

The Highs and Lows of CBD Research

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SVHP Annual Conference
June 5, 2023

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SVHP Lecture Objectives

- Pharmacists
 - Understand PK profile
 - Recall common AEs
 - Review current literature
- Technicians
 - Recall common AEs
 - Understand reported dosing protocols
 - Recall reported diseases treated by CBD in the literature

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Disclosure Statement

- Dr. McGrath serves on the scientific advisory board for Panacea Life Sciences

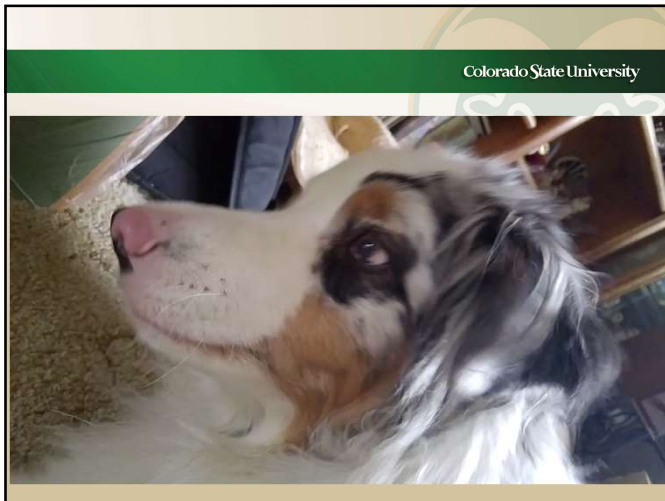
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Outline and Objectives

- Background
- Pharmacokinetic and tolerability studies
- Clinical trials
- Future directives

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Epilepsy

- **MOST** common neurological condition in dogs
- Many dogs ***continue to have seizures*** after being treated
- Dogs ***euthanized*** because of medication side effects
- We **NEED** something better!

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How many of you have been asked about CBD or cannabis by pet owners?

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Cannabis

- ✓ Spasticity
- ✓ Central pain
- ✓ Lower urinary tract symptoms
- ✓ Multiple sclerosis
- ✓ Sleep disturbances
- ✓ Peripheral neuropathic pain
- ✓ Brachial plexus avulsion
- ✓ Nausea secondary to chemotherapy
- ✓ Dystonia
- ✓ Loss of appetite
- ✓ Rheumatoid arthritis
- ✓ Intractable cancer pain
- ✓ Spinal cord injuries
- ✓ Tourette's syndrome
- ✓ Psychoses
- ✓ Epilepsy
- ✓ Glaucoma
- ✓ Parkinson disease

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Raise your hand if you have felt uncomfortable or ill-prepared to discuss CBD with pet owners?

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Legal issues

- 2018 Farm Bill
 - Hemp removed from the list of controlled substances (previously ok for research purposes in Colorado - 2014 Farm Bill)
 - Allows states to regulate production
 - Descheduled but not legal for therapeutic use
- Made it easier for research purposes but not for veterinary use

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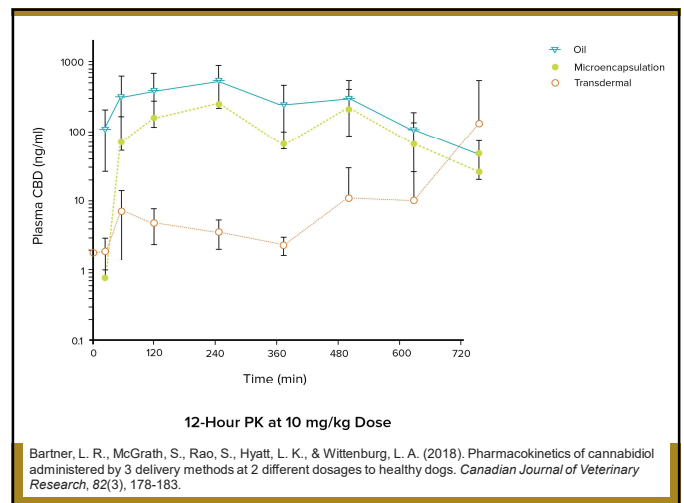
PK Study

Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs

Lisa R. Bartner, Stephanie McGrath, Sangeeta Rao, Linda K. Hyatt, Luke A. Wittenburg
The Canadian Journal of Veterinary Research 2018;82:178-183

- 30 dogs
- 3 formulations
 - Capsules
 - Oil
 - Transdermal cream
- 2 doses
 - 5 mg/kg or 10 mg/kg for PK

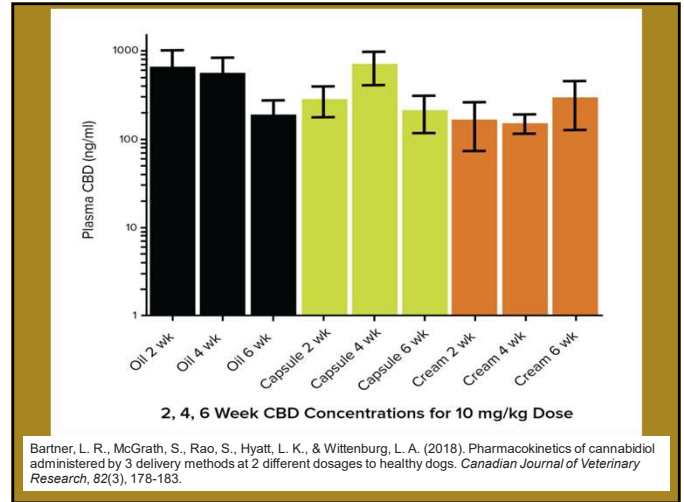
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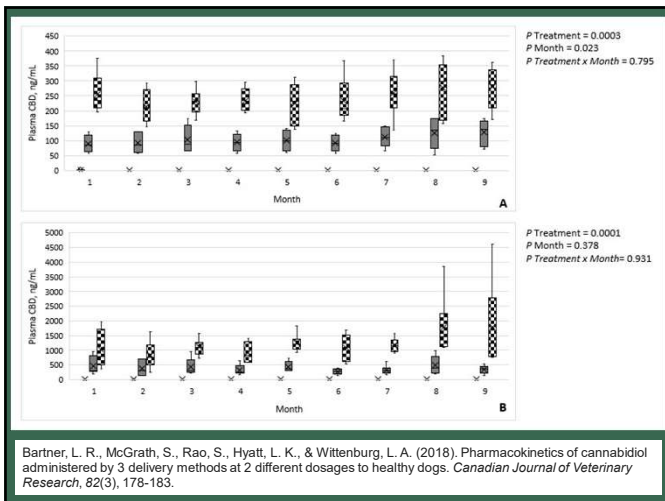
Parameter	Units	5 mg/kg			10 mg/kg		
		Oil	Capsules	Transdermal Cream	Oil	Capsules	Transdermal Cream
C _{max}	ng/mL	625.3	346.3	74.3	845.5	578.1	277.6
AUC	min*µg/mL	135.6	98.0	11.7	297.6	162.8	29.7
T _{1/2}	min	199.7	95.4	ND	127.5	115.9	ND

Bartner, L. R., McGrath, S., Rao, S., Hyatt, L. K., & Wittenburg, L. A. (2018). Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Canadian Journal of Veterinary Research*, 82(3), 178-183.

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- 11 more published PK/PD studies
- Half-life = 2-4 hours
- Substantial interindividual variability
- Fed vs fasted
 - Higher bioavailability in fed patients in human studies
 - Higher C_{max} in fed animals
- CBD accumulates over time

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Which following statement is true about CBD in dogs?

- The transdermal form of CBD offers the highest Cmax in dogs.
- Half life of CBD in dogs is approximately 2-4 hours.**
- CBD is not absorbed when given orally.

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Drug interactions

- No changes in Pb or KBr with CBD treatment (McGrath et al., 2019)
- No PK interaction between CBD and Pb (Doran et al., 2022)

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Clinical Adverse Effects

- Diarrhea
 - Reported as a side effect in 6-19% of human patients
- Hypersalivation
- Vomiting
- Inappetence
- Ataxia
- Lethargy

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Laboratory Adverse Effects

- ALP Elevation
 - Appears dose dependent
 - Bile acid tests remain normal
- ALT Elevation
 - Not previously reported

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Which of the following adverse events of CBD have been observed in dogs?

- Seizures, vomiting, lethargy
- Kidney failure, vomiting, KCS
- Elevated liver enzymes, diarrhea, ataxia**

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Conclusions of PK/PD Studies

- What we know:
 - CBD is reasonably **well-tolerated** short term
 - CBD is **measurable** in the plasma
- What we don't know:
 - Correct dose
 - Adequate plasma concentrations
 - Effectiveness
- Next step → **Clinical trials...**

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Outline and Objectives

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- Potassium Bromide ✓
- Phenobarbital ✓
- Zonisamide ✓
- Keppra ✓

Animal Information
Name: Teosony Sex: Age: 4 Years

Diagnosis
HISTORY: Epilepsy; multiple cluster episodes. Please see complete history in record.
FINAL DIAGNOSES:
...brain is unremarkable, consistent with most cases of idiopathic epilepsy...

Photo Credit: Stephanie McGrath

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Epilepsy Pilot Study

Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy

Stephanie McGrath DVM, MS
Lisa R. Bartner DVM, MS
Sangeeta Rao BVSc, PhD
Rebecca A. Packer DVM, MS
Daniel L. Gustafson PhD

JAVMA | JUN 1, 2019 | VOL 254 | NO. 11

Aim: To assess the short-term effect of CBD on seizure frequency in poorly controlled epileptic, client-owned dogs

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MOA

- Lower intracellular calcium
 - Antagonist of GPR55
 - Agonist of TRPV1
- Inhibition of adenosine reuptake
- Unknown

McGrath, S., Bartner, L. R., Rao, S., Packer, R. A., & Gustafson, D. L. (2019). Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *Journal of the American Veterinary Medical Association*, 254(11), 1301-1308.

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Group	Timepoint	Median	Median % Change	Dogs w/ seizure reduction
CBD	Pre-study	4.0	33%	89%
	During study	2.7		
Control	Pre-study	2.0	0%	43%
	During study	2.0		

McGrath, S., Bartner, L. R., Rao, S., Packer, R. A., & Gustafson, D. L. (2019). Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *Journal of the American Veterinary Medical Association*, 254(11), 1301-1308.

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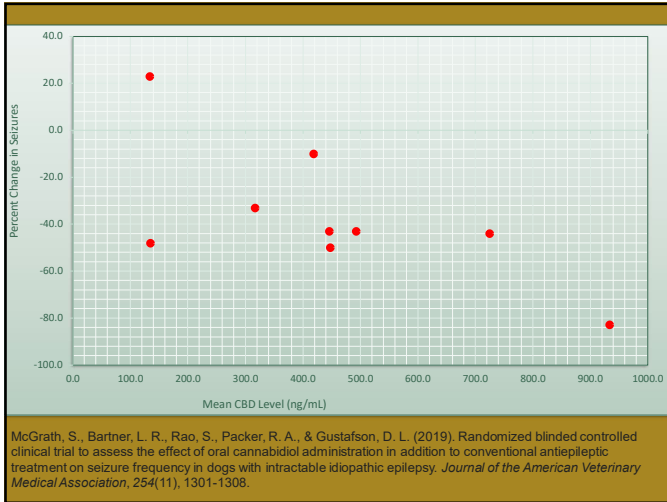
ALP Elevation

- Significant elevation in ALP (liver enzyme) in the treatment group
 - 8/9 dogs
 - Mean = 473.2 IU/L (15 – 140 IU/L)

McGrath, S., Bartner, L. R., Rao, S., Packer, R. A., & Gustafson, D. L. (2019). Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *Journal of the American Veterinary Medical Association*, 254(11), 1301-1308.

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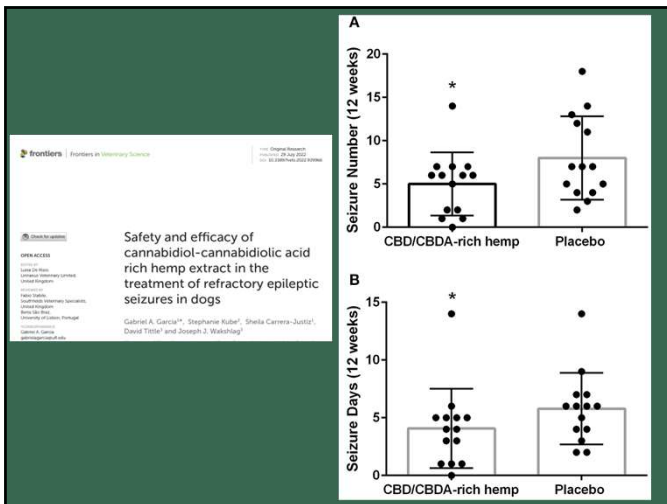
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Conclusions of Pilot Study

- **Significant reduction in seizure activity** in dogs receiving CBD
- Number of responders not significant
- No clinically relevant adverse effects
- Need to monitor bile acids and liver enzymes
- More studies necessary

McGrath, S., Bartner, L. R., Rao, S., Packer, R. A., & Gustafson, D. L. (2019). Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *Journal of the American Veterinary Medical Association*, 254(11), 1301-1308.

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Recent Epilepsy Clinical Trial

- Prospective, double-blinded, placebo-controlled, **crossover** study
- **60** client-owned dogs with intractable epilepsy
- Treated with conventional antiseizure drugs

Garcia, G. A., Kube, S., Carrera-Justiz, S., Tittle, D., & Wakshlag, J. J. (2022). Safety and efficacy of cannabidiol-cannabidiolic acid rich hemp extract in the treatment of refractory epileptic seizures in dogs. *Frontiers in veterinary science*, 1098.

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Epilepsy Clinical Trial

- Dose increased to 4.5 mg/kg CBD PO every 12 hours based on results of pilot study and FDA drug

FDA NEWS RELEASE

FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy

f share | tweet | linkedin | email | print

For Immediate Release: June 26, 2018

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Epilepsy Clinical Trial

Group	Median	Q1	Q3	Min	Max
Placebo	~0	~-50	~50	~-100	~800
CBD	~-20	~-40	~10	~-100	~500

Group	Median	Q1	Q3	Min	Max
Placebo	~0	~-50	~50	~-100	~400
CBD	~-10	~-20	~10	~-100	~300

Garcia, G. A., Kube, S., Carrera-Justiz, S., Tittle, D., & Wakshlag, J. J. (2022). Safety and efficacy of cannabidiol-cannabidiolic acid rich hemp extract in the treatment of refractory epileptic seizures in dogs. *Frontiers in veterinary science*, 1098.

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Dose Finding Epilepsy Study

Garcia, G. A., Kube, S., Carrera-Justiz, S., Tittle, D., & Wakshlag, J. J. (2022). Safety and efficacy of cannabidiol-cannabidiolic acid rich hemp extract in the treatment of refractory epileptic seizures in dogs. *Frontiers in veterinary science*, 1098.

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Osteoarthritis Studies

> J Am Anim Hosp Assoc, 2021 Mar 1;57(2):81-90. doi: 10.5326/JAAHA-MS-7119.

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


Sebastian Mejia, Felix Michael Duerr, Gregg Griffenhagen, Stephanie McGrath

- Objective gait analysis
 - One parameter (%BWD) showed improvement at certain time points within CBD group
- Client outcome assessment
 - Improvement at certain time points during CBD treatment
- Accelerometry
 - No significant differences noted

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- Gamble, et al., *Frontiers* (2018)
 - CBPI = outcome
 - Significant improvement
- Verrico, et al., *Pain* (2020)
 - Helsinki Pain Index = outcome
 - Significant improvement
- Brioschi, et al., *Animals* (2020)
 - CBPI = outcome
 - Significant improvement




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Anxiety

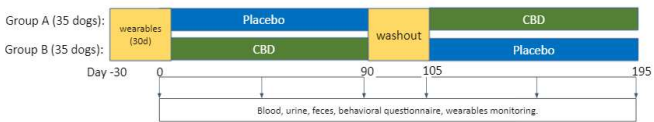
- Shelter dogs (Corsetti, et al., 2021)
 - Reduction in aggression
 - No improvement in other stress related behaviors
- Noise-induced fear (Morris, et al., 2020)
 - No improvement



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- Current study – CSU, unpublished




Group A (35 dogs): wearables (30s) | Placebo | washout | CBD

Group B (35 dogs): CBD | washout | Placebo

Day -30 0 90 105 195

Blood, urine, feces, behavioral questionnaire, wearables monitoring.




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Atopic Dermatitis

- Loewinger, et al., 2022
 - Canine Atopic Dermatitis Scoring Index (veterinarian) & Vertical Analog Pruritus assessments (owner)
 - Cytokine measurement
 - CBD/CBDA – significant reduction in pruritus **per owners**



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- Morris, et al., 2021
 - Healthy dogs with accelerometers
 - Alteration in “itching” behaviors

Morris, E. M., Kitts-Morgan, S. E., Spangler, D. M., Gebert, J., Vanzant, E. S., McLeod, K. R., & Harmon, D. L. (2021). Feeding cannabidiol (CBD)-containing treats did not affect canine daily voluntary activity. *Frontiers in Veterinary Science*, 8, 645667.

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Cognitive Dysfunction

- Antiinflammatory
- Antioxidant
- Reduction in misfolded protein production

Morris, E. M., Kitts-Morgan, S. E., Spangler, D. M., Gebert, J., Vanzant, E. S., McLeod, K. R., & Harmon, D. L. (2021). Feeding cannabidiol (CBD)-containing treats did not affect canine daily voluntary activity. *Frontiers in Veterinary Science*, 8, 645667.

Group	GFP+ transgenic cell number
Ctrl	~100
Aβ 10 μg ml ⁻¹	~400
Aβ 10 μg ml ⁻¹ + CBD 2.5 mg kg ⁻¹	~250
Aβ 10 μg ml ⁻¹ + CBD 10 mg kg ⁻¹	~150

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Which of the following diseases has *not* yet been studied in veterinary medicine?

- Osteosarcoma
- Epilepsy
- Anxiety
- Osteoarthritis

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Recent Review Papers


- Ukai M, McGrath S, Wakshlag J. The clinical use of cannabidiol and cannabidiolic acid-rich hemp in veterinary medicine and lessons from human medicine, *Journal of the American Veterinary Medical Association* 2023;261(5):623-631.
- Corsato Alvarenga I, Panicker KS, Hess H, McGrath S. Scientific validation of cannabidiol for management of dog and cat diseases. *Annu Rev Anim Biosci*. 2023;11:227-46. doi: 10.1146/annurev-animal-081122-0-70236.
- Potschka H, Bhatti S F M, Tipold A, McGrath S. Cannabidiol in canine epilepsy. *Vet J*. 2022 Dec;290:105913. doi: 10.1016/j.tvjl.2022.105913.
- Yu C, Rupasinghe V. Cannabidiol-based natural health products for companion animals: Recent advances in the management of anxiety, pain, and inflammation. *Research in Veterinary Science* 2021;140:38-46.

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Outline and Objectives

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- Clinical trials
- Future directives



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Future Directives

- Identify effective doses
- Disease-specific efficacy
 - Epilepsy, mobility, dementia, anxiety, cancer, appetite, others
- Drug-drug interaction
- Long-term safety



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Thank you!

- CSU Neurology Clinical Trials team
- Pharmacology Shared Resource Laboratory at CSU
- Moreno Lab



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