Critical appraisal – Randomised controlled trial questions

Gamble LJ, Boesch JM, Frye CW, Schwark WS, Mann S, Wolfe L, Brown H, Berthelsen ES, Wakshlag JJ (2018). Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs. *Front Vet Sci.* 5:165.

Introduction	
Are the aims clearly stated?	Yes - to determine basic oral pharmacokinetics, and assess safety and analgesic efficacy versus placebo of a cannabidiol (CBD) based oil in dogs with osteoarthritis (OA).
Methods	
Is the study design suitable for the aims?	Yes – randomised controlled trial (RCT) crossover design
Which population was studied?	Client owned dogs with radiographic changes and clinical signs (pain and lameness) associated with OA. Dogs could already be receiving non-steroidal anti-inflammatory drugs (NSAIDs), fish oil or glucosamine as standard care.
Were the treatments randomly allocated? If yes, how was the randomisation done?	Yes iPhone randomiser app
Were the groups comparable prior to intervention?	Not reported, though it was a crossover trial. Sequence of treatments data appears to be missing from Table 2.
Was the person who administered the interventions blinded?	Yes
Is it clear what measurements were carried out in the study?	Yes

Were the correct measurements chosen?	Yes
Do they reflect (or are they strongly related to) the outcome of interest?	Yes
Were previously established validated methods used to make the measurements? (e.g. Glasgow pain score, International Units etc)	Yes, canine brief pain inventory (CBPI) is well validated, Hudson is commonly used; both assess pain. Their veterinary scoring system has previously been described, but not clear whether it has been validated.
What outcomes were measured?	Owner assessed pain via CPBI Owner assessed activity via CPBI and Hudson Vet assessment of pain, lameness, weight-bearing Blood biochemistry and complete blood count (CBC)
Are the outcomes clinically relevant?	Yes
Were the outcomes assessed blind?	Yes However, it wasn't stated whether the vets were blinded to if the animal was on NSAIDs
Are the statistical methods described?	Yes
Was the statistical significance level stated?	Yes
Was the sample size justified?	Yes Power calculation: power 0.8, alpha 0.05, change in score 15 points, standard deviation 20, n = 14
Was ethical approval obtained?	Yes, from Cornell University

Are the methods described in enough detail that you could repeat them?	Yes Veterinary assessment method is not described in the paper, but is included in legend of Table 3
Results	
Were the basic data adequately described?	Yes Some characteristics of subjects listed in Table 2. Groups aren't compared but is cross-over design. Dogs on NSAIDs are identified, but no reporting whether any dogs were on fish oil or glucosamine/chondroitin sulfate More detail is needed to in order to adequately appraise results from mixed modelling.
Do the numbers add up? Are all subjects accounted for?	Yes Yes - 6 excluded - 1 at time of enrollment,4 due to medical illness, 1 due to behaviour
Was the statistical significance (p value) stated in the results? Is this consistent with the methods? (It should be stated in the sample size or power calculation)	Yes Yes
Were any side effects of the intervention reported if applicable?	Not stated whether the 5 exclusions after start of study were thought to be as a result of treatment or concurrent disease. Report 'no observed side effects at 2mg/kg and 8 mg/kg dose' (8 mg/kg dose was used in a pharmacokinetic study reported in the same paper, 2 mg/kg dose was used in the clinical trial of dogs with OA)

What were the main findings/key results?	Owners reported decreased pain and increased activity with CBD oil compared at 2 and 4 weeks post treatment compared to before treatment (baseline). No significant changes were reported by owners when animal was on placebo

Overall, vets reported decreased pain on palpation with CBD oil at weeks 2 and 4 post treatment compared to baseline. Week 2 CBD oil pain assessment was lower than placebo at baseline and placebo at week 4.

No changes were detectable with vet lameness and vet weight-bearing scores in both CBD oil and placebo groups at any of the measured times. Vet pain scores decreased from baseline in dogs on NSAIDs. Lameness assessed by vets increased from baseline with age of animal and if on NSAIDs, the lameness scores decreased from baseline. |
| **Discussion and conclusion** | |
| What do the main findings/key results mean? | In this small, short trial owners appear to detect a decrease in pain related behaviours and an increase in activity in dogs receiving 2mg/kg twice daily of a specific CBD preparation.

Vets appear to detect a decrease in pain on palpation but the scoring system is crude and not validated so it is difficult to understand the meaning of this result. Vets didn't detect changes when assessing animals by lameness and weight-bearing scores. Whether the animal was on NSAIDs or not seems to influence vet scoring of pain and lameness. It is unclear whether the vets were blinded to whether |

	an animal was on NSAIDs or not.
Are the negative findings discussed? How are the negative findings interpreted?	Reasons for minimal change in veterinarian assessments not discussed in much detail. The authors suggest using dogs with single joint disease may make interpretation of veterinary tests easier.
Does the discussion reflect the results?	Yes
Interpretation	
What are the clinical implications of this study? Are the subjects in the study similar to those in the BET/your own?	The CBD trial only lasted four weeks but does suggest some owner reported efficacy in clinically relevant outcomes that were not seen in the placebo group. Ideally this should be repeated in a larger patient population before clear conclusions are drawn. Commercially available CBD preparations may contain different active ingredients, or different quantities of those ingredients so efficacy should not be extrapolated to other products. Heterogenous concurrent medications, OA locations and OA severities make clear extrapolation to other patient groups challenging, but the patient population are likely to reflect those seen in practice.
General	
Who funded this study?	Ellevet LLC who manufacture CBD products for pets