CBD/CBDA rich hemp and pain; intricacies of treatment!

Joseph Wakshlag

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CVMO Ellevet Sciences

Professor Cornell University

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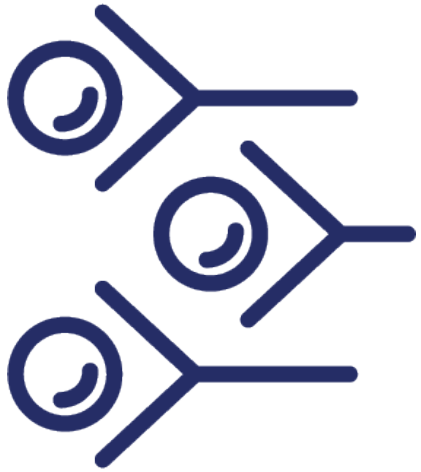
Endocannabinoid system (ECS)

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



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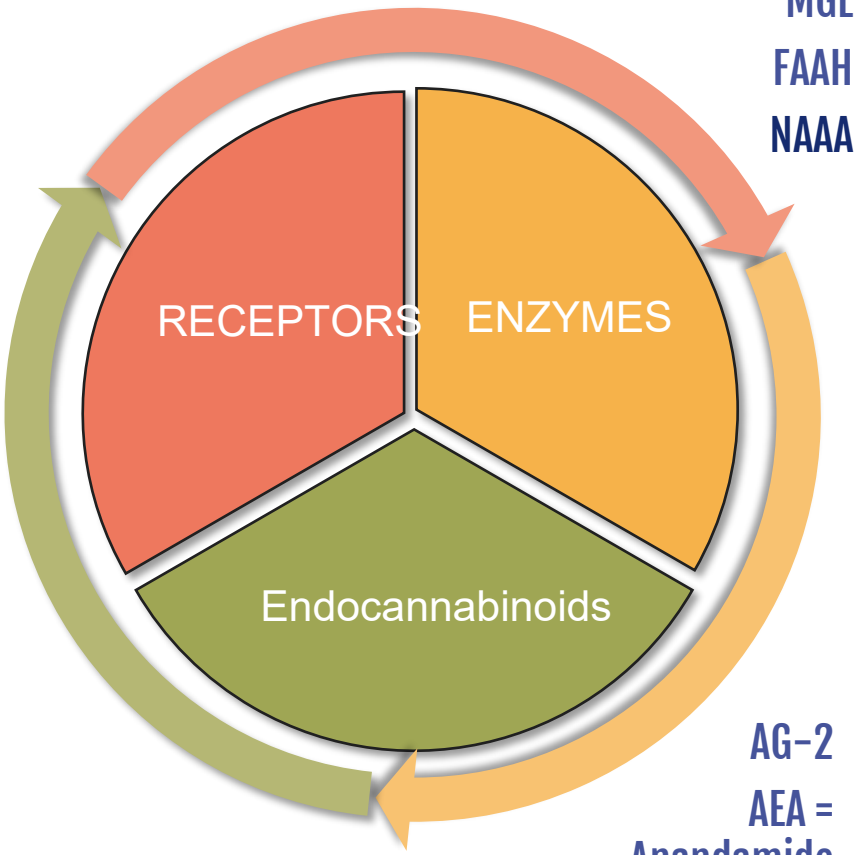
The Endocannabinoid System (ECS)

- 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

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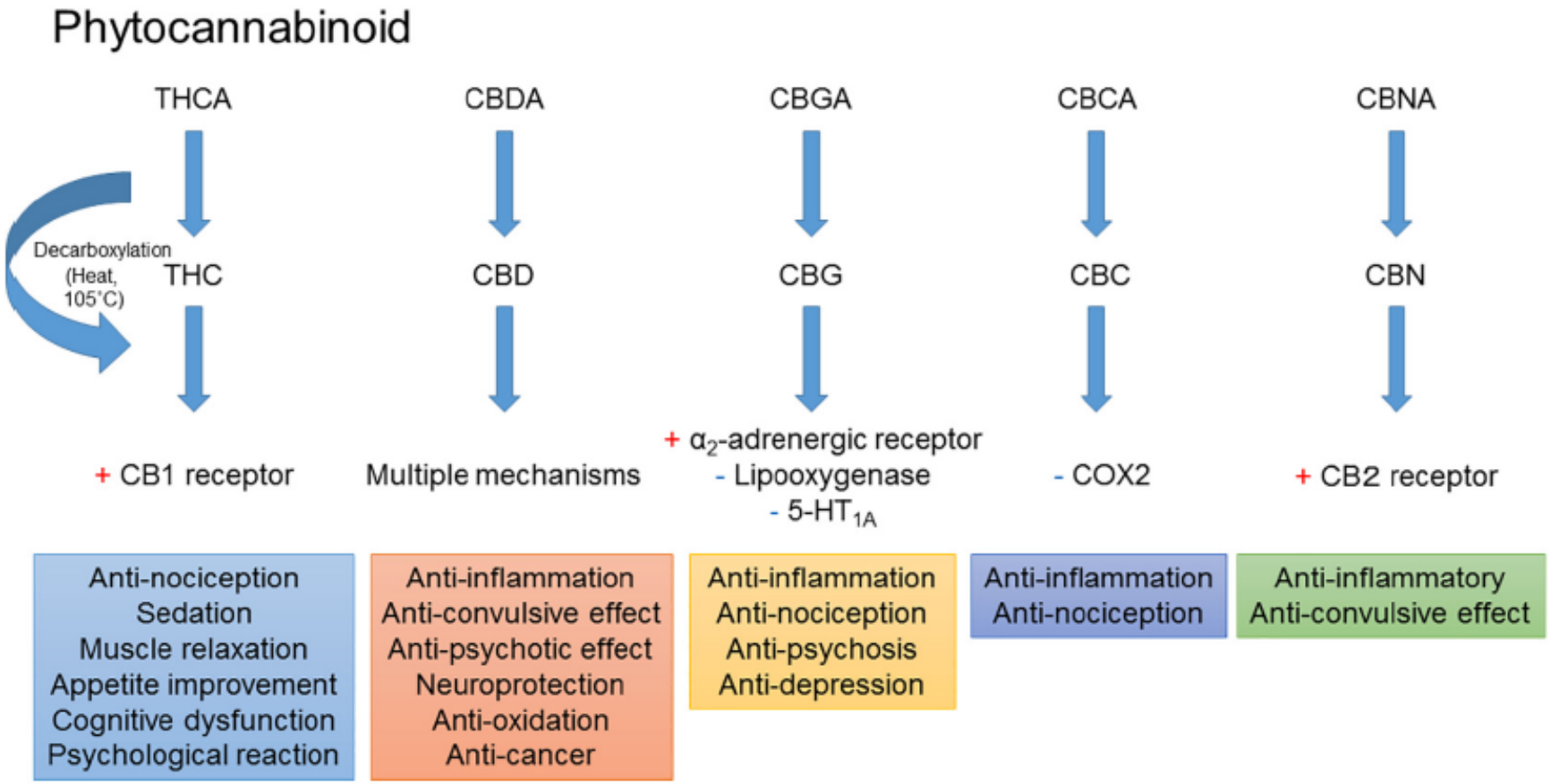
Cannabinoids Mechanism of Action



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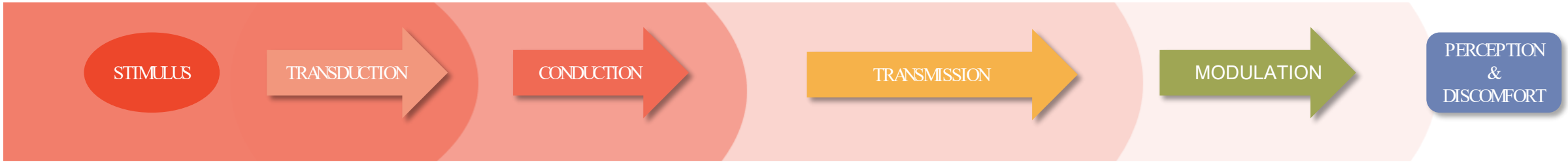
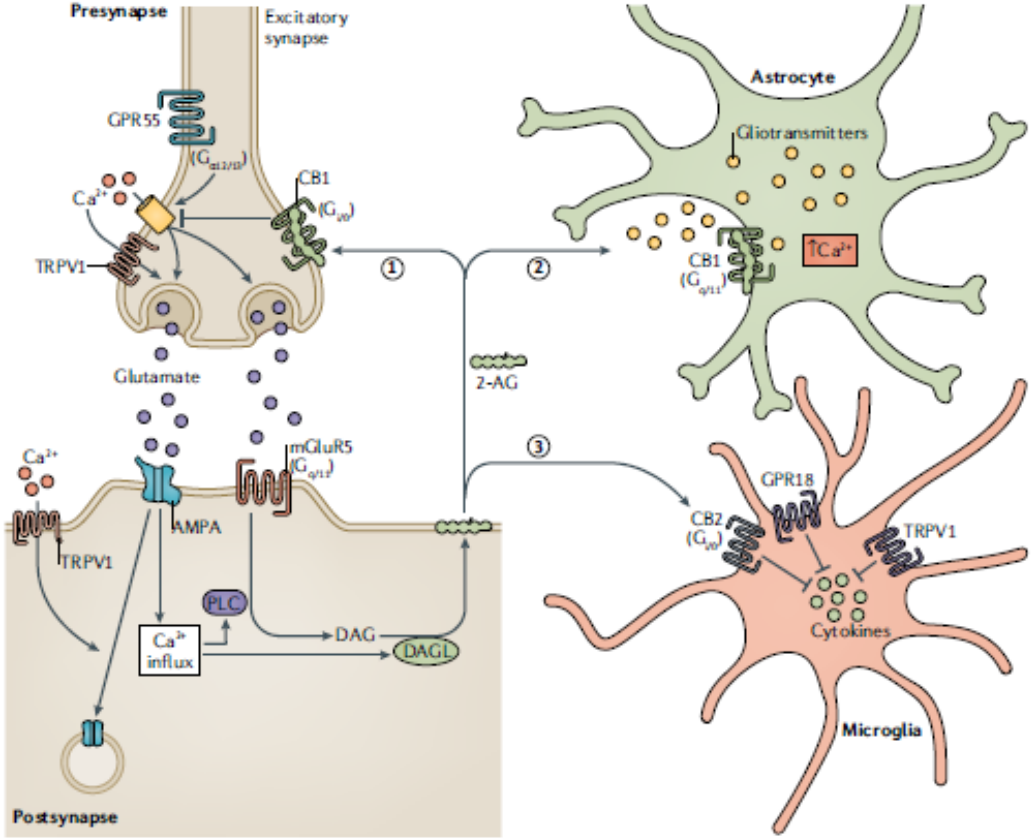
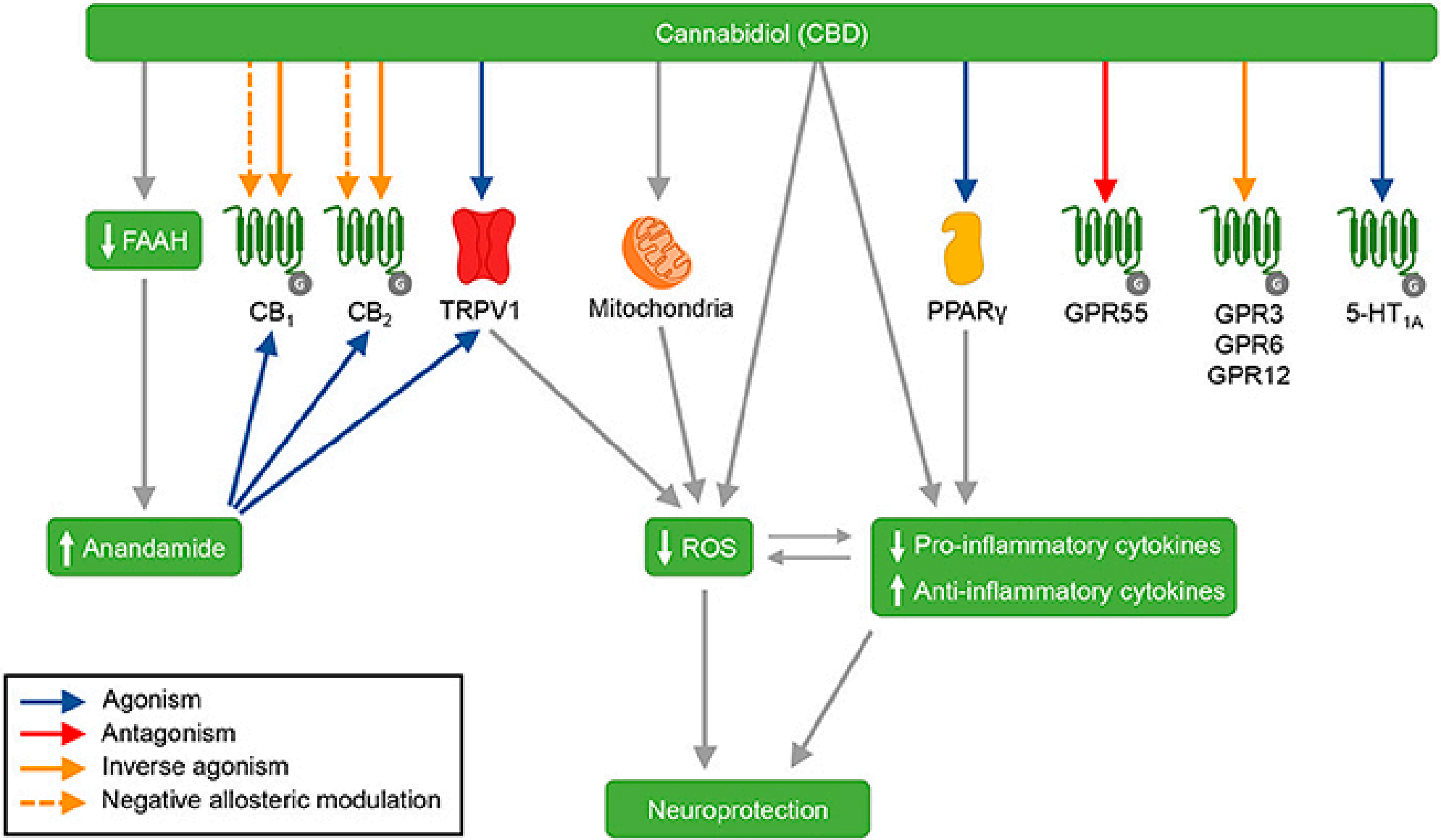
Phytocannabinoids on Nociception





Cristino et al - Nat Reviews, 2020



Peres, Front in Pharm, 2019

"Cannabis is a heterogenous botanical mixture and the results from one study cannot to be applied generally to other plants or products."

– Dr. Ethan Russo

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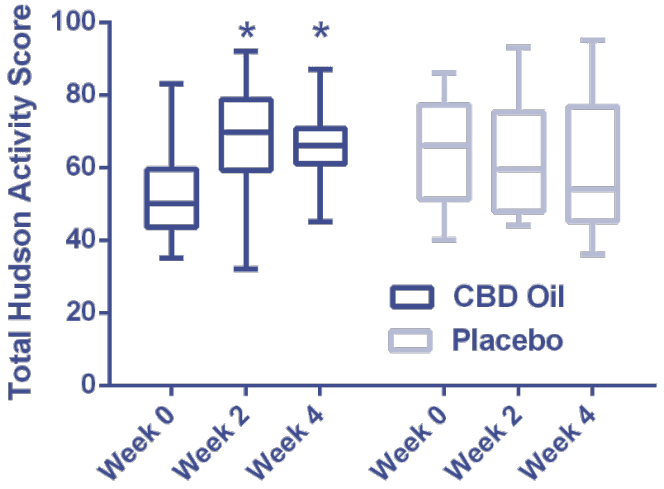
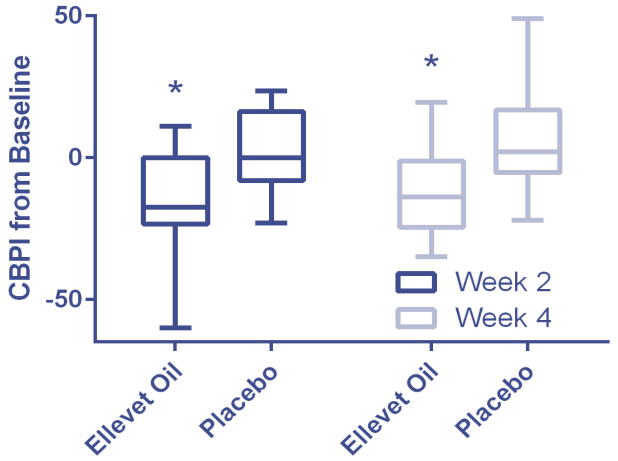
OA Pain in Dogs Clinical Trial

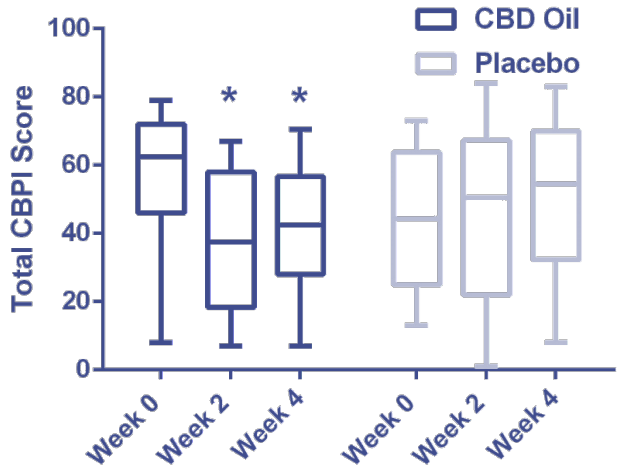
(Wakshlag, 2020)

Cornell University
College of Veterinary Medicine

- 22 dogs enrolled – 16 completed
- ElleVet COMPLETE Oil 2mg (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







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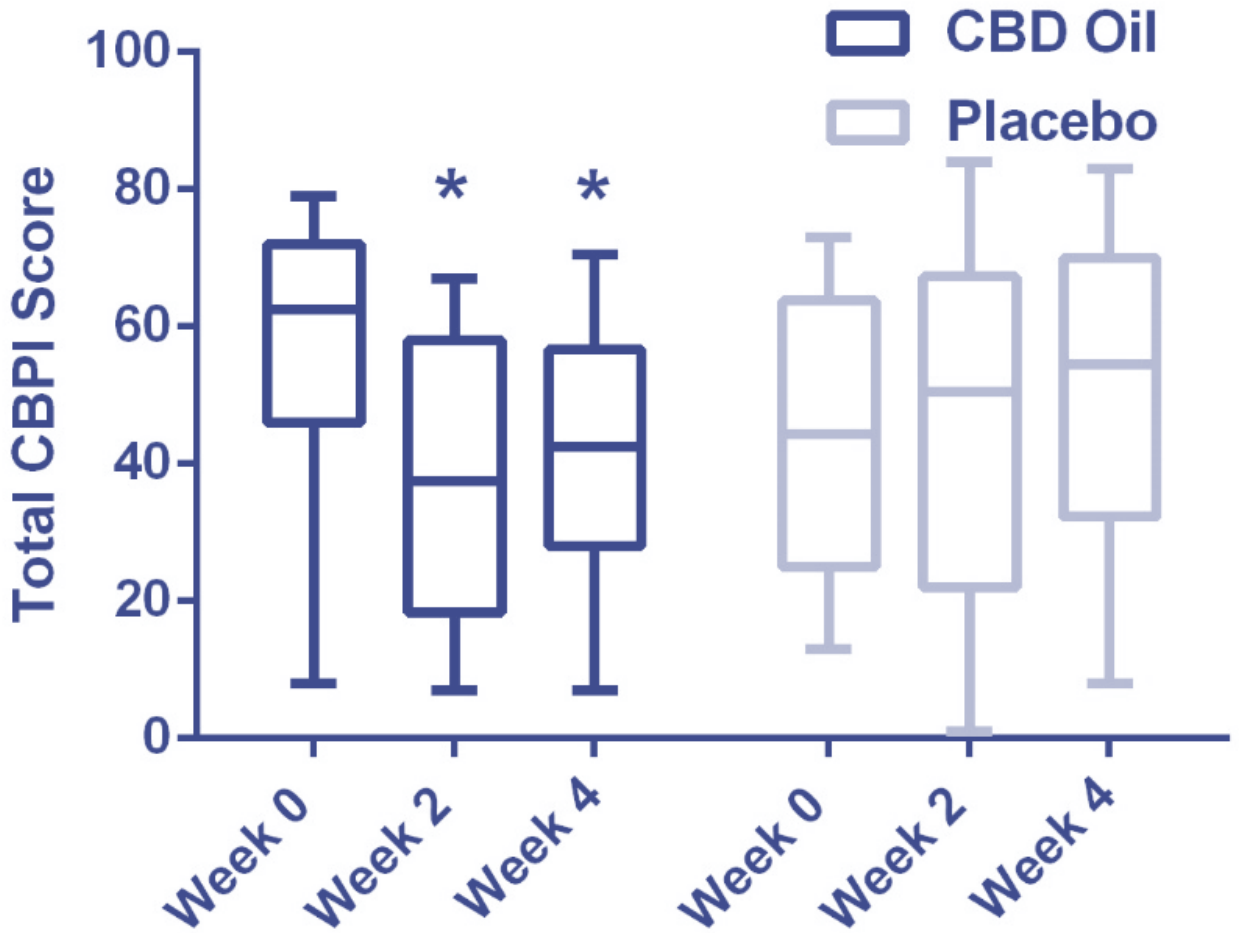
Canine Brief Pain Inventory



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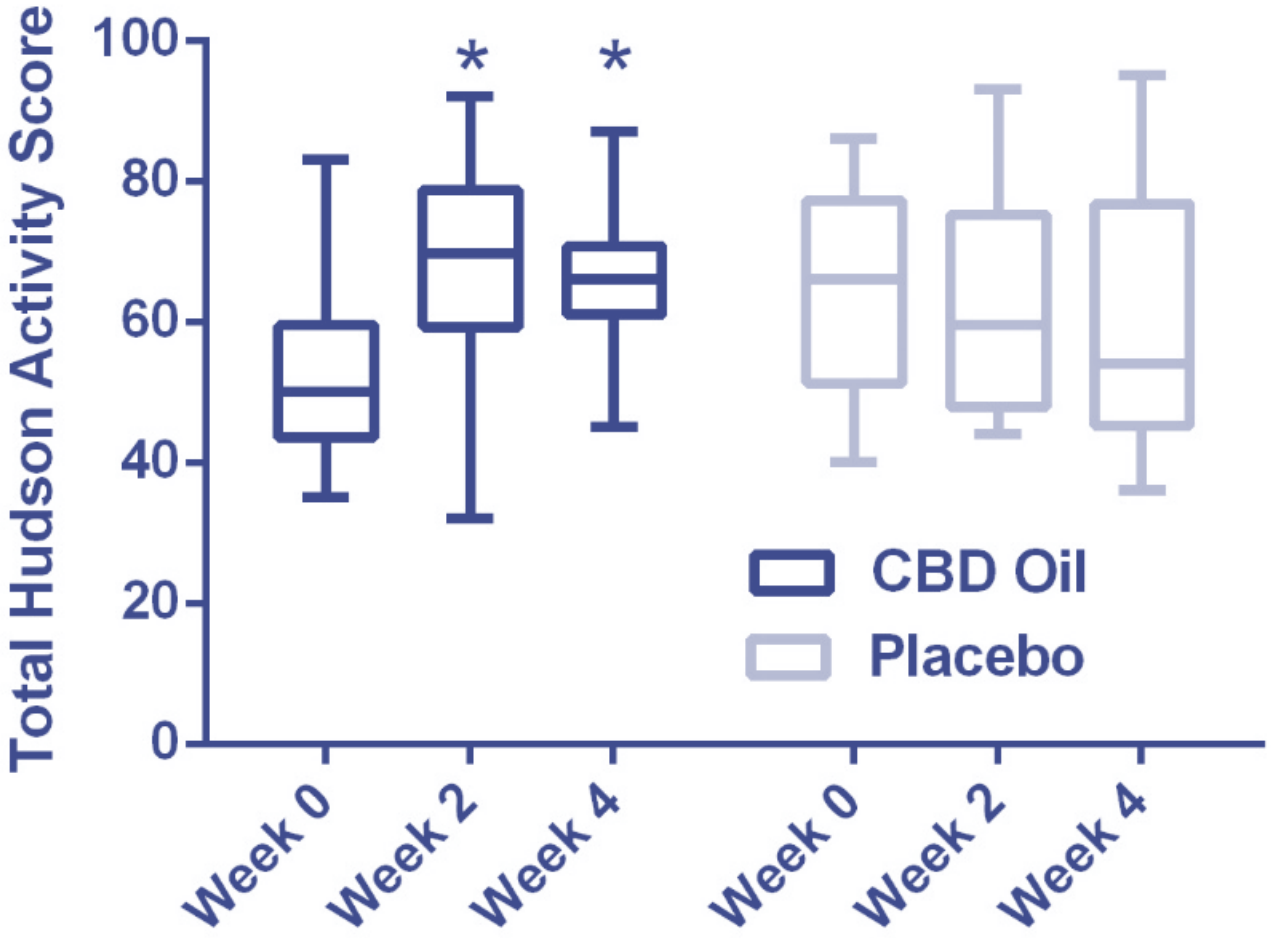
Hudson Activity Scale



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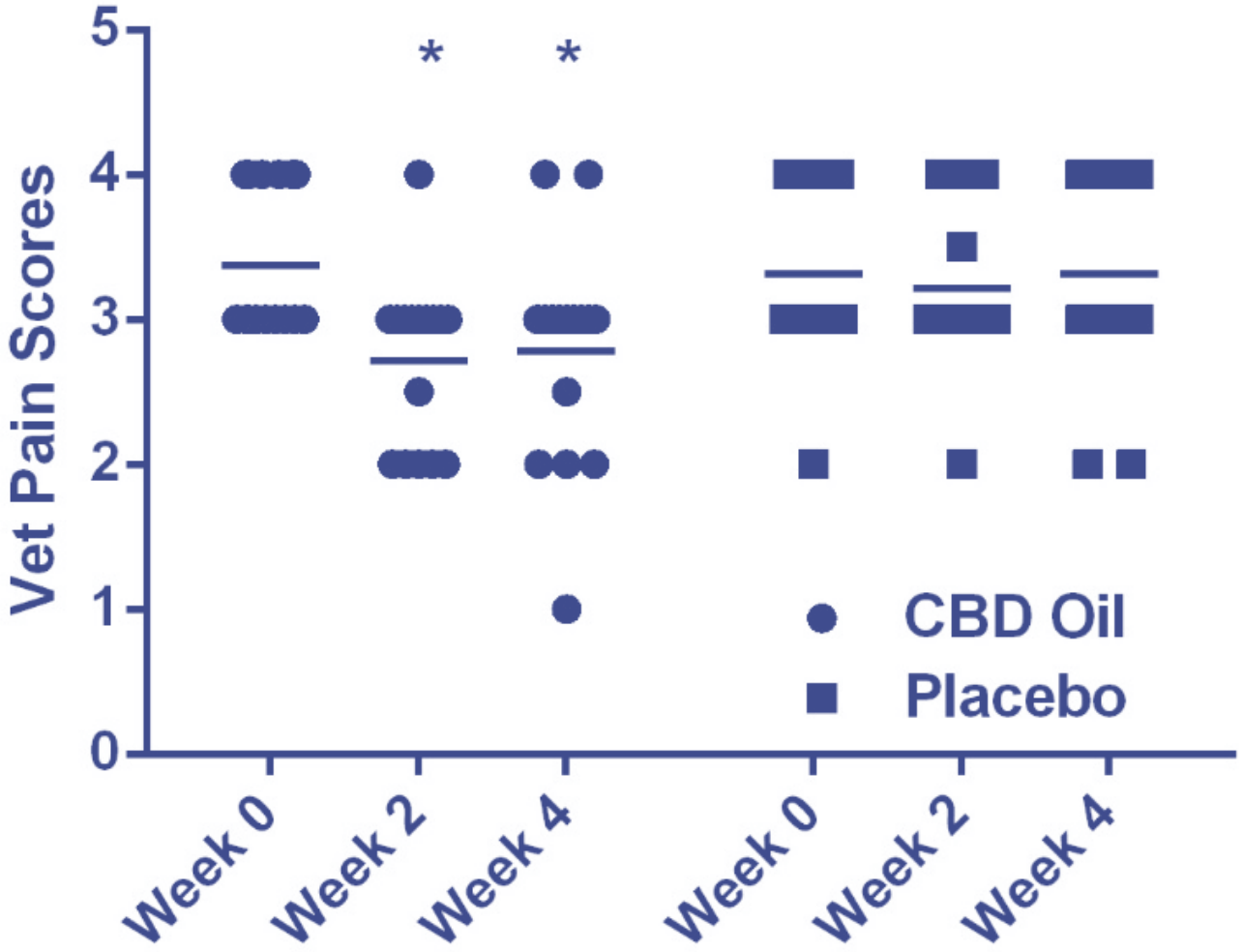
Vet Pain Scoring



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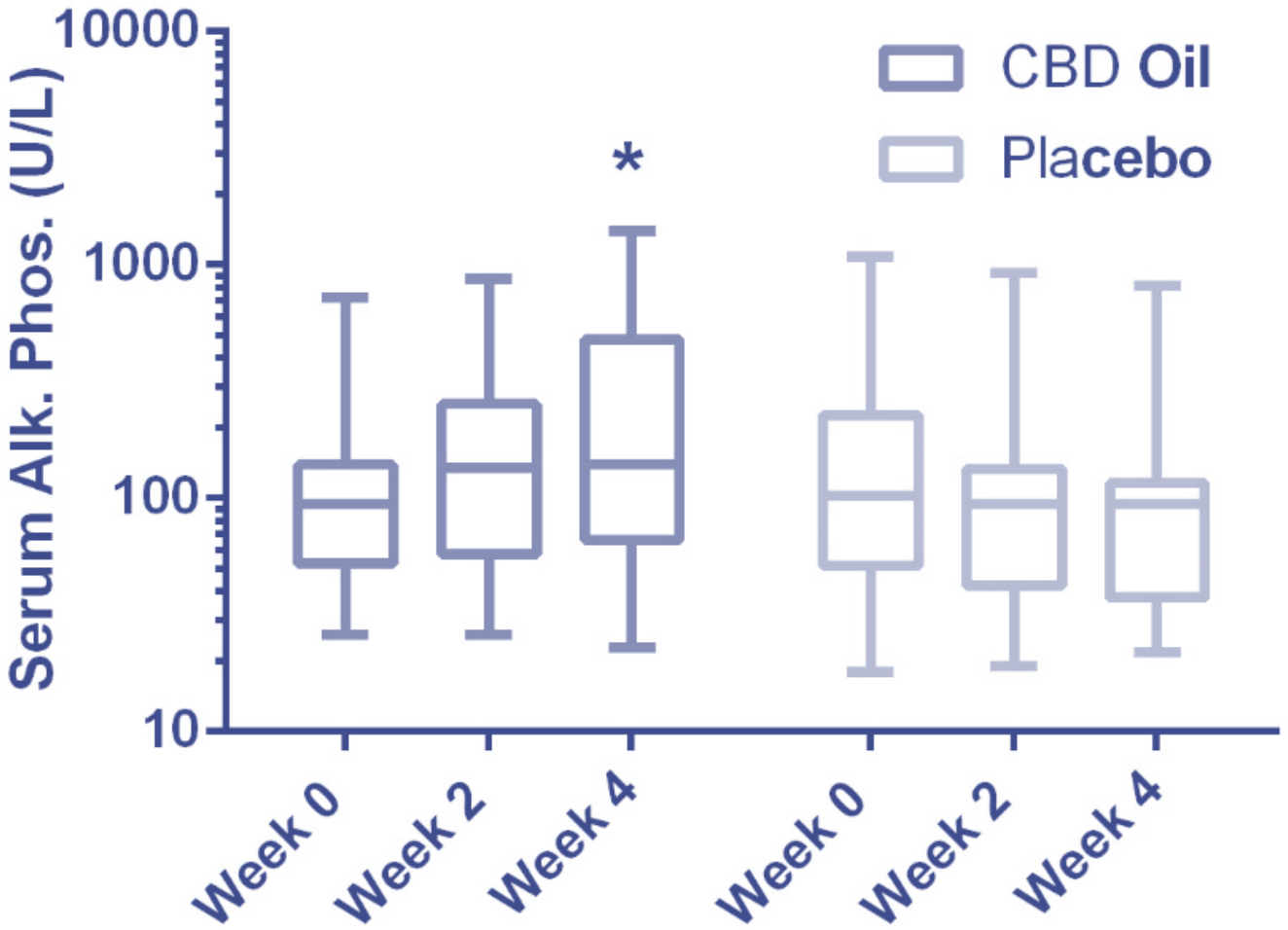
Alkaline Phosphatase



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Second Study

- Dose escalation study in 37 dogs – 0.25 mg/kg up to 4 mg/kg q 2 wks
- Longer duration – 90 days
- 32 dogs completed the study – no NSAIDS, Only Gabapentin (13 dogs) +/- other modalities (acupuncture, laser, PT).
- Assessed gait and pain and activity scores via Cincinnati Scores
- 30 of 32 responded according to owner assessments

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

Lori Kogan, PhD, Peter Hellyer, DVM, Robin Downing, DVM, MS

Cannabinoid (HPLC)		Results	
	LOD (mg/g)	Percent	mg/mL
Δ8-Tetrahydrocannabidol	<0.2		
Cannabidiolic acid (CBD-A)	<0.2		
Cannabigerolic acid (CBG-A)	<0.2		
Cannabigerol (CBG)		0.090%	0.84
Cannabidiol (CBD)		3.337%	30.83
Cannabidivarin (CBDV)	<0.2		
Cannabinol (CBN)	<0.2		
(−)-trans-Δ⁹-tetrahydrocannabinol (THC)		0.133%	1.23
Tetrahydrocannabivarin (THCV)	<0.2		
Cannabichromene (CBC)	<0.2		
Δ9-Tetrahydrocannabinolic acid A (THC-A)		0.122%	1.13
Cannabinoids Total		**Percent**	**mg/g**
Max Active THC		**0.24%**	**2.40**
Max Active CBD		**3.34%**	**33.37**
T. Active Cannabinoids		**3.56%**	**35.60**
Total Cannabinoids		**3.68%**	**36.82**
Ratios			
13.09 :1 CBD to THC		**0.08 :1 THC to CBD**	

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Second Study

Table 2. Starting and Ending Numeric Rating Score, CBD Dose, and Gabapentin Doses in a Clinical Trial of Dogs Receiving CBD for the Treatment of Chronic Pain

	Pre	Post	Change
Numeric Rating Score*	3.2 ± 2.2	0.97 ± 0.81	–2.23 ± 2.3
CBD dose (mg/kg)	0.31 ± 0.04	1.67 ± 0.09	1.36 ± 0.88
Gabapentin dose (mg/day)**	1,846 ± 1,756	710 ± 1,112	–1,263 ± 1,314

*NRS ($t = 5.35$, $df = 29$, $P < .001$); **Gabapentin ($t = 5.12$, $df = 29$, $P = .001$).

Data are presented as mean ± standard deviation.

Abbreviations: *df*, degrees of freedom; NRS, Numeric Rating Scale.

Table 3. Changes in Liver Enzymes (ALKP) in Dogs With Chronic Pain Receiving CBD in a 90- Day Trial

Starting ALKP (U/L)	Ending ALKP (U/L)	Change in ALKP (U/L)*
133.3 ± 118	264 ± 233.2	130.8 ± 135

*ALKP ($t = –5.22$, $df = 28$, $P = .001$).

Biochemistry values were obtained before beginning the clinical trial and at 90 days.

Abbreviation: *df*, degrees of freedom.

Table 4. Changes in Liver Enzymes (ALT) in Dogs With Chronic Pain Receiving CBD in a 90- Day Trial

Starting ALT (U/L)	Ending ALT (U/L)	Change in ALT (U/L)*
93.5 ± 69.3	91 ± 60.4	–2.5 ± 43

*ALT ($t = .31$, $df = 29$, $P = .76$).

Biochemistry values were obtained before beginning the clinical trial and at 90 days.

Abbreviation: *df*, degrees of freedom.

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Third Study

- Enrolled 20 dogs divided into 4 groups
  - Placebo – coconut oil
  - 20 mg CBD SID (coconut oil)
  - 50 mg CBD SID (coconut oil)
  - 20 mg lecithin liposomal CBD SID
  - No dosing based on weight.
- Inclusion – exclusion
  - Healthy
  - Naturally occurring OA – no trauma or end stage
  - No medications
- Randomized, double-blind, placebo-controlled
  - Helsinki index of pain and vet assessment - blinded

PAIN

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

Chris D. Verrico[a,b], Shonda Wesson[c], Vanaja Konduri[d], Colby J. Hofferek[d], Jonathan Vazquez-Perez[d], Emek Blair[e], Kenneth Dunner Jr[f], Pedram Salimpour[g], William K. Decker[d,h,i], Matthew M. Halpert[d,*]

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Third Study

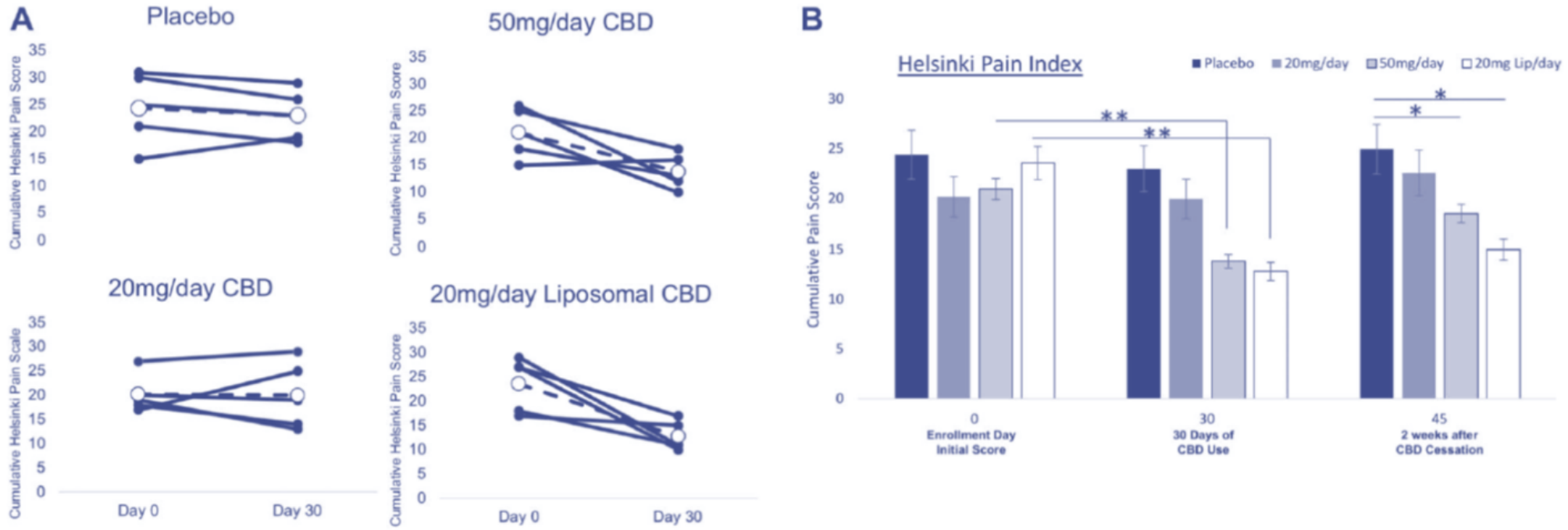

Figure 4. Daily administration of CBD for 30 days improves owner-perspective quality of life scores among large dogs with affirmative diagnosis of osteoarthritis. Twenty large domestic canines with affirmative diagnosis of osteoarthritis were enrolled in a double-blind, placebo-controlled randomized study. Animals were administered coconut oil placebo, 20-mg/day naked CBD, 50-mg/day naked CBD, or 20-mg/day liposomal CBD. Owners assessed their animals by means of the Helsinki Chronic Pain Index (HPCI) on days 0, 30, and 45. (A) Individual HPCI values were plotted for each study cohort on days 0 and 30. (B) Cohort HPCI values were plotted on days 0, 30, and 45. Error bars ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ by Student's two-tailed *t* test. CBD, cannabidiol.

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Third Study

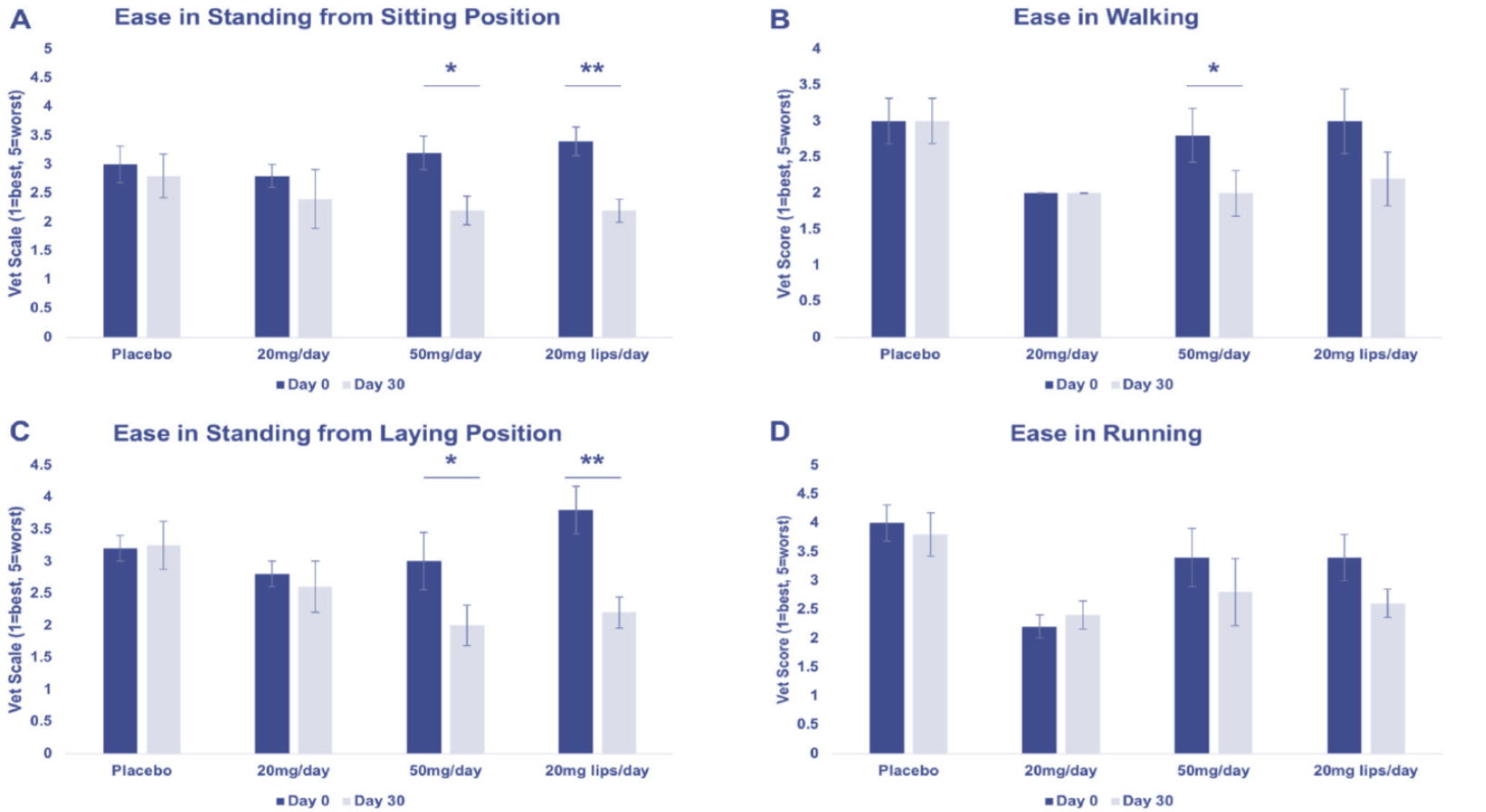

Figure 5. Daily administration of CBD for 30 days improves veterinarian-perspective subset quality of life scores among large dogs with affirmative diagnosis of osteoarthritis. Study enrolled canine subjects were scored by the (blinded) study veterinarian on days 0 and 30 using a scale of 1 (best) to 5 (worst) for 4 different movements consisting of sitting to standing (A), lying to standing (B), walking (C), and running (D). Subset scale data comparing day 0 and day 30 scores for each task are shown by cohort. Error bars ± SEM. *$P < 0.05$, **$P < 0.01$ by Student's two-tailed t test. CBD, cannabidiol.

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Liver Enzymes

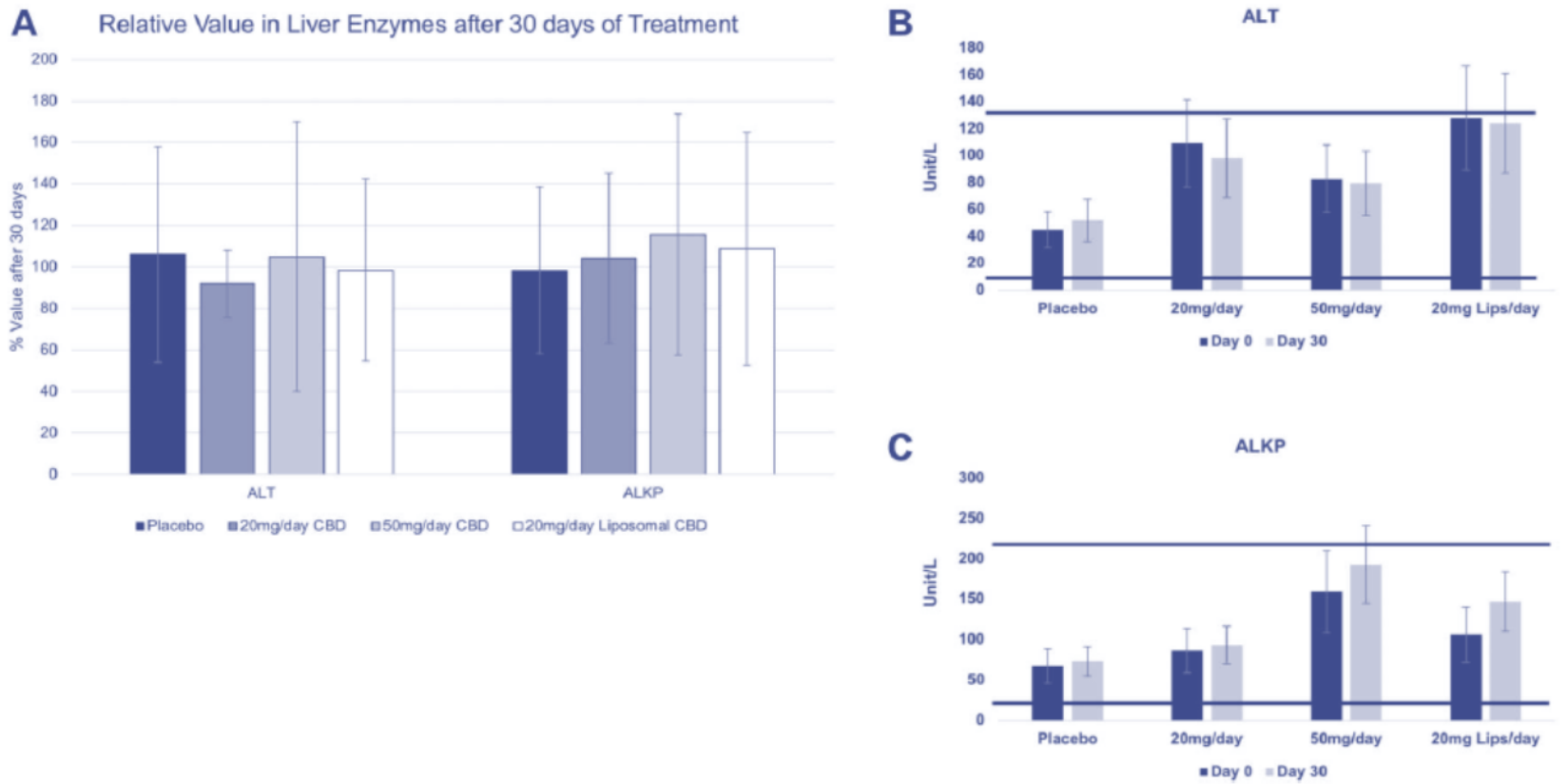

Figure 7. Daily administration of CBD for 30 days does not alter alanine aminotransferase (ALT) or alkaline phosphatase (ALKP) levels. Blood was drawn from animals we enrolled in the clinical study on days 0 and 30, and Chem10 analysis was performed. (A) Relative changes in circulating ALT and ALKP values over the 30-day period. (B, C) Specific changes in circulating ALT and ALKP values over the 30-day period. Dark horizontal lines outline normal range. Error bars ± SD. No statistically significant changes were observed. CBD, cannabidiol.

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Fourth Study

- Dogs with chronic OA pain were evaluated using 2 mg/kg PO BID for 12 weeks
- 21 dogs enrolled - 9 dogs received pure CBD; 12 dogs didn't
- Delivery was claimed to be small amount orally for transmucosal absorption (never been substantially proven to work) – fasted
- More of a CBD isolate product – only trace amounts of other cannabinoids (<0.01mg/mL)
- Dogs were also started on pred or firocoxib as well as gabapentin and amitriptyline
- CBPI survey was provided to owners at 0, 1 wk ,
  2 wk, 4 wk and 12 weeks

Article

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

Federica Alessandra Brioschi [1], Federica Di Cesare [2], Daniela Gioeni [1], Vanessa Rabbogliatti [3], Francesco Ferrari [3], Elisa Silvia D'Urso [4], Martina Amari [3] and Giuliano Ravasio [1,*]

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Fourth Study

Table 3. Pain Severity Score (PSS), Pain Interference Score (PIS) and Quality of Life Index (QoL) (adopted by Brown et al., 2008) of the dogs enrolled in CBD ($n = 9$) and C ($n = 12$) groups.

	Pre			One week			Two Week			Four Week			12 Week		
Time Point	T0			T1			T2			T3			T4		
Score Sig.	PSS a,b	PIS c,d,e,f	QoL g,h,i	PSS *	PIS *,c	QoL *,g	PSS *,a	PIS *,d	QoL h	PSS *,b	PIS e	QoL	PSS	PIS *,f	QoL i
CBD															
mean	5.33	6.33	2.55	2.66	2.44	3.55	3	3	3.11	3.22	4.33	3.22	3.66	2.44	3.44
SD	2.4	2.2	0.7	1.6	1.4	0.5	1.2	1.1	0.6	1.5	1.6	0.6	1.4	1.1	0.7
Control															
mean	5.83	7.25	2.25	6.58	6.66	2.08	5.3	6.41	2.58	5.33	5.25	2.66	4.92	6.33	2.83
SD	2.2	1.9	0.8	1.8	1.7	0.9	2.0	2.2	0.9	2.0	2.1	1.0	2.1	2.3	0.9

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Fifth Study

- 23 dogs completed a cross over design for 6 weeks of placebo/treatment
- Assessments
  - CBC/Chemistry
  - Owner surveys
    - CBPI and LOAD before and end of study
    - Load bearing

ORIGINAL STUDIES

Evaluation of the Effect of Cannabidiol on Naturally Occurring Osteoarthritis-Associated Pain: A Pilot Study in Dogs

Sebastian Mejia, DVM*, Felix Michael Duerr, DVM, MS, DACVS-SA, DECVS, DACVSMR, Gregg Griffenhagen, DVM, MS, DACVAA, Stephanie McGrath, DVM, MS, DACVIM (Neurology)

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Fifth Study

TABLE 2

Baseline and Post-Treatment Median (±SD) Scores and Associated *P* Values for the CMI Data (CBPI and LOAD) Comparing Time Points Within Each Treatment Group (CBD and Placebo) and Between Treatment Groups

CMI	Treatment Group	Baseline CMI Score, Median ± SD	Post-Treatment CMI Score, Median ± SD	*P* Value Comparing Time Points Within Treatment Groups	*P* Value Comparing Time Points Between Treatment Groups
CBPI PSS (0–40)	CBD	17.64 ± 6.37	14.73 ± 7.08	.018*	.89
	Placebo		14.86 ± 5.74	.093	
CBPI PIS (0–60)	CBD	32.76 ± 11.80	26.71 ± 13.12	.016*	.59
	Placebo		24.81 ± 12.91	.007*	
LOAD (0–52)	CBD	28 ± 6.88	24.91 ± 8.05	.019*	.74
	Placebo		25.05 ± 8.48	.09	

* Indicates statistically significant values ($P \leq .05$)
CBD, cannabidiol; CBPI, Canine Brief Pain Inventory; CMI, clinical metrology instrument; LOAD, Liverpool Osteoarthritis in Dogs; PIS, pain interference score; PSS, pain severity score; SD, standard deviation.

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Fifth Study

TABLE 3

Mean (±SD) Data and Associated *P* Values of Ground Reaction Forces Comparing Time Points (i.e., Baseline to W3/W6) Within Each Treatment Group (CBD and Placebo) and Between Treatment Groups

Ground Reaction Forces	Treatment	Baseline Mean ± SD	W3 Mean ± SD	*P* Value Comparing Time Points Within Treatment Groups	*P* Value Comparing Time Points Between Treatment Groups	W6 Mean ± SD	*P* Value Comparing Time Points Within Treatment Groups	*P* Value Comparing Time Points Between Treatment Groups
PVF%	CBD	52.32 ± 16.95	54.25 ± 19.97	.085	.735	53.86 ± 19.11	.15	.77
	Placebo		54.63 ± 20.39	.1377		53.63 ± 18.69	.23	
%BWD	CBD	21.59 ± 3.81	22.47 ± 4.43	.0013*	.24	22.17 ± 4.03	.05*	.73
	Placebo		22.07 ± 4.38	.22		22.07 ± 4.37	.16	

* Indicates statistically significant values ($P \leq .05$).
%BWD, percentage of body weight distribution; CBD, cannabidiol; PVF%, peak vertical force normalized by body weight; SD, standard deviation; W3, Week 3; W6, Week 6.

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Fifth Study

- Assumptions about the product
  - Hempseed oil is the base
  - Dogs on placebo had CBD and THC in bloodstream
- No other cannabinoids analyzed
- Hempseed oil has alpha - linolenic and gamma linoleic acid – anti-inflammatory fatty acids
- Product for sale is 20 mg/ml
  - Average (30 kg) lab would have gotten 75 mg which is 3.5 ml BID
- Is the low cannabinoid and fatty acid milieu having a clinical effect in placebo treated dogs?

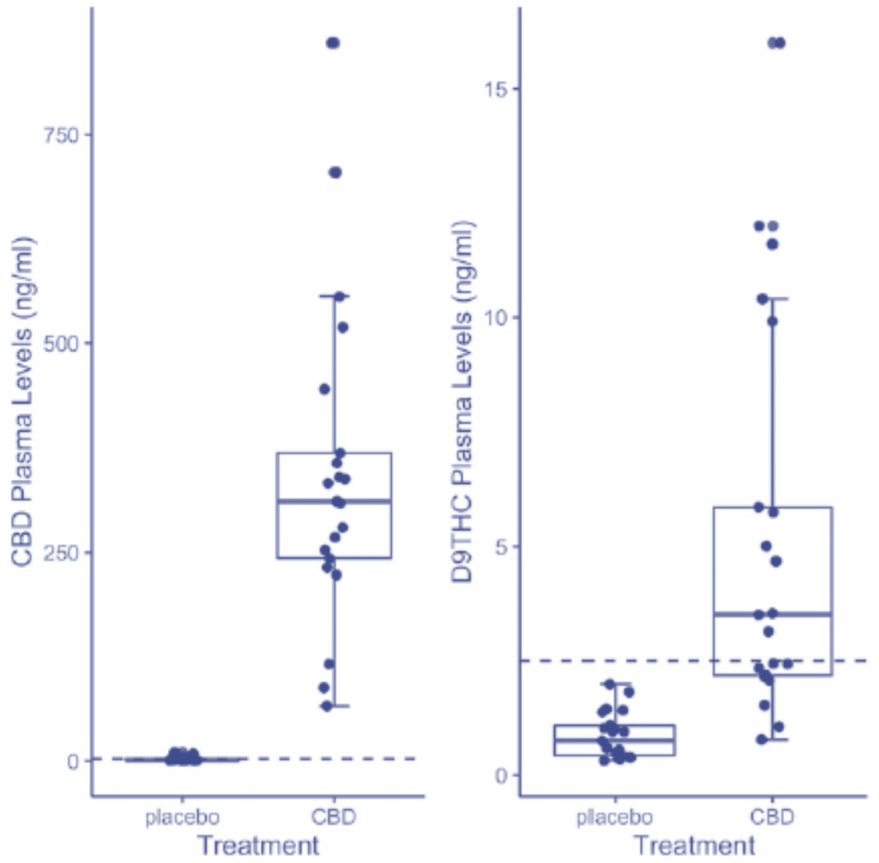

FIGURE 2

Box plot comparing median CBD and D9THC plasma levels (ng/mL) after 6 wk of treatment with either placebo or CBD oil. The dotted line represents the LLOQ. CBD, cannabidiol; D9THC, delta-9-tetrahydrocannabinol; LLOQ, lower limit of quantification.

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)

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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

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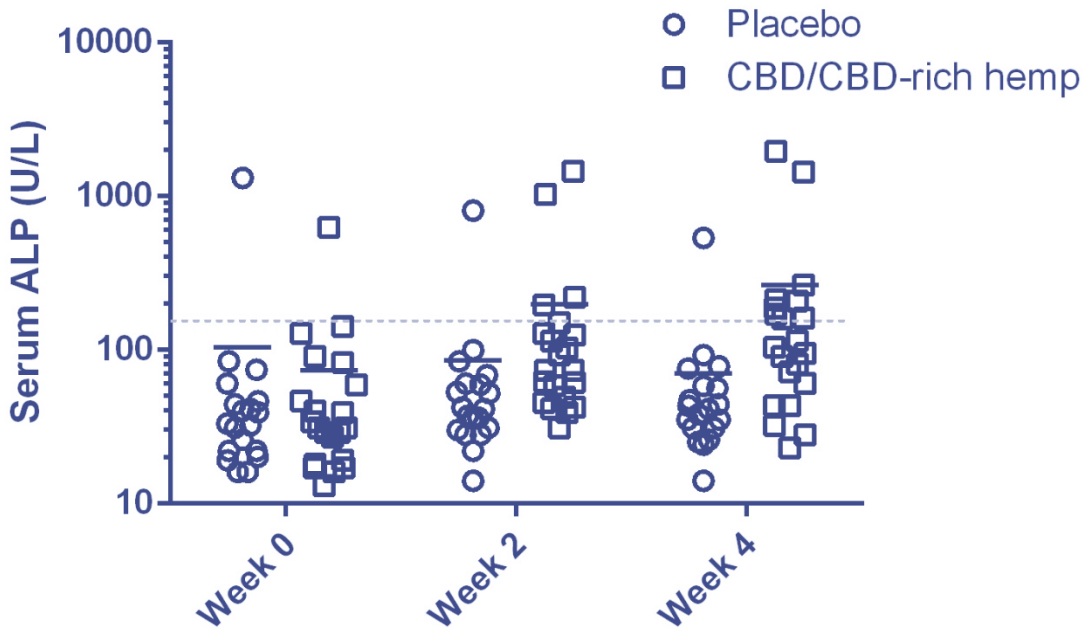
Acute Pain TPLO Model

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



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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.

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.

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.

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Acute Pain TPLO Model

- Takeaways
  - CBD/CBDA hemp product at 2-2.5 mg/kg PO twice daily
  - Did not significantly impact pain
  - No alterations to bone healing
  - Reduced post-operative anxiety and trazodone use
  - Similar increase in ALP

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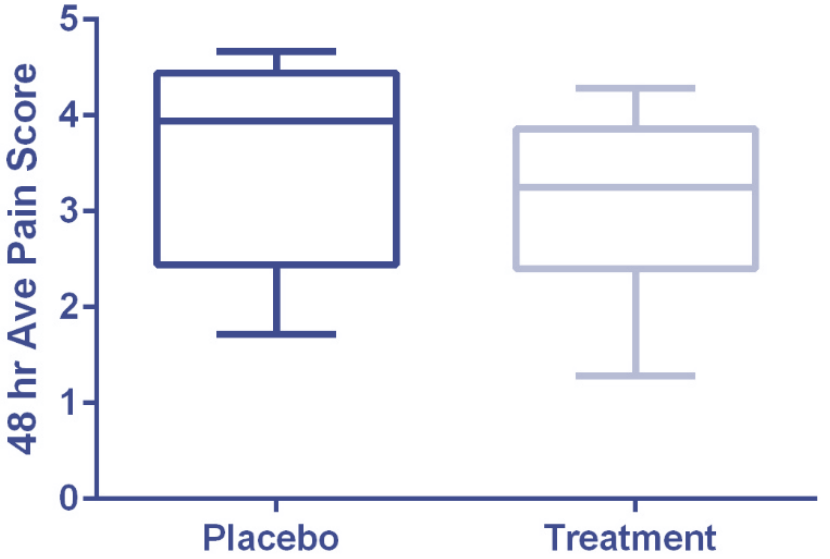
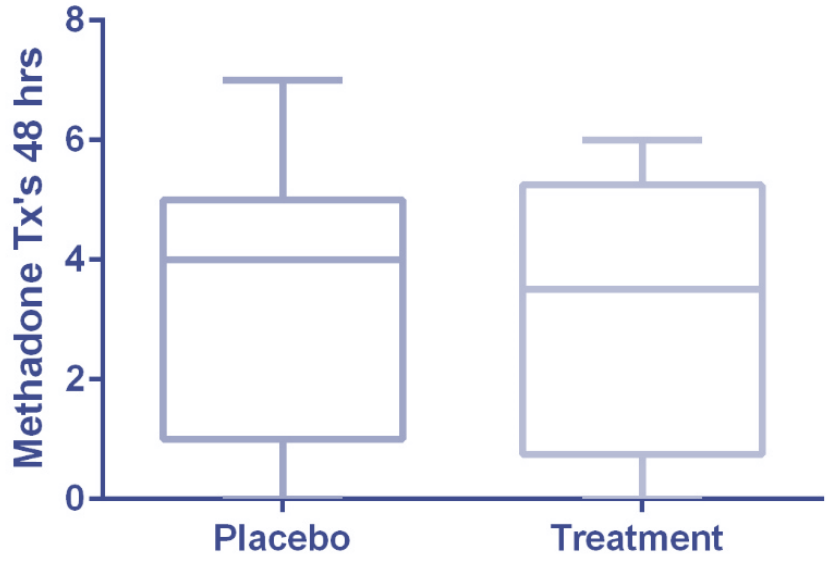
Acute Pain IVDD Model

- 20 dogs completed the study
- All dogs received Ellevet at 4 mg/kg BW or placebo immediately post op in conjunction with gabapentin
- Followed q 2 hrs for 24 hr using Glasgow pain scoring
  - If pain score of 6/20 or greater received methadone injection IV for pain
- ALP rises were not observed in the 48 hours of treatment BID.





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Acute Pain IVDD Model

- Takeaways
  - CBD/CBDA hemp product at 4mg/kg PO twice daily
  - Trended to significance in time to rescue methadone treatment
  - No significant difference in avg pain scores
  - No adverse events nor ALP elevations

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On to some case examples!

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LONG TERM CLINICAL APPLICATION:

Dave Tittle
BVetMed CertVA GPCert(WVA & CPM) MRCVS
RCVS Advanced Practitioner in Veterinary Anaesthesia
Charter Veterinary Hospital, Devon, UK

- Runs referral chronic pain clinics utilising a variety of techniques.
- Has been using Ellevet – known as Ellevance in the UK for over 3 years

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‘Shankley’ – 11 yr, 50kg, ME, Labrador

- Sedentary lifestyle and morbidly obese (BCS 5/5)
- Doesn’t go faster than gait of walk; needs to climb stairs to enter house and needs to be able to get into 4x4 to enable transportation
- Meds:
  - Firocoxib 227mg Q24 – started 5 years earlier by referring vet for L elbow OA signs
- Acute deterioration in mobility associated with marked pain response on manipulation of R shoulder and elbow – distal limb swelling
- Rescue analgesia:
  - Methadone Q4hrs
  - Gabapentin 200mg Q8hrs
  - Ketamine infusion
  - Firocoxib 227mg Q24
  - Paracetamol 500mg Q8hrs
  - Lidocaine infusion added after poor response to above therapy

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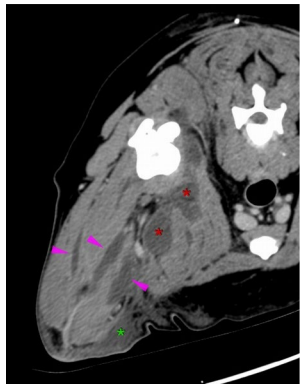
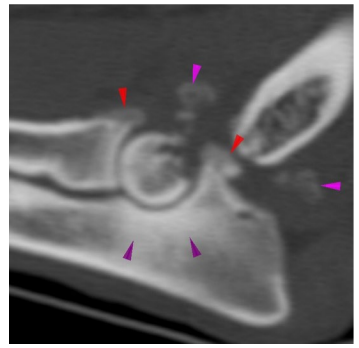
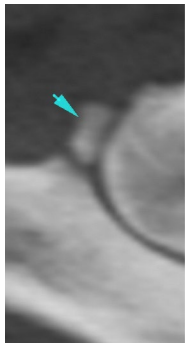
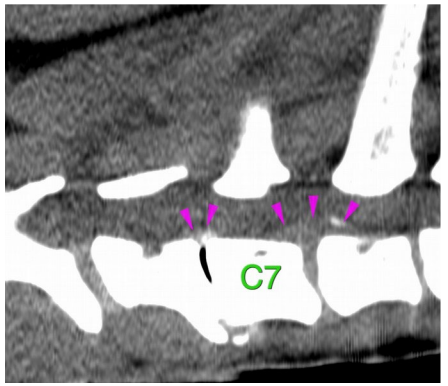
CT –

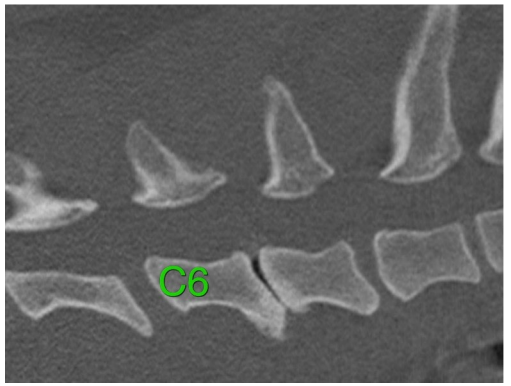
1. Right forelimb cavitary lesions and cellulitis/oedema
2. Reactive right prescapular and axillary lymphadenomegaly.
4. Bilateral shoulder degenerative arthropathy and bicipital tendinopathy.
5. Right elbow dysplasia.
    a) fragmented medial coronoid process
    b) degenerative arthropathy
6. Left elbow advanced degenerative changes.
    a) degenerative arthropathy
    b) synovial hypertrophy and osteochondromatosis
7. Concomitant bilateral elbow flexor and extensor enthesiopathy.
8. C6/7 intervertebral joint collapse.
9. C7/T1 disc herniation, equivocal related compression.
10. Bilateral chronic otitis externa











‘Shankley’ – 11 yr, 50kg, ME, Labrador

- Bloods - raised CRP, with profile suggestive of septic focus (inc WBC’s, TP etc); T4/TSH normal
- CT suggestive of septic OA
- Six weeks co-amoxiclav Q12 and weaned from methadone onto tramadol Q6hrs – contd gabapentin, acetaminophen and NSAID
- Discharged after seven days

- At revisit 2 weeks later – increased sedation with tramadol and gabapentin, despite o’s decreasing tramadol to 1mg/kg Q12hrs and gabapentin to Q12hrs – equivocal improvements in lameness with infection subsided.
- After discussion, opt to withdraw tramadol, but encourage to give gabapentin Q8hrs
- Add ElleVet to aid – counselled to expect some somnolence still with this combination – more acceptable to owners
- **After six weeks:**
  - Bloods all normal
  - Significant improvement in lameness scoring
  - Brighter in self
  - Gained further 1kg!!

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‘Shankley’ – 11 yr, 50kg, ME, Labrador

- Current Meds:
  - Firocoxib 227mg Q24hrs
  - Paracetamol 500mg Q12hrs
  - Gabapentin 200mg Q8-12hrs
  - ElleVet 50mg Q12hrs

- Dietary management has been unsuccessful to date
- He remains bright and has improved mobility and quality of life
- He has improved pain and gait scores – continued for 18 months before neoplasia found and elected euthanasia

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Signalment: ‘Millie’, 13 year old, FN, Mixed breed Canine

History and co-morbidities:

- 4 year history of diabetes mellitus
- 3 year history bilateral diabetic cataracts
- Referred to Pain Clinic due to progressing OA with NSAID intolerance
- Gastro-intestinal disease, especially during periods of stress
- Travel/motion sickness
- Waning/variable appetite

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Signalment: ‘Millie’, 13 year old, FN, Mixed breed Canine

Current Medications:

- Eye Drops:
  - Hyaluronic acid drops (Remend, Bayer) Q4-8hrs
  - Sodium chloride 5% (Akorn Pharma) Q6hrs
  - Bromfenac 0.9mg/ml (Yellox, Bausch & Lomb UK) Q12

- **ADDITION:** Cannabinoid and Terpene Oil 50mg/ml (ElleVet, Ellevet Sciences) 30 drops q12 (capsulated)

Tablets:

- Cetirizine 10mg (Piriteaze, GSK) Q12hrs
- Robenacoxib 40mg (Onsior, Elanco) Q24hrs
- Gabapentin 300mg (Milpharm, UK) Q24
- Metronidazole 500mg (Metrobactin, Dechra) Q12
- EFA Supplement with glucosamine/chondroitin = Large Dog (Synoquin EFA, VetPlus) Q24
- S-adenosylmethionine [SAMe] 400mg (Zentonil Advanced, Vetoquinol) Q12
- Probiotic capsules (YuDigest, Lintbells) 2, Q12

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14 Month Assessment

Date: 30th November 2019

Dog name: Millie

Pet owner name: Sam Corby

Vet name: Dave Tittle

Pain management score = 0.5 content to slightly unsettled.

Dosage: 22 drops AM / 22 drops PM (bottle – drop dispenser different to previous version)

November has been fairly stable, no significant changes. Millie has been eating well, on the whole her eyes and mobility OK.

Pain management MEDS – Ellevet 22 x drops am & 22 drops PM. 1 x Onsior before breakfast and 1 x Gabapentin before diner.

Area of improvement:

Pain & mobility – Millie's arthritis seems to be pretty stable this month. At times Millie needs a little push to get up, but once she is up, she is walking quite well. Millie not able to squat down as low as she used to, to take a pee. Also, some shaking in hind legs when she has a poo and hind legs give out intermittently when walking. Millie eats all her meals in the laying down position. However, Millie doesn't display any signs of physical pain when her legs give out.

Horner's – we believe that the Ellevet has helped with Millie's Horner's syndrome. We found at the start of the year – that on the days Millie did not consume the Ellevet, the Horner's was far more prominent throughout the day. Millie has taken her Ellevet every day in November so we have only witnessed the odd 'flash' of Horner's, usually after Millie has been resting and also around meal / Ellevet time.

Demeanour – on the whole Millie has been a happy girl this November, we noticed a big improvement in Millie demeanour since Millie has been taking the Ellevet every day. We administer the Ellevet in a capsules as she refused to eat the Ellevet in her food. Millie has been in good spirits and at times she has been quite wilful. Weather permitting – Millie has enjoyed spending time in garden sat up and aware of surroundings. Millie has still been enthusiastic about going out for 7.00am & her mid-morning walk. Back in February we noticed that, on the days Millie refused to eat her food containing the Ellevet, she was noticeably more subdued all day and less enthusiastic to go out for any of her walks.

Comments:

Glucose – since starting the trials a year ago there has been a reduction in insulin required from: 15 units AM and & 19 units PM to – 14 1/2 units AM & 17 units PM. Since changing Millie's wet food back to either Hills WD or, Royal Canin Diabetic food, she has been eating well however, Millie's insulin dosage is still less than when we started the trials, so we can't completely rule out that the Ellevet may have slightly reduced Millie's daily insulin requirement.

IBD/Colitis – The Ellevet definitely helps with Millie's IBD/Colitis. Back in February we found that when Millie did not consume the Ellevet her poo's were a little looser. We have also found the Ellevet has helped with Millie's travel sickness, we used to have to give Mills an Omeprazole before all car journeys taking over 10-15 mins long, we have not had cause to do this anymore which is excellent.

Appetite – Food has always been a bit of a challenge however, since Mills has been taking the Ellevet every day there has been a drastic improvement to Millie's appetite. Currently Mills has free range chicken, north east Atlantic cod, broccoli, mix of Hills ID, WD and Royal Canin diabetic biscuits and (either) Royal Canin diabetic wet, Hills ID low fat chicken stew or, Hills WD low fat wet. We got to the point where Millie refused to consume any food containing the Ellevet, this issue has now been resolved by transferring the Ellevet to a capsule which we are then able to pop down Millie's throat, we administer the capsules immediately before each meal.

Exercise – Millie's arthritis has been stable this month. Mills still goes on a short walk to the top of the road at 7.00am and at 4.30pm. Millie is still happy to walk down to Hillsborough at 10.00am, we then bring her back up the hill in the car. Back legs give out intermittently, Millie sitting with back left leg straight out. Millie no longer sitting down when we walk her down to Hillsborough. Millie does not show any physical signs of pain. Millie can be a bit restless after last car journey to Barnstaple which takes around 50 mins, I have added some nice soft padding to rear of car, which appears to be helping.

Gastroenteritis/Motion Sickness:

- Owner would administer omeprazole 20mg prior to car journeys to the Hospital
- Maropitant administration had little benefit
- Often visits would result in a few days of anorexia and colitis diarrhea
- Ultimately opted for long term administration of metronidazole as an adjunctive therapy to control marked GI signs. This controlled more severe signs of GI disease.
- However, it is strongly believed that her GI signs are managed ongoing utilizing the benefits of administration of ElleVet

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‘Josh’ – 11.5 yr, 41.4kg

- MN GSD - bilateral cruciate surgery and subsequent stifle OA; due to increased weight bearing forelimbs additional elbow and carpal OA.
  - Meds: Meloxicam, gabapentin, chondroitin/glucosamine and ASU (Dasuquin, Protexin)
  - Fortnightly electro-acupuncture
  - Periodic lidocaine CRI
  - ElleVance 25 drops Q12
  - Positive response – see video testimonial

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Pusherman?

On Tue, Mar 7, 2023 at 11:09 AM Thomas Joseph Divers <tjd8@cornell.edu> wrote:
Hi Joe Stella is on the soft chews. She was really paretic and horribly lame (RF and LR) and looked like she was miserable the end of last week. We started the ElleVet Friday afternoon and it may be chance but within 36 hours she was less lame and noticeably happier. We will be happy to give a couple of updates as we evaluate the 15 day treatment(62 soft chews) Best wishes Tom

Wed, Mar 29, 9:28 AM
Hi Joe, Stella is doing pretty well, definitely improved from 1 month ago. We have ordered more Ellevet but it will not arrive until Friday and I only have 1 more treat left. Would you have a one or two treats in your office to spare so I can keep Stella on the BID schedule? thanks, Tom

Hey Manuel
Know we chatted in the hall about how your pup was doing on the Ellevet being more mobile and happier. We are a few weeks out now - still the same response??

Hi Joe. She's doing very well. She went from barely wanting to walk and looking all hunched and uncomfortable to walking around and looking like our normal (but still quite old) dog. Her appetite is better too. We're doing once a day and I've ordered for delivery every 8 weeks
Thanks
manuel

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Questions or comments?

Dr Joe Wakshlag

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