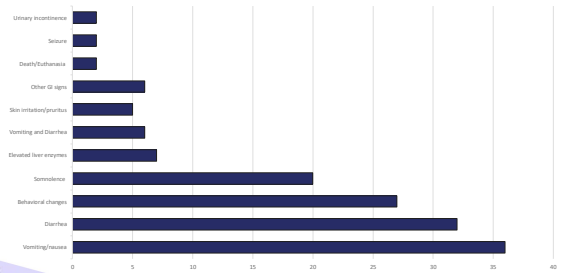
- Safety data collection and coding
- Case management
- Monitoring
- Reporting
- Product recovery and analysis
- Communication

ElleVet SCIENCES

16

16

Classification of reported events per 10,000 unit sold

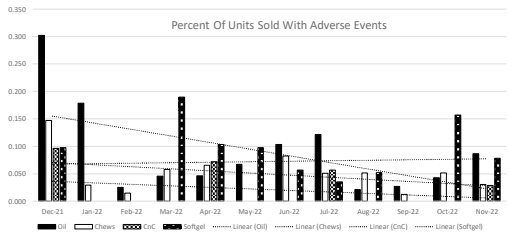


ElleVet SCIENCES

17

17

Adverse Reporting Ellevet



ElleVet SCIENCES

18

18

Reported Adverse Events

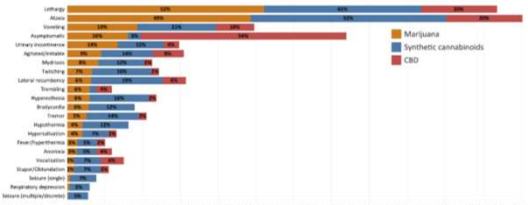


Fig. 1. Clinical signs associated with exposure to marijuana (ie, THC containing products, ~2200 cases), synthetic cannabinoids (~60 cases), and CBD (~50 cases) as reported to Pet Poison Helpline. Canines represent ~96% of the displayed data. Confirmation of exposure was not obtained in all cases, nor could co-ingestants such as chocolate or other toxicants be ruled out. Therefore, these data are meant to portray general trends only. Clinical signs reported in less than 5% of cases were excluded from this graphic.

Brutlag, VCNA, 2018

19

19

Safety of cannabidiol products

frontiers | Frontiers in Veterinary Science

Safety study of cannabidiol products in healthy dogs

William Bookout[1], Margitta Dziwenka[2]*, Kaiti Valm[2] and Jennifer Kovacs-Nolan[2]

- Randomized, non-blinded
- 5 mg/kg daily administration for 90 days
  - MCT oil (neg control)
  - Broad spectrum CBD
  - Broad spectrum CBD + CBG
  - Broad spectrum CBD + CBDA

Cannabinoids were well tolerated when healthy male and female beagles were dosed for 90 consecutive days. Annual post-market surveillance data for hemp-derived supplement products sold for use in dogs from 2010 to 2023 (partial year) shows that the rate per 1 million administrations sold is 2.10 for adverse events and 0.01 for serious adverse events. Based on the results of this study, other published studies, and data from extensive post market surveillance, hemp-derived cannabinoids are well tolerated in healthy dogs at a dose of 5 mg/kg body weight/day.

NASC Adverse Event Reporting data 2010 –2023

Year	Adverse events (report rate/ million administrations sold)	Serious adverse events (report rate/million administrations sold)	Administrations sold*
Grand Total	2.19	0.01	1,977,144,007

20

20

CBD long-term/dosing studies

RESEARCH PAPER

Species-specific susceptibility to cannabis-induced convulsions

mg/kg QD; 15/sex/group + 10/sex/group for C and HD recovery), no dose-limiting toxicity was observed. The primary target organ was liver, with hepatocellular hypertrophy, accompanied by slight (1.2-1.4 fold) increases in ALT and ALP, observed at the MD and HD in males and females. No effects were observed on sperm parameters, interstitial cell hyperplasia in ovary was observed at the MD and HD. In the 39-week study (0, 10, 50, or 100 mg/kg QD; 4/sex/group + 2/sex for C and HD recovery), there were no deaths; the only clinical sign was soft/liquid/mucoid feces. Decreases in absolute body weight (compared to C) were observed at all doses in males (5, 15, and 12% at LD, MD, and HD, respectively) and females (22, 29, and 32% at LD, MD, and HD, respectively). As in rat, the primary target organ was liver, with hepatocellular hypertrophy detected at all doses (dose-related only in males), accompanied by increases in ALT (slight) and ALP (up to 8-fold).

The toxicokinetic (TK) data at the highest doses tested in rat and dog and at the maximum recommended dose in humans are summarized in the following table.

SPECIES	DOSE (mg/kg)	SEX	CBD C_{max} (ng/mL)	CBD $AUC_{(0-24h)}$ (ng*hr/mL)	7-OH-CBD C_{max} (ng/mL)	7-OH-CBD $AUC_{(0-24h)}$ (ng*hr/mL)	7-COOH-CBD C_{max} (ng/mL)	7-COOH-CBD $AUC_{(0-24h)}$ (ng*hr/mL)
Rat	150	M	6160	60000	334	2560	4180	37100
		F	7530	67500	625	6730	2710	40500
Dog	100	M	2570	20500	134	1380	82.1	994
		F	2660	22400	117	1090	137	1560
Human*	10 BID	M/F	--	2790	--	1562	--	137886

*Data were extrapolated (by the sponsor) from data in humans at 750 mg BID, following the first daily dose (Study GWEP1544).

21

21

Pharmacokinetics & Safety in Dogs & Cats (Deabold, 2019)

8 Dogs | 2mg/Kg Total cannabinoids | BID | 12wks

- ElleVet Mobility Chews
- mean maximum concentration (Cmax) of 301 ng/mL
- area under the curve (AUC) of 1297 ng-h/mL
- time to maximal concentration (Tmax) of 1.4 h

8 Cats | 2mg/Kg Total cannabinoids | BID | 12wks

- ElleVet blend-infused fish oil
- mean maximum concentration (Cmax) of 43 ng/mL
- area under the curve (AUC) of 164 ng-h/mL
- time to maximal concentration (Tmax) of 2h

UF UNIVERSITY of FLORIDA

Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats

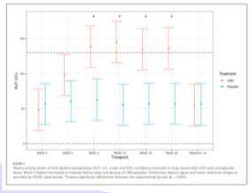
22

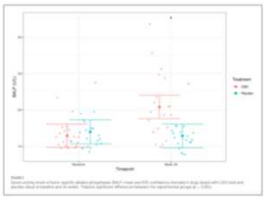
22

Safety? 6 month Dogs – 4 mg/kg SID

Long-term daily feeding of cannabidiol is well-tolerated by healthy dogs

Sophie Bradley, Scott Young, Anne Marie Bakke, Lucy Holcombe, Daniel Waller, Alysia Hunt, Kathleen Pinfold, Phillip Watson and Darren W. Logan*



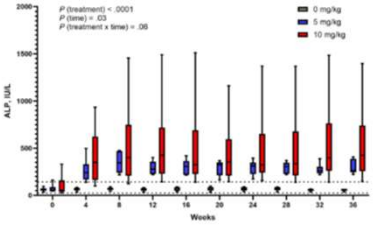


23

23

Long Term Safety CBD – 36 weeks

- 6 dogs per group
- Daily treatment –morning
  - 50 mg/ml and 100 mg/ml
  - CBD in MCT
- Ave 2.3 yrs; 9.5 kg
  - Placebo
  - 5 mg/kg
  - 10 mg/kg
  - Daily treatment
- CBC/Chem/Bile Acids/
- PE/Fecal

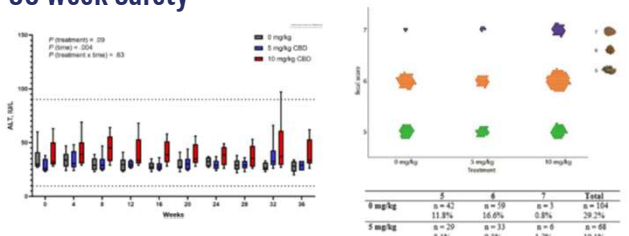


Corsato Alvarenga, JVIM, 2023

24

24

36 week Safety



	5	6	7	Total
0 mg/kg	n = 42 11.8%	n = 59 16.6%	n = 3 0.8%	n = 104 29.2%
5 mg/kg	n = 29 8.1%	n = 33 9.3%	n = 6 1.7%	n = 68 19.1%
10 mg/kg	n = 46 12.9%	n = 103 28.9%	n = 35 9.8%	n = 184 51.7%
Total	n = 117 32.9%	n = 195 54.8%	n = 44 12.4%	n = 356 100%

ElleVet SCIENCES

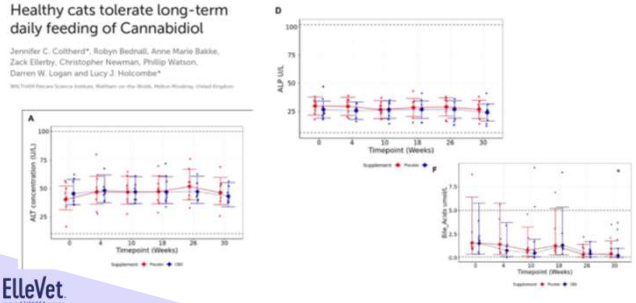
25

25

6 Month Safety Study in Cats – 4 mg/kg SID

Healthy cats tolerate long-term daily feeding of Cannabidiol

Jennifer C. Coltherd*, Robyn Bednall, Anne Marie Bakke, Zack Ellerby, Christopher Newman, Phillip Watson, Darren W. Logan and Lucy J. Holcombe*

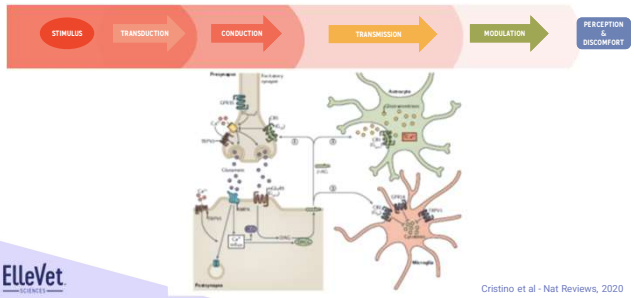


ElleVet SCIENCES

26

26

Phytocannabinoids on Nociception



Cristino et al - Nat Reviews, 2020

ElleVet SCIENCES

27

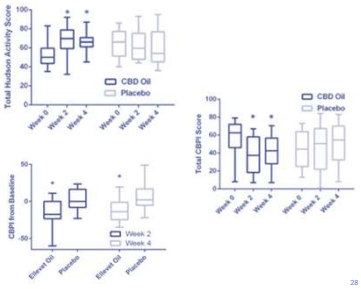
27

OA Pain in Dogs Clinical Trial

Cornell University College of Veterinary Medicine

(Wakshlag, 2020)

- 22 dogs enrolled – 16 completed
- ElleVet COMPLETE Oil 2mg/kg BID (CBD/CBDA)
- Inclusion-exclusion
  - Radiographically confirmed osteoarthritis.
  - Pain meds except for NSAID – 9 on NSAID
  - No Concurrent organ failure
- Double Blinded 4-week cross over design with 2-week washout
  - Canine brief pain inventory and Hudson Activity scale
  - Vet pain, gait, crepitus & CBC and Chemistry

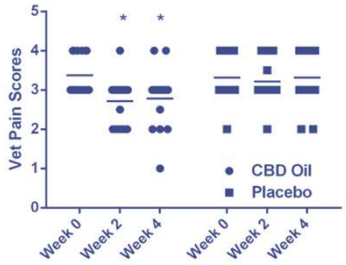


ElleVet SCIENCES

28

28

Vet Pain Scoring

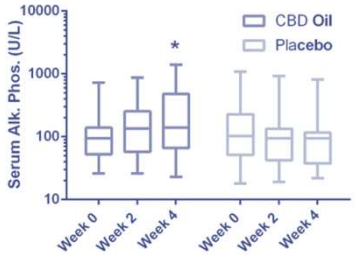


ElleVet SCIENCES

29

29

Alkaline Phosphatase



ElleVet SCIENCES

30

30

Other Positive Studies

- Kogan et al – 32 dogs -Open Label
  - Full spectrum Hemp product - dose 1.7 mg/kg BID
  - Could decrease Gabapentin dose by 2/3rds.
  - Mild ALP rise only chem finding
- Verrico et al – 5 dogs/group placebo blinded
  - CBD isolate ? - 1 mg/kg one month – small sample sizes
  - Vet and owner perceived positive response
- Brioschi et al – 9 dogs/ placebo blinded 12 week study
  - CBD isolate – 2 mg/kg BID
  - All dogs on Gabapentin, NSAID/Pred, Amitriptyline
  - Positive response over 12 weeks
- Talsma et al – 38 dogs crossover design
  - CBD isolate - 4.5 mg/kg BID
  - Positive responses by owners and vet assess, not force mat
  - NSAID examined as covariate and safe to give in tandem
  - ALP rise with CBD – no ALT

The Use of Cannabidiol-Rich Hemp Oil Extract to Treat Canine Osteoarthritis-Related Pain: A Pilot Study

PAIN

A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain

Oral Transmucosal Cannabidiol Oil Formulation as Part of a Multimodal Analgesic Regimen: Effects on Pain Relief and Quality of Life Improvement in Dogs Affected by Spontaneous Osteoarthritis

Evaluation of the effect of cannabidiol administration with and without nonsteroidal anti-inflammatory drugs in dogs with mobility disorders: a prospective, double-blind, crossover, placebo-controlled study

31

So, what about acute pain?

Less challenging to manage than chronic pain

- Available pharmacologic treatments
- Protective mechanism vs cascade of complex pathophysiologic processes (central sensitization)

32

Assessment of the nociceptive response to the use of cannabidiol alone and in combination with meloxicam through infrared pupillometry in female dogs undergoing elective ovariohysterectomy

Dog OVH Surgery

- Premed with 2 mg/kg CBD infused oil
  - Given every 12 hours
- Meloxicam 0.2 mg/kg IV
- OR both
- Pupillometer parameters different with melox, CBD and both

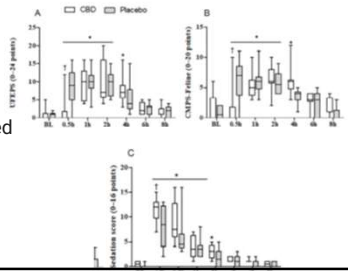
Parameter	Treatments	Post-surgical Events										P value
GCMPS-SF												

33

Perioperative Analgesic and Sedative Effects of Cannabidiol in Cats Undergoing Ovariohysterectomy

Cat OVH Surgery

- 2 mg/kg oral oil one hour before surgery
- Only time point of lower PS time 0.5 hrs post
- 1-8hrs no differences observed
- Pre sedation possible within half hour.
- Minimal response



34

Acute Pain TPLO Model

- 41 dogs completed the study – 22 ElleVet 2 mg/kg; 19 placebo
- Assessment of vet pain scores, CBPI scores from owners, Chemistry evaluation at 2 and 4 wks post op
- Bone healing scores at 4 weeks post op by blinded radiologist

35

Acute Pain TPLO Model

TABLE 2 Results of lameness, pain, and weight-bearing scores graded on a 1–5 scale (1 = best; 5 = worst) in dogs treated with either a cannabidiol (CBD) and cannabidiolic (CBDA) rich hemp product (2–2.5 mg/kg orally every 12 h; $n = 22$) or a placebo (sesame seed oil every 12 h, $n = 19$) for 4 weeks after a tibial plateau leveling osteotomy surgery.

Vet Scores

Score	Placebo T0	Placebo T1	Placebo T2	Tx T0	Tx T1	Tx T2	P site	P_{Tx}	P_{Time}	$P_{Tx*time}$
Lameness	3 (1–4)	2.5 (2–3)	2 (1–3)	3 (1–4)	3 (2–4)	2 (1–3)	0.92	0.25	<0.001	0.98
Pain	3 (1–3)	1 (1–3)	1 (1–3)	3 (2–3)	2 (1–2)	1 (1–3)	<0.001	0.91	<0.001	0.66
Weight-bearing	3 (1–4)	3 (2–3)	2 (1–3)	3 (1–5)	3 (2–3)	2.5 (1–3)	0.28	0.17	<0.001	0.70

Results reported as median (range) at week 0 (T0; initial evaluation before surgery) and at 2 and 4 weeks post-operatively (T1 and T2, respectively). P-values < 0.05 considered significant and evaluated effect of site (FL vs. RB) treatment (P_{Tx}), effect of time (P_{Time}), and effect of treatment over time ($P_{Tx*time}$) by a mixed model analysis of Wilcoxon Signed rank test and Tukey's tests.

TABLE 3 Results of pain severity score (PSS) and pain interference scores (PIS) in dogs treated with either a cannabidiol (CBD) and cannabidiolic (CBDA) rich hemp product (2–2.5 mg/kg orally every 12 h; $n = 22$) or a placebo (sesame seed oil every 12 h, $n = 19$) for 4 weeks after a tibial plateau leveling osteotomy surgery.

Owner CBPI

Score	Placebo T0	Placebo T1	Placebo T2	Tx T0	Tx T1	Tx T2	P site	P_{Tx}	P_{Time}	$P_{Tx*time}$
PSS	19 ± 7	12 ± 6	6 ± 6	20 ± 9	12 ± 8	6 ± 6	0.37	0.88	<0.001	0.77
PIS	30 ± 12	21 ± 12	10 ± 8	38 ± 15	23 ± 15	11 ± 11	0.78	0.24	<0.001	0.29

Results reported as mean ± SD at week 0 (T0; initial evaluation before surgery) and at 2 and 4 weeks post-operatively (T1 and T2, respectively). P-values < 0.05 considered significant and evaluated effect of site (FL vs. RB) treatment (P_{Tx}), effect of time (P_{Time}), and effect of treatment over time ($P_{Tx*time}$) by a mixed model analysis of Wilcoxon Signed rank test and Tukey's tests.

36

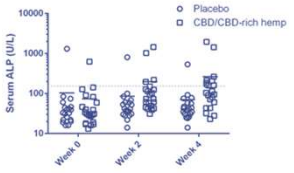
Acute Pain TPLO Model

Bone Healing

Assessment	Placebo	Treatment	P value
Callus formation[a]	1 (0-3)	1 (0-4)	0.67
Healing score[a]	1 (0-3)	1 (0-4)	0.53

Trazodone use

Assessment	Placebo	Treatment	P value
Week 0	8	9	0.89
Week 2	4	0	0.03



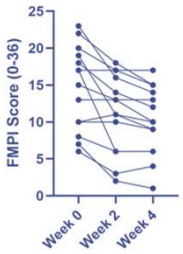
ElleVet SCIENCES

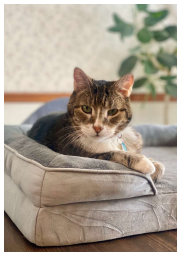
37

37

What about the Cats? Open Label Cat Paste Study

- 14 cats have completed the FMPI
- 10 geriatric cats with Blood work before and after treatment





ElleVet SCIENCES

38

38

Renal and hepatic screens:

- 4 Week trial – 14 completers (average age 14)
- CBC, Chemistry unchanged at week 4

Parameter	Glucose (mg/dL)	ALT (U/L)	AST (U/L)	GGT (U/L)	ALP	BUN (U/L)	Creatinine (mg/dL)	SDMA
Week 0	178 (124)	90 (60)	27 (12)	0.6 (0.5)	36 (14)	35 (12)	1.7 (0.8)	15 (5)
Week 4	173 (135)	71 (43)	23 (10)	0.8 (0.6)	38 (18)	35 (12)	1.7 (0.5)	14 (3)

* Several cats were less vocal, more interactive, less reactive, decreased house soiling – Pain? Anxiety? Cognition?

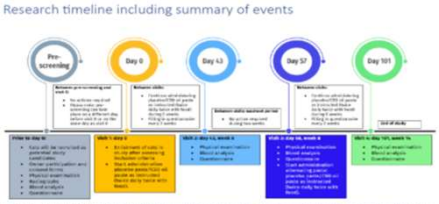
ElleVet SCIENCES

39

39

Ellevet OA Trial – Placebo Blinded

- Cats were all suffering from OA based on radiographs and activity
- 14 of 26 cats completed study



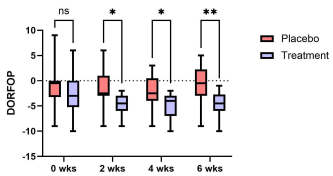
ElleVet SCIENCES

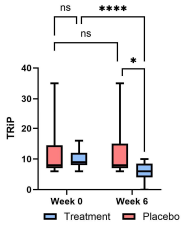
40

40

Results:

- CBC and Chem parameters
- All within normal limits throughout study



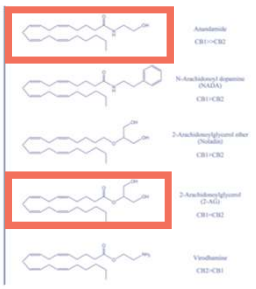


ElleVet SCIENCES

41

41

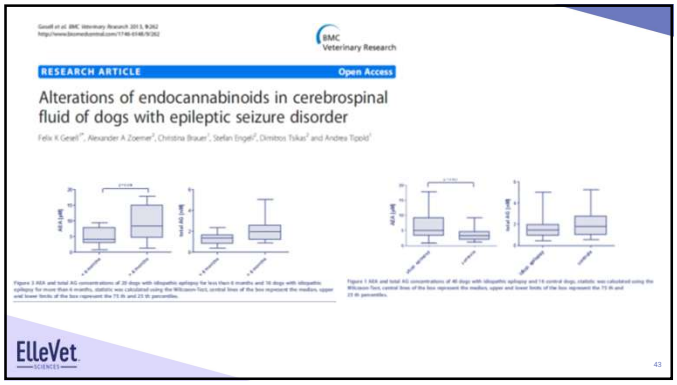
Endogenous Cannabinoids and the Brain – Seizure Control?



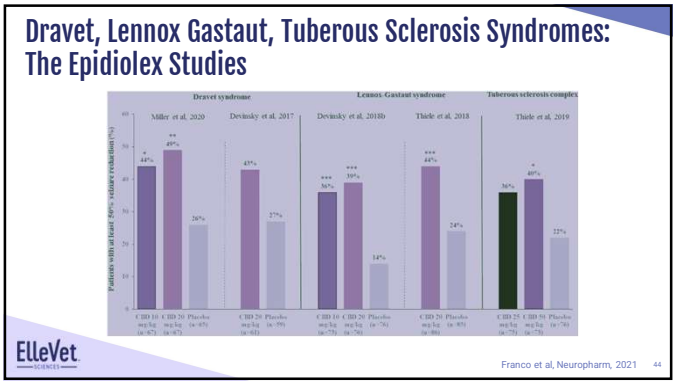
ElleVet SCIENCES

42

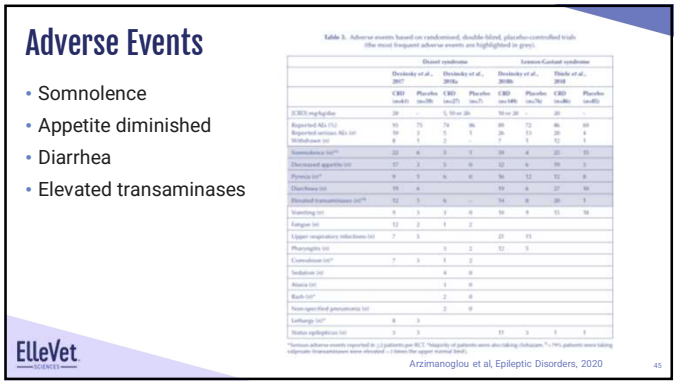
42



43

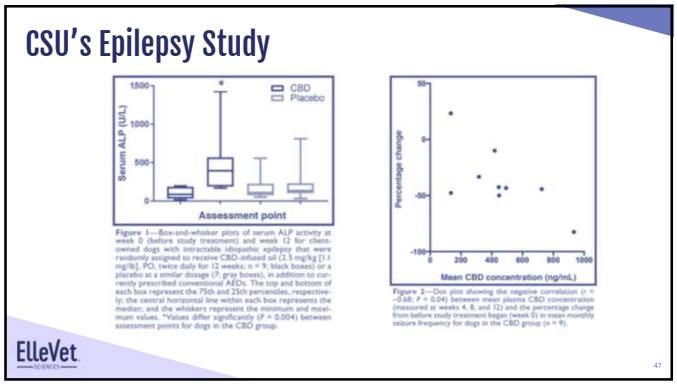


44

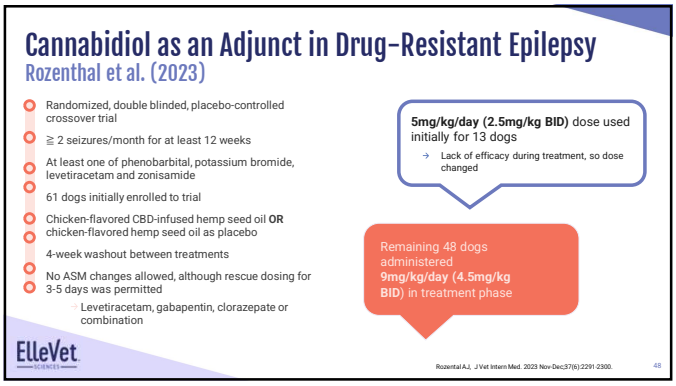


45

46



47



48

Cannabidiol as an Adjunct in Drug-Resistant Epilepsy

Rozenthal et al. (2023)

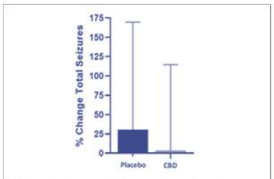


FIGURE 1 Means and SD of percent change of total seizures from baseline averaged over the course of 3 months while taking 9 mg/kg/day of CBD oil versus placebo, along with conventional ASD treatment ($n = 39$). Treatment $P = .04$. CBD, cannabidiol.

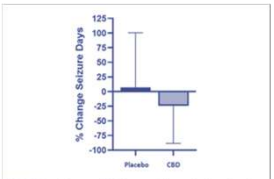


FIGURE 2 Means and SD of percent change of seizure days from baseline averaged over the course of 3 months while taking 9 mg/kg/day of CBD oil versus placebo, along with conventional ASD treatment ($n = 39$). Treatment $P = .002$. CBD, cannabidiol.

ElleVet SCIENCES

49

49

Cannabidiol as an Adjunct in Drug-Resistant Epilepsy

Rozenthal et al. (2023)

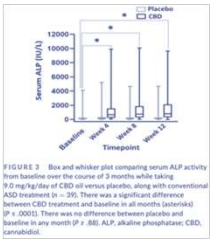


FIGURE 3 Box and whisker plot comparing serum ALP activity from baseline over the course of 3 months while taking 9.0 mg/kg/day of CBD oil versus placebo, along with conventional ASD treatment ($n = 39$). There was a significant difference between CBD treatment and baseline in all months (asterisks) ($P \leq .0001$). There was no difference between placebo and baseline in any month ($P \geq .88$). ALP, alkaline phosphatase; CBD, cannabidiol.

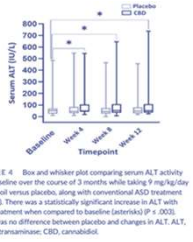


FIGURE 4 Box and whisker plot comparing serum ALT activity from baseline over the course of 3 months while taking 9 mg/kg/day of CBD oil versus placebo, along with conventional ASD treatment ($N = 39$). There was a statistically significant increase in ALT with CBD treatment when compared to baseline (asterisks) ($P < .003$). There was no difference between placebo and changes in ALT. ALT, alanine transaminase; CBD, cannabidiol.

Also showed no alterations in phenobarbital or bromide during treatment!

ElleVet SCIENCES

50

50

ElleVet Seizure Study

- Two Centers participated
  - University of Florida – Dr. Gabriel Garcia
  - Vet. Neuro. and Pain Mngmt Center of NE
    - Dr. Stephanie Kube
- Placebo Blinded Crossover Design
  - Dogs with at least monthly grand mal seizures.
  - Refractory to common medications
  - Can be on zonisamide, keppra, phenobarbital, potassium bromide.
  - 10 of 14 dogs enrolled have MRI and CSF tap negative for infectious or structural
  - 4 dogs refractory multiple year treatment – refractory epilepsy based on history.

Safety and efficacy of cannabidiol-cannabidiolic acid rich hemp extract in the treatment of refractory epileptic seizures in dogs

Gabriel A. Garcia[1]*, Stephanie Kube[2], Sheila Carrera-Justiz[1], David Tittle[3] and Joseph J. Wakshlag[3]

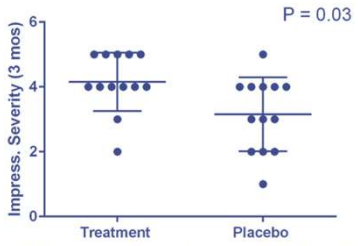
- Randomized into treatment groups
  - Treatment phase – 2 mg/kg of a full spectrum hemp containing 50:50 mix of CBD:CBDA in sesame seed oil filled capsules
  - THC less than 0.3% with ratio of CBD/CBDA to THC/THCA being 27:1
  - Placebo Group – sesame seed oil
  - All placebo jars liked with hemp oil to provide distinctive smell.
- 14 dogs finished with data for examination.

ElleVet SCIENCES

51

51

ElleVet Results: Owner Survey



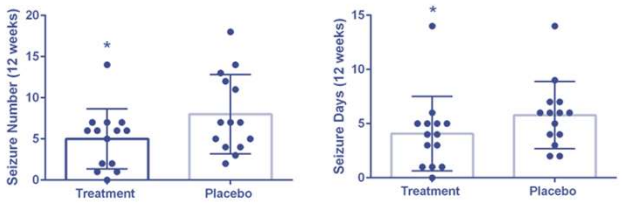
(1 - lot worse; 3 - no change; 5 - lot better)

ElleVet SCIENCES

52

52

ElleVet Results: Seizure Diary



6 dogs during ElleVet treatment has a 50% decrease in frequency or days – none during placebo treatment

ElleVet SCIENCES

53

53

ElleVet Results: Adverse Events

- Owners surveyed at 3 months
- Owners asked about increased hunger, vomiting, diarrhea, weight gain, thirst, urination, sleepiness, restlessness/anxiety, ataxia.
- Scores of 1-3 (no change or decrease) vs 4 or 5 (increased)
- Fisher's Exact test performed

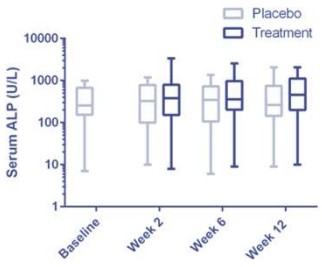
Adverse Events 13 respondents	Placebo	Treatment	Fisher's Exact
Increased appetite	0	3	p = 0.22
Increased GI signs (vomit/diarrhea)	0	2	p = 0. 48
Increased thirst/urination	3	2	p = 1.0
Increased Ataxia	1	4	p = 0.32
Increased Anxiety	3	2	p = 1.0
Increased lethargy/somnolence	1	3	p = 0.59

ElleVet SCIENCES

54

54

ElleVet Results: Serum Chemistry

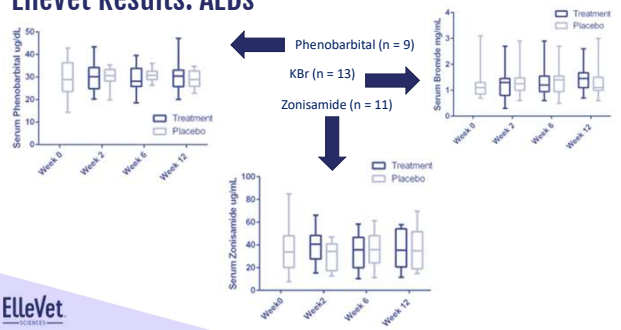


ElleVet SCIENCES

55

55

ElleVet Results: AEDs



ElleVet SCIENCES

56

56

Human Seizure Work

frontiers in Neurology

Dosage Related Efficacy and Tolerability of Cannabidiol in Children With Treatment-Resistant Epileptic Encephalopathy: Preliminary Results of the CARE-E Study

Richard J. Huntsman[1,2*], Richard Tang-Wai[1,2], Jane Alcorn[1,2], Stephanie Young[2], Bryan Acton[1,2], Scott Corley[1,2], Robert Laprairie[1,2], Andrew W. Lyon[1,2], Simona Mese[1], Darrell D. Mousseau[1,2], Doris Newmeyer[2], Erin Prosser-Loose[2], Blair Seifert[1,2], Jose Tellez-Zenteno[1,2,3], Linda Huh[1,2], Edward Leung[1,2] and Philippe Major[1,2]

Conclusion: The preliminary data suggest an initial CBD target dose of 5–6 mg/kg/day when a 1:20 THC:CBD CHE is used. Possible non-linear pharmacokinetics of CBD and CBC needs investigation. The reduction in seizure frequency seen suggests improved seizure control when a whole plant CHE is used. Plasma THC levels suggest a low risk of THC intoxication when a 1:20 THC:CBD CHE is used in doses up to 12 mg/kg CBD/kg/day.

ElleVet SCIENCES

57

57

Human Seizure Work

frontiers in Neurology

Potential Clinical Benefits of CBD-Rich *Cannabis* Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis

Fabricio A. Pamplona[1], Lorenzo Rotim da Silva[2] and Ana Carolina Coan[1]*

(94/223, 42%). Patients treated with CBD-rich extracts reported lower average dose (6.0 mg/kg/day) than those using purified CBD (25.3 mg/kg/day). The reports of mild (158/216, 76% vs. 148/447, 33%, $p < 0.001$) and severe (41/155, 26% vs. 23/328, 7%, $p < 0.0001$) adverse effects were more frequent in products containing purified CBD than in CBD-rich extracts. CBD-rich extracts seem to present a better therapeutic profile than purified CBD, at least in this population of patients with refractory epilepsy. The roots of this difference is likely due to synergistic effects of CBD with other phytocompounds (aka Entourage effect), but this remains to be confirmed in controlled clinical studies.

ElleVet SCIENCES

58

58

Anxiety and People and Dogs

Journal of the American Pharmacists Association

REVIEW

Use of cannabidiol in anxiety and anxiety-related disorders

Jessica W. Skelley, Crystal M. Deas, Zachary Curren, Jonathan Ennis

- Theory behind use is CBD ability to decrease natural anandamide metabolism increasing cannabinoid tone
- Activation of the 5HT1 receptor
- Humans – Mild anxiety disorders and PTSD positive results

The Impact of Feeding Cannabidiol (CBD) Containing Treats on Canine Response to a Noise-Induced Fear Response Test

Elizabeth M. Morris[1], Susanna E. Kitts-Morgan[2], Dawn M. Spangler[2], Kyle R. McLeod[2], Joan H. C. Costa[1] and David L. Harmon[1*]

ElleVet SCIENCES

59

59

CBD Anxiety in Dogs

- 24 dogs recruited from shelter after screening – 16 finished study.
- Housed at LMU in one of two kennels during stay and fed a standard diet.
- Given control treat, trazodone, CBD treat (1.4 mg/kg ave), or both.
- 3 days of room acclimation for 6 minutes
- Then fireworks testing – 3 minutes no noise and then 3 minutes of fireworks.
- Dogs rotated randomly through protocol treatment each week with daily acclimation to the room
- CBD given 4-6 hrs before test; trazadone given 2-4 hrs before test.
- Blood collected before, immediately after and 1 hr after for cortisol and CBD analysis.

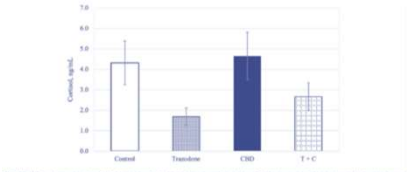
ElleVet SCIENCES

60

60

Results

- Heart rate mildly higher in CBD group (p = 0.09) – Interesting since THC is tachy and CBD is not.
- Serum cortisol lower is lower with trazadone from baseline – not CBD or both together.



ElleVet SCIENCES

61

61

Anxiety Behavioral Outcomes

TABLE 5 | Effect of trazodone (T), CBD (C), CBD by trazodone interaction (C*T), time (Pre-Noise and Noise), CBD by trazodone by time interaction (C*T*Time), and period on the duration of behavioral parameters (s) for 1-min immediately prior to (Pre-Noise) and the first minute (Noise) of the noise-induced fear response tests administered after each 7-d treatment period.

Parameter, s	Treatment				SE[1]	P-value				
	Control	Trazodone (T)	CBD (C)	T+C		Trazodone	CBD	C*T	Time	C*T*Time	Period
Inactive	55.35	56.33	55.21	56.26	1.214	0.329	0.918	0.971	0.011	0.092	0.993
Facing door	37.45	33.90	34.96	37.70	4.198	0.872	0.796	0.217	0.561	0.556	0.786
Glancing around	16.90	15.65	17.93	15.91	3.460	0.396	0.736	0.841	<.001	0.142	0.819
Other eyes	5.10	13.33	4.10	5.48	1.885	0.044	0.072	0.182	<.001	0.469	0.792
Ears relaxed	11.37	7.76	12.35	11.43	4.913	0.179	0.168	0.422	<.001	0.868	0.567
Ears erect	29.33	34.29	29.93	29.80	5.614	0.264	0.408	0.279	<.001	0.747	0.982
Ears moving	19.25	17.79	17.20	18.78	2.076	0.970	0.742	0.351	<.001	0.457	0.493
Tail relaxed	37.90	49.86	38.93	50.96	4.857	0.001	0.753	0.992	0.611	0.898	0.990
Tail stiff	18.45	5.55	16.39	6.65	4.582	0.002	0.887	0.644	0.010	0.757	0.896

ElleVet SCIENCES

62

62

OPEN

Cannabis sativa L. may reduce aggressive behaviour towards humans in shelter dogs

Sara Corsetti[✉], Simona Borruso[2], Livia Malandrucco[3], Valentina Spalluzzi[2], Laura Maregliano[1], Raffaella Perino[1], Pietro D'Agostino[3] & Eugenia Natoli[2]

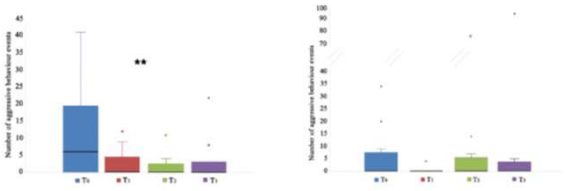
- Shelter situation with behavioral scoring of aggressive tendencies towards humans
- 12 treatment dogs 12 placebo treatment dogs
  - Obscure treatment of 1 drop per 2 kg of a "CBD olive oil"
  - 150 mg/L of cannabinoids
  - 150 mg/ml assuming a drop between 0.05-1 ml – somewhere between 3.5-7.5 mg/kg assumption
- Dogs acclimated to observation by 2 blinded observers – behavioral experts.
- Observed 1 hr three times a day on each study day for aggressive behaviors, stereotypic stress behaviors and mentation environmental interactions
- Baseline – 15 days, 45 days and 15 days after stopping administration.

ElleVet SCIENCES

63

63

Aggressive Behaviors



Stereotypic kenneled behaviors and mentation/environment interactions were not different between groups or over time in either placebo or treatment groups

ElleVet SCIENCES

64

64

Cancog Car Ride Model

- 10 dogs in each group
  - Placebo soft gel
  - 4 mg/kg ElleVet
  - 6 mg/kg ElleVet
- 10-minute car ride model on week one without treatments
- Week later repeated with treatments 1.5 hrs after given treatment
  - Serum cortisol
  - Heart rate Variability
  - Video assessment – salivation, lip licking, sitting/standing/lying, vocalization, cage escape.
- Goal to assess apples to apples – car ride 1 vs car ride 2

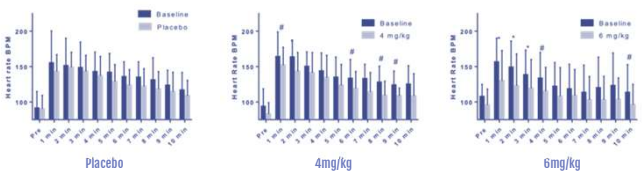
ElleVet SCIENCES

65

65

CanCog Car Ride Model

Heart Rate:



Placebo 4mg/kg 6mg/kg

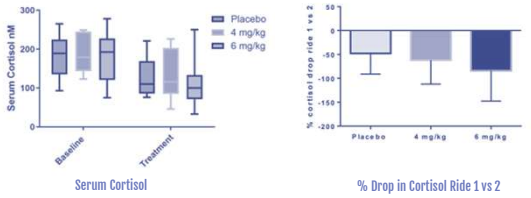
ElleVet SCIENCES

66

66

CanCog Car Ride Model

Cortisol:



Serum Cortisol | % Drop in Cortisol Ride 1 vs 2

ElleVet SCIENCES

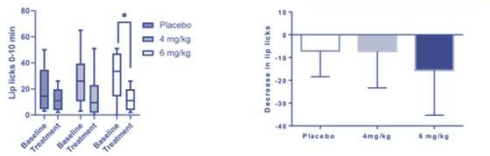
67

67

CanCog Car Ride Model

Lip Licking:

P = 0.012
Cohen's D:
4 mg/kg = 0.26 - weak
6 mg/kg – 0.70 - mod/strong



Number of Lip Licks in 10 mins | Decrease in Lip Licks

ElleVet SCIENCES

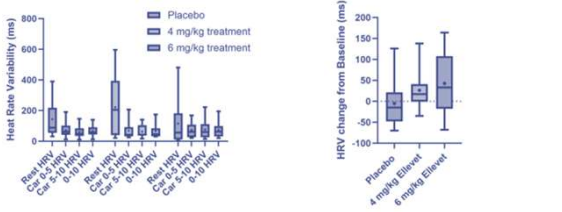
68

68

CanCog Car Ride Model

Heart Rate Variability:

P = 0.18
Cohen's D 4 mg/kg = 0.59 - mod
Cohen D 6 mg/kg = 0.71 - strong

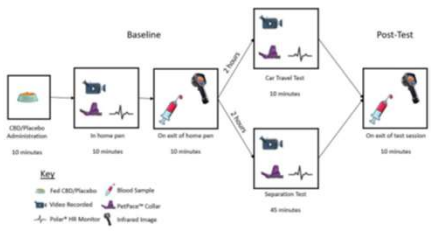


ElleVet SCIENCES

69

69

A single dose of cannabidiol (CBD) positively influences measures of stress in dogs during separation and car travel



Alysia B. G. Hunt, Hannah E. Flint, Darren W. Logan and Tammie King*
Waltham Petcare Science Institute, Waltham on the Wolds, United Kingdom

ElleVet SCIENCES

70

70

Traditional Measures of Anxiety

Serum Measures

- Cortisol
- Serum glucose
- Serum IgA

TABLE 2 Ethogram used to measure dog behavior during the separation and car travel tests.

Behavior	Type		Definition
Repetitive pacing/circling	State	Start	Repeats behavioral sequence 2 or more times without a specific goal, following a fixed route. May pause for up to 2 s
		Finish	Dog ceases the repetitive nature of the movement or begins a different behavior
Panting	State	Start	Increased shallow respiration through an open mouth, may have tongue out (70)
		Finish	Mouth is closed—normal breathing resumes
Whining	State	Start	Dog produces sound such as whines, whimpers, and yelps originating from the throat and mouth
		Finish	Sounds production ceases
Barking	Event		Head and lips forward, mouth opening and shutting repeatedly to emit a large, sharp, short sound from the throat (63)*
Howling	Event		Raised muzzle perpendicular to ground and emits a long drawn-out sound through semi-closed jaw (63)*
Play behavior	State	Start	Interaction (e.g., mouthing/pawing) with toys and/or box whilst exhibiting soft relaxed body language
		Finish	Dog ceases behavior
Digging	State	Start	Mouth/front paws and claws used to attempt movement/displacement of substrate other than external door
		Finish	Dog ceases behavior
Escape behavior	State	Start	Tries to dig, bite, or scratch at the external door—not directed at themselves
		Finish	Dog ceases behavior
Elimination	Event		Squat/leg raised in order to urinate and/or hind end lowered and back arched in order to defecate (63)*
Vomiting	Event		Open mouth and retch causing vomit from the mouth
Yawning (car test only)	Event		An involuntary take of breath through a wide-open mouth (71)
Lip licking (car test only)	Event		Dog flicks tongue around the outside of mouth, on lips and/or quickly over the nose

ElleVet SCIENCES

71

71

TABLE 1 Terms included in the Qualitative Behavioral Assessments (QBAs) used to measure dog behavior during baseline, the separation, and car travel tests.

Term	Definition
Anxious	Worried, unable to settle or cope with the environment, apprehensive
Alert	Vigilant, inquisitive, on guard
Calm	Absent of strong positive/negative emotions
Comfortable	Without worries, settled in environment, peaceful with external stimuli
Depressed	Dull, sad demeanor, disengaged from and unresponsive to the environment, quiet, apathetic
Explorative	Confident in exploring the environment or new stimuli, investigative
Fearful	Timid, scared, shows postures typical of fear
Lethargic	Sluggish, inactive, unresponsive or slow to respond to external stimuli
Nauseous (car test only)	Salivating, lip licking, facial tension, excessive swallowing, retching, hunched body posture
Nervous	Unsure, agitated, shows fast arousal, unsettled, restless, hyperactive
Reactive	Responsive to external stimuli
Relaxed	Easy going, calm with no visual evidence of tension in the body
Restless	Unable to rest or relax
Sad	Unhappy, downcast
Stressed	Tense, shows signs of distress
Tense	Stiff, rigid posture, on edge
Uncomfortable	Uneasy, nervous, tense, restless

control and nine treatment) experiencing car travel. Dogs in the separation group were habituated to the testing room until they were deemed comfortable in the environment with their experienced handler present. Dogs in the car travel group were trained to enter a crate within the car *via* a ramp or box setup voluntarily and habituated to the crate.

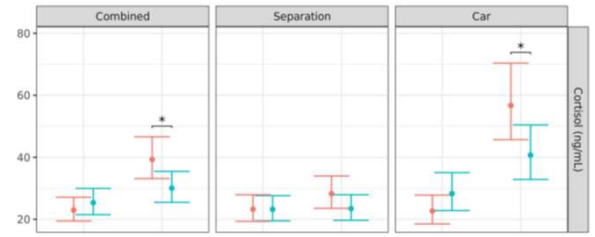
- Three raters with good interrater reliability for videos
  - 10 minutes for car ride
  - First, middle, last 5 minutes of 45 minutes separation
- Assessed QBA
  - Differences in sadness, stressed, tense, and uncomfortable and more explorative in separation only.

ElleVet SCIENCES

72

72

Serum Cortisols

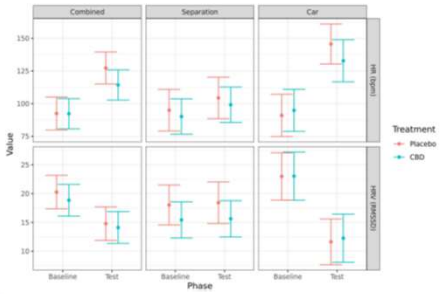


ElleVet SCIENCES

73

73

Heart Rate and Variability

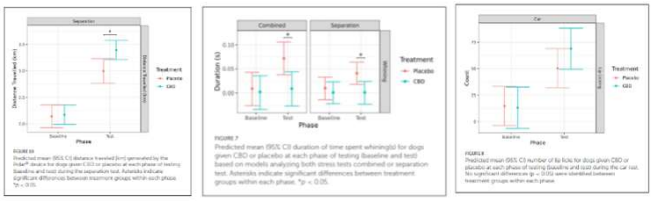


ElleVet SCIENCES

74

74

Typical Measures of Anxiety



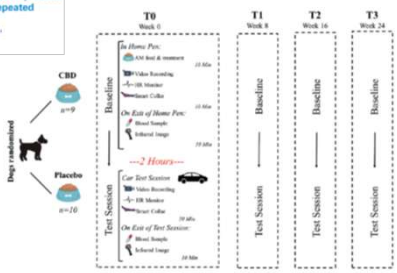
ElleVet SCIENCES

75

75

Administered CBD isolate soft gels 4 mg/kg SID

Daily dosing of cannabidiol (CBD) demonstrates a positive effect on measures of stress in dogs during repeated exposure to car travel

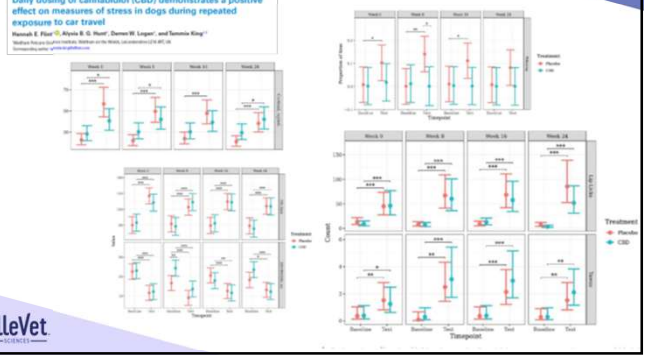


ElleVet SCIENCES

76

76

Daily dosing of cannabidiol (CBD) demonstrates a positive effect on measures of stress in dogs during repeated exposure to car travel



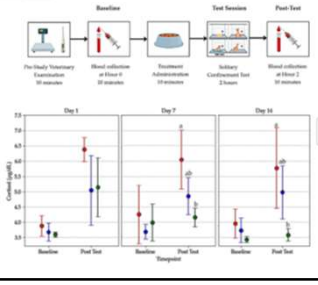
ElleVet SCIENCES

77

77

A Preliminary Evaluation of the Comparative Efficacy of Gel-Based and Oil-Based CBD on Hematologic and Biochemical Responses in Dogs

- Study used shelter dogs (N= 4 per group)
  - Placebo oleogel
  - 4 mg/kg full spectrum MCT oil
  - 4 mg/kg full spectrum oleogel
  - Added to a daily meatball
- Treated for two weeks SID
  - CBC, chemistry pre and post 2-hour isolation test
  - Did not assess any behaviors in isolation.



ElleVet SCIENCES

78

78

What needs to be done!

in the dogs tested (38, 83). Only three dog breeds were represented, all clinically healthy and living in a homogeneous environment, and they were not "owned" pets selected for displaying separation-related anxiety or travel-related stress. Therefore, confirming these research findings in pet dogs in traditional home environments will be beneficial. Doses >4 mg/kg, have caused mild side effects in tolerance studies (39), but testing the efficacy of lower or multiple dosing of CBD in the same stress paradigms may also be worthwhile.

Data is currently being collected using ElleVet at 6 mg/kg, 9 mg/kg and 12 mg/kg in noise phobia testing, and all doses are showing positive results – full results will be available in spring of 2026!

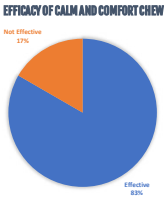
ElleVet SCIENCES

79

79

Why Do We Think it Works?

- Real-life study of 24 dogs with
  - Car ride anxiety
  - New person aversion
  - Noise phobia
- Observed dog under stimuli
- Provided around 3.5 mg/kg per dog
- Looked for onset of effect
  - 4/24 within 30 minutes
  - 10/24 within 60 minutes
  - 6/24 within 120 minutes
- Still the leading indication based on sales

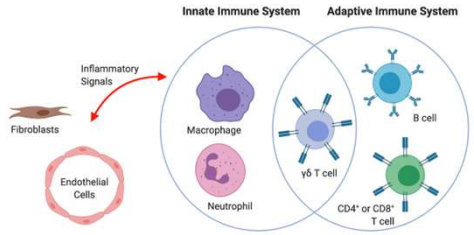


ElleVet SCIENCES

80

80

CBD and the Immune System?

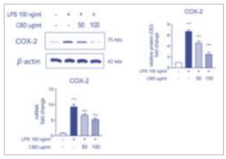


ElleVet SCIENCES

81

81

Immune Cell Work in Canine

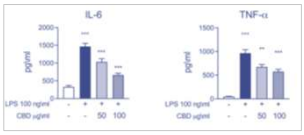


Article

Effect of Cannabidiol (CBD) on Canine Inflammatory Response: An Ex Vivo Study on LPS Stimulated Whole Blood

Enrico Guglielmo [1], Patrizia Licata [1], Alessio Filippo Peritore [2], Rosalba Siracusa [2], Ramona D'Amico [2], Marika Cordaro [2], Roberta Fusco [2], Daniela Impellizzeri [2], Rosanna Di Paola [2,3], Salvatore Cuzzocrea [1,4,5], Rosalia Crupi [1,2] and Claudia Dina Interlandi [1,2]

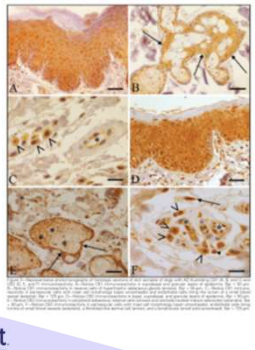
- Whole blood from 6 German Shepard dogs
- Incubated with vehicle control or CBD at 50 ug/mL of 100 ug/mL for 24 hrs
- Then stimulated with LPS to induce cytokine production
- Assessed IL-6, TNF alpha, Nf-KB and COX-2 expression
- This is 100-fold higher than we can reach in the plasma!



ElleVet SCIENCES

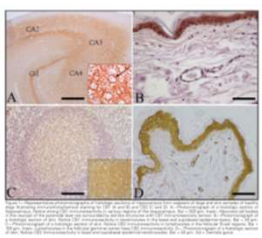
82

82



Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis

Luca Cerquetti, DVM, PhD, Vincenzo Mosciatello, DVM, PhD, Emanuela Ricci, DVM, PhD, Giorgia Cristiano, Biol D, PhD, Vincenzo Di Marco, Chem D, PhD, Francesco Albanese, DVM, Maria Federica della Valle, MSc, Francesco Abramo, DVM



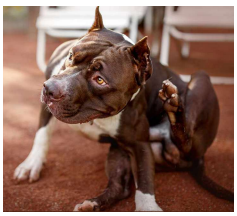
ElleVet SCIENCES

83

83

Receptors and Atopic Dermatitis?

- We currently do not understand the receptor biology as it relates to Cannabinoids in the skin
  - Immune Cells – Mast cells, lymphocytes, plasma cells, APC (monocytes)
  - Keratinocytes and the adnexal structures
  - CB1 and CB2 receptors upregulated in skin of atopic dogs
  - Receptors CB2, GPR55, TRPV1, TRPM, 5HT, all CBD, CBDA, CBG, CBGA targets
  - Dr. Roberto Chiochetti - IHC
- Do cannabinoids alter inflammation and/or can they alter the pruritus?



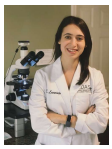
ElleVet SCIENCES

84

84

Atopic Dermatitis Study

- Accepted and published in Vet Derm!
- Double-blinded placebo controlled
  - 17 Treatment Group/ 12 Placebo
  - 2 mg/kg BID for one month
  - Assessing CADESI-04 scoring (vet)
  - VAS pruritus (owner)
  - Owner satisfaction
  - Serum Cytokines
  - IL-34 - associated with CADESI score
  - IL-31 – associated with pruritus
  - CBC and serum chemistry
  - Serum cannabinoids



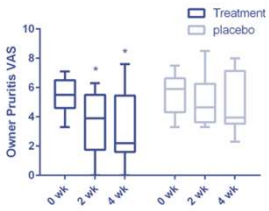
ADAS
ANIMAL DERMATOLOGY & ALLERGY SPECIALISTS

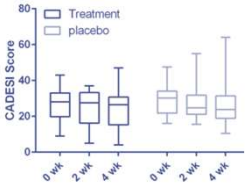
ElleVet SCIENCES

85

85

VAS and CADESI Scores





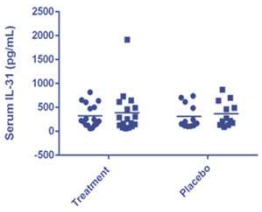
Fisher's Exact = 0.0256	Responded/would continue	No Response
Treatment	10	7
Placebo	2	10

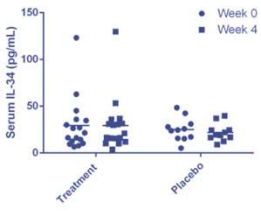
ElleVet SCIENCES

86

86

IL-34 (CADESI) and IL-31 (Pruritus)



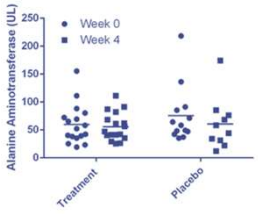


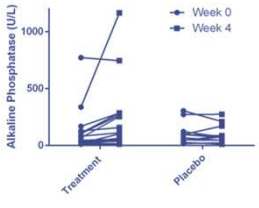
ElleVet SCIENCES

87

87

Liver Enzymes – ALP and ALT



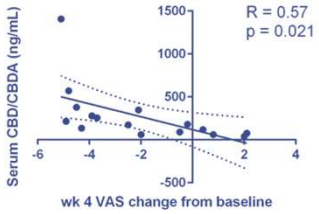


ElleVet SCIENCES

88

88

Regression of CBD/CBDA and VAS Change



ElleVet SCIENCES

89

89

CBD and Pruritus?

Feeding Cannabidiol (CBD)-Containing Treats Did Not Affect Canine Daily Voluntary Activity

…During the PM session, dogs receiving 4 mg CBD/kg BW/d tended (P=0.091) to be less active than control. During AM and PM sessions, CBD reduced scratching compared with CON (P=0.030). CBD did not affect activity duration during exercise periods (P=0.143). These results indicate that when supplemented with up to 4 mg CBD/kg BW/d, CBD does not impact the daily activity of adult dogs but may exert an antipruritic effect.

ElleVet SCIENCES

90

90

Pandora Syndrome/FIC

- Urinary Signs
  - Hematuria
  - Dysuria
  - Pollakiuria
  - Inappropriate urination
  - Urethral obstruction
- **Estimated to affect 250-500K cats yearly**

ElleVet SCIENCES

91

91

FIC Management

- Identify and relieve stress
- Provide an "Enriched Feline Environment"
- Radiation therapy (no, really!)
- Our call to action - time to try a new approach

ElleVet SCIENCES

92

92

There is precedence for cannabinoids in treatment

Cannabidiol as a Promising Therapeutic Option in IC/BPS: In Vitro Evaluation of Its Protective Effects against Inflammation and Oxidative Stress

ElleVet SCIENCES

93

93

Summary

- We are understanding how CBD/CBDA can be used to mitigate refractory seizures -40% response rate at 2 mg/kg and up
  - Can be used with other medication safely in epilepsy
  - Watch for somnolence primarily
- Anxiety and behavioral issues are possible venues
  - Hemp CBD/CBDA products may be used in situational events
  - Dose may be higher 3-6 mg/kg
  - No adverse events are noted at higher doses.
  - Still leading reason for use in clients – further real-life studies are needed
- Don't forget the atopic itchy dogs!
- Don't forget pain – dogs and cats and may be FIC/urinary spraying

ElleVet SCIENCES

94

94

How does ElleVet stack up to other clinically studied products in the USA??

Comparing CBD Products	Product A	Product B	Product C	ElleVet
Long Term Safety Study	✓	✗	✗	✓
Proven Effective for Mobility	✓ 4.5mg per kg BID	✗	✓ Unknown S/D	✓ 2mg per kg BID
Proven Effective for Neuro	✗	✓ 4.5mg per kg BID	✗	✓ 2mg per kg BID
Proven Effective for Skin	✗	✗	✗	✓ 2mg per kg BID
NASC Certified	✗	✓	✓	✓
Controlled Supply Chain	✗	✗	✗	✓
1:1 CBD to CBDA Ratio for Best Absorption	✗	✗	✗	✓
Veterinary Efficacy Guarantee	✗	✗	✗	✓
Veterinary Professional Guided Support	✗	✗	✗	✓
Price per Milligram	$0.08	$0.09	$0.05	$0.06

95

Thank you for attending!

Looking for Free CE? Go to: www.ellevetacademy.com
Questions?

Joseph Wakshlag
DVM, PhD, DACVIM (nutrition), ACVSMR
CVO –ElleVet Sciences
joe.wakshlag@ellevetsciences.com

ElleVet SCIENCES

96

96