CBD for veterinary professionals

"But There's No Research"

Misc.

- R C Coelho MP, de O P Leme F, A Moreira F, E M T Branco S, M Melo M, G de Melo E. Current review of hemp-based medicines in dogs. J Vet Pharmacol Ther. 2021;44(6):870-882. doi:10.1111/jvp.13016

Outline

- Case Series
- Evidence based medicine
- Evidence for/against cannabidiol
- Arthritis
- Seizures
- Atopy
- Anxiety
- Cognitive dysfunction
- Cancer

Case study #1:

- 8yo MN Dachshund “Charlie”
- O calls, frantic that he suddenly can’t walk
- UTD vaccines
- Grade 3 perio dz
- Hx of arthritis, on fish oil and a “hemp treat” from the pet store
- PE and diagnostics support medical management for IVDD
- Rx – Steroid or NSAID, gabapentin, methocarbamol

Case Study #2

- 3 yo FS DSH
- Adopted from shelter as a kitten
- Lysine to treat recurrent viral URI

Case study #3:

- 14 yo FS obese lab
- You're seeing her the day after an ER visit for sudden collapse -> splenic mass/hemo abdomen, O elected palliative care
- Hx end-stage arthritis
- Chronic meds – Carprofen, gabapentin, amantadine, and Tylenol3
- Added last night – Yunnan baiyao

Evidence based medicine

As you move up the pyramid:

- Stronger methodology
- Less Bias
- Controls for comparison
- Fewer studies

PubMed: (Cannabidiol) AND (Dog)

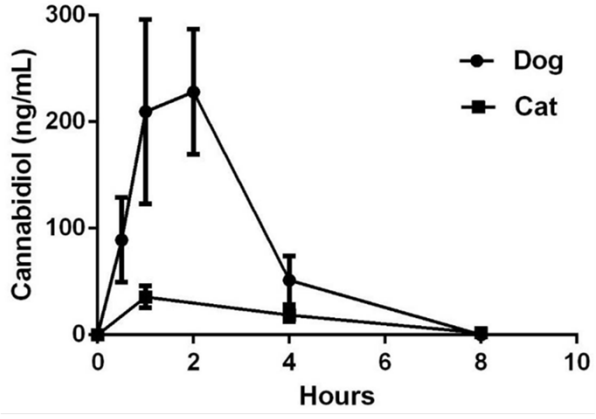
- 53 papers, >11/year for the past 3 years
- Pharmacokinetics: 11
- RCTs: 11
- Other (toxicology/safety, in vitro): 8
- Reviews: 6
- Textbook: 1

Buyer Beware

- Wakshlag JJ, Cital S, Eaton SJ, Prussin R, Hudalla C. Cannabinoid, Terpene, and Heavy Metal Analysis of 29 Over-the-Counter Commercial Veterinary Hemp Supplements. Vet Med (Auckl). 2020;11:45-55. Published 2020 Apr 15. doi:10.2147/VMRR.S248712

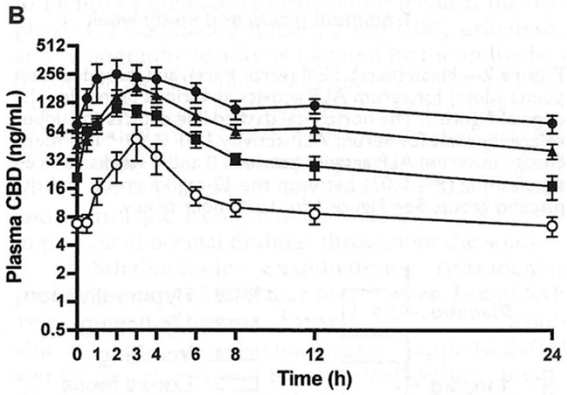
Pharmacokinetics of oral CBD in dogs and cats

- Deabold KA, Schwark WS, Wolf L, Wakshlag JJ. Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats. Animals (Basel). 2019;9(10):832. Published 2019 Oct 19. doi:10.3390/ani9100832
- Chews have good absorption, maybe faster than oil
  - Coadministration with food recommended
- Cats are not small dogs



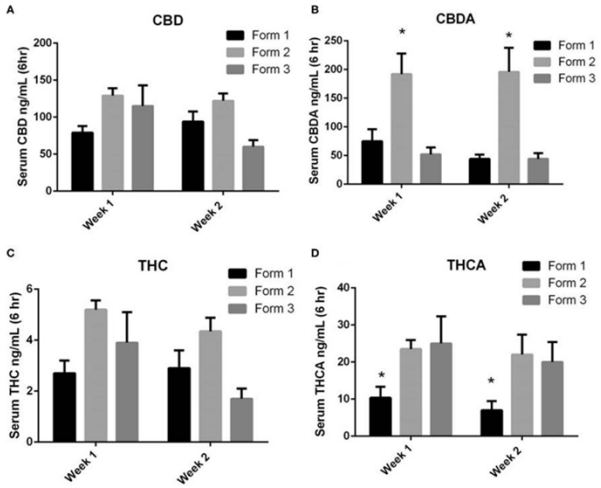
Safety and Steady State Study

- Vaughn DM, Paulionis LJ, Kulpa JE. Randomized, placebo-controlled, 28-day safety and pharmacokinetics evaluation of repeated oral cannabidiol administration in healthy dogs. Am J Vet Res. 2021;82(5):405-416. doi:10.2460/ajvr.82.5.405
- SID Dosing → Steady State in 2 Weeks
- No changes in IOP or tear production
- CBD isolate in MCT oil
- Adverse events typically GI related and increase with dose



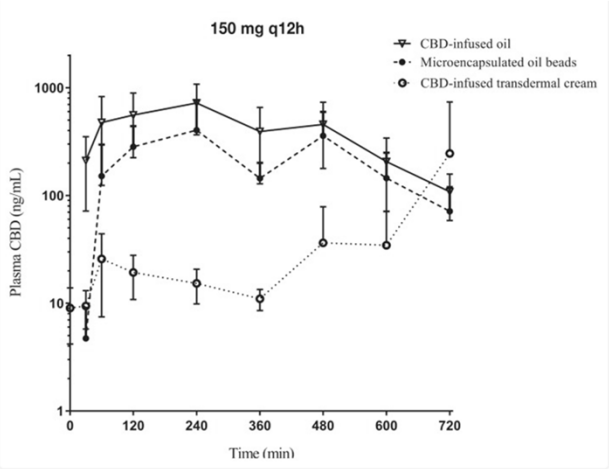
Pharmacokinetics of CBD, THC, and Metabolites

- Wakshlag JJ, Schwark WS, Deabold KA, et al. Pharmacokinetics of Cannabidiol, Cannabidiolic Acid, Δ9-Tetrahydrocannabinol, Tetrahydrocannabinolic Acid and Related Metabolites in Canine Serum After Dosing With Three Oral Forms of Hemp Extract. Front Vet Sci. 2020;7:505. Published 2020 Sep 4. doi:10.3389/fvets.2020.00505
- Carrier oils affect absorption
- Give with a meal
- Dogs produce different metabolic products
  - Don't really produce high levels of the metabolites detected in human marijuana urine tests
- No liver enzyme elevations



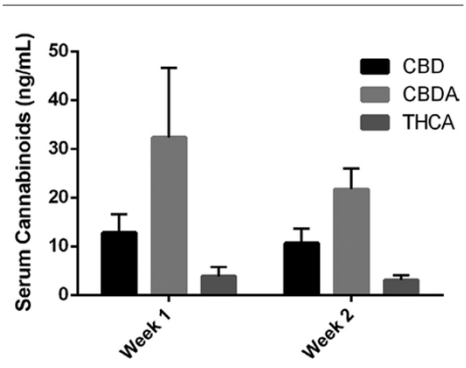
Pharmacokinetics of CBD – oral vs transdermal

- Bartner LR, McGrath S, Rao S, Hyatt LK, Wittenburg LA. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can J Vet Res. 2018;82(3):178-183.
- Transdermal poor absorption
- Oil may be better than oral capsules, but pretty equivocal



Pharmacokinetics of Transdermal: 2020 Update

- Hannon MB, Deabold KA, Talsma BN, et al. Serum cannabidiol, tetrahydrocannabinol (THC), and their native acid derivatives after transdermal application of a low-THC Cannabis sativa extract in beagles. J Vet Pharmacol Ther. 2020;43(5):508-511. doi:10.1111/jvp.12896
- 2x the dose → <1/10 serum levels vs oral CBD (probably need 40 mg/kg TD vs 2 mg/kg PO)
- Acid forms of the cannabinoids absorbed better



Drug Interaction Study

- Doran CE, McGrath S, Bartner LR, Thomas B, Cribb AE, Gustafson DL. Drug-drug interaction between cannabidiol and phenobarbital in healthy dogs. Am J Vet Res. 2021;83(1):86-94. Published 2021 Nov 1. doi:10.2460 /ajvr.21.08.0120
- No significant changes in blood levels for either CBD or Phenobarb when given together vs alone
- No need to adjust doses

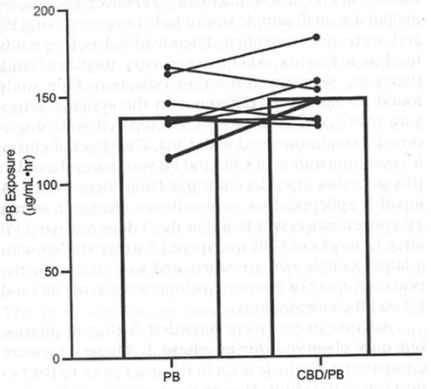


Figure 5—Before-after graph of PB AUC_{0-t} for all 9 dogs in both single oral 4mg/kg PB administration and 4mg/kg PB with concurrent 10 mg/kg CBD oral administration. The bar height represents mean AUC_{0-t} and individual dog AUC_{0-t} is represented by a dot, which is connected to the same dogs AUC_{0-t} in the other treatment group from phase 2.

Safety Study – Immune Suppression?

- Morris EM, Kitts-Morgan SE, Spangler DM, McLeod KR, Suckow MA, Harmon DL. Feeding treats containing cannabidiol (CBD) did not alter canine immune response to immunization with a novel antigen. Res Vet Sci. 2022;143:13-19. doi:10.1016/j.rvsc.2021.12.012
- 32 shelter dogs fed 5 mg/kg/day
- No difference vs control in immune response to an injected novel antigen

Safety Study and Arthritis Efficacy

- Gamble LJ, Boesch JM, Frye CW, et al. Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs. Front Vet Sci. 2018;5:165. Published 2018 Jul 23. doi:10.3389/fvets.2018.00165

	CBD oil			Placebo oil		
	Week 0	Week 2	Week 4	Week 0	Week 2	Week 4
CBPI Pain (0–40)	21 ± 8	14 ± 6*	14 ± 8*	17 ± 7	19 ± 9	19 ± 9
CBPI activity interference (0–60)	35 ± 15	25 ± 15*	26 ± 14*	27 ± 15	29 ± 15	31 ± 16
Hudson (0–110)	54 ± 13	67 ± 15*	67 ± 10*	65 ± 14	64 ± 16	60 ± 19
Veterinary lameness§	3 (1–4)	3 (1–4)	3 (1–4)	3 (2–4)	3 (2–4)	3 (1–4)
Veterinary pain ∫	3 (3–4)	3 (2–4)*	3 (1–4)*	3 (2–4)**	3 (2–4)	3 (2–4)**
Veterinary weight-bearing =	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)

*Represents significant difference ($p < 0.05$) from baseline week 0 of CBD treatment. **Represents significant differences ($p < 0.05$) from week 2 of CBD oil treatment. §Lameness was scored as follows: 1 = no lameness observed/walks normally, 2 = slightly lame when walking, 3 = moderately lame when walking, 4 = severely lame when walking, 5 = reluctant to rise and will not walk more than 5 paces. ∫Pain on palpation was scored as follows: 1 = none, 2 = mild signs, dog turns head in recognition, 3 = moderate signs, dog pulls limb away, 4= severe signs, dog vocalizes or becomes aggressive, 5 = dog will not allow palpation. =Weight-bearing was scored as follows: 1 = equal on all limbs standing and walking, 2 = normal standing, favors affected limb when walking, 3 = partial weight-bearing standing and walking, 4 = partial weight-bearing standing, non-weight-bearing walking, 5 = non-weight-bearing standing and walking.

Arthritis

- Verrico CD, Wesson S, Konduri V, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. Pain. 2020;161(9):2191-2202. doi:10.1097/j.pain.0000000000001896
- 20 client owned dogs at private practice
- CBD isolate at 0.5 mg/kg (naked or liposomal) or 1.2 mg/kg (naked)
  - Higher dose and liposomal (improved absorption) groups had better improvement
- Owner and DVM assessment
- Authors = MDs, study included mice and in vitro models of inflammation

Arthritis

- Brioschi FA, Di Cesare F, Gioeni D, et al. 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. Animals (Basel). 2020;10(9):1505. Published 2020 Aug 26. doi:10.3390/ani10091505
- "Oral transmucosal" CBD isolate in MCT oil, 2mg/kg BID
  - No placebo control to blind, but owners were unaware of the other group so didn't know what treatment was being tested
  - Both groups received anti-inflammatory (NSAID or steroid), gabapentin, amitriptyline
- Owner assessment
  - Both groups experienced improved pain control and QOL, but CBD group had statistically significant improvement

Seizures

- McGrath S, Bartner LR, Rao S, Packer RA, Gustafson DL. 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. J Am Vet Med Assoc. 2019;254(11):1301-1308. doi:10.2460/javma.254.11.1301
- 8/9 dogs in CBD group had >50% reduction in seizure frequency
- 3/7 dogs in placebo group had >50% reduction
  - Treatment groups were not comparable with respect to baseline seizure frequency
- Small study size, retention bias (10% met initial inclusion criteria, of those 35% did not complete study)
- Treatment nonresponsive epilepsy so not typical as seen in GP

Activity and Pruritus

- Morris EM, Kitts-Morgan SE, Spangler DM, et al. Feeding Cannabidiol (CBD)-Containing Treats Did Not Affect Canine Daily Voluntary Activity. Front Vet Sci. 2021;8:645667. Published 2021 Apr 29. doi:10.3389/fvets.2021.645667
- 30 shelter dogs in vet school housing, 1.25 and 2.5 mg/kg BID dosing
- Decreased scratching activity but no decrease in overall activity, no evidence of sedative effects

Noise Phobia

- Morris EM, Kitts-Morgan SE, Spangler DM, McLeod KR, Costa JHC, Harmon DL. The Impact of Feeding Cannabidiol (CBD) Containing Treats on Canine Response to a Noise-Induced Fear Response Test. Front Vet Sci. 2020;7:569565. Published 2020 Sep 22. doi:10.3389/fvets.2020.569565
- 16 shelter dogs in vet school housing
- 0.7 mg/kg BID CBD treats vs 5-10 mg/kg Trazodone vs CBD + Trazodone
- No change in cortisol levels from baseline after exposure to fireworks soundtrack
- Trazodone kept cortisol lowest

Aggressive Behavior

- Corsetti S, Borruso S, Malandrucco L, et al. Cannabis sativa L. may reduce aggressive behaviour towards humans in shelter dogs [published correction appears in Sci Rep. 2021 Dec 9;11(1):24029]. Sci Rep. 2021;11(1):2773. Published 2021 Feb 2. doi:10.1038/s41598-021-82439-2
- 24 shelter dogs in an Italian shelter
- 1.25 mg/kg CBD in olive oil
- Decrease in aggression but not statistically significant

Cancer

- Inkol JM, Hocker SE, Mutsaers AJ. Combination therapy with cannabidiol and chemotherapeutics in canine urothelial carcinoma cells. PLoS One. 2021;16(8):e0255591. Published 2021 Aug 5. doi:10.1371/journal.pone.0255591
- Henry JG, Shoemaker G, Prieto JM, Hannon MB, Wakshlag JJ. The effect of cannabidiol on canine neoplastic cell proliferation and mitogen-activated protein kinase activation during autophagy and apoptosis. Vet Comp Oncol. 2021;19(2):253-265. doi:10.1111/vco.12669
- In vitro cancer cell death with CBD alone
  - Synergistic potentiation of apoptosis in combo with mitoxantrone and vinblastine but not carboplatin

Things to Consider When Evaluating CBD Studies

- Potentially significant variability between CBD formulations and administration methods
  - Carrier oils, chew form, with or without food
  - Chemical composition
    - Minor cannabinoids, terpenes, etc.
  - Dose of CBD
  - BID vs SID
- Small study sizes
  - Usually blinded and placebo controlled, sometimes crossover-controlled
  - ~20-30 study subjects
- Limitations with subjective measurements

Need for more research

- CBD Vet Products is awaiting pharmacokinetic results on SimpliSolve Transmucosal absorption