Critical appraisal – Randomised controlled trial questions

McGrath S, Bartner LR, Rao S, Packer RA, Gustafson DL (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. *J Am Vet Med Assoc.* 254(11):1301-1308.

Introduction	
Are the aims clearly stated?	Yes - to assess the short-term effect of addition of cannabidiol (CBD) to standard anti-epileptic drug (AED) treatment on seizure frequency in dogs with intractable idiopathic epilepsy.
Methods	
Is the study design suitable for the aims?	Yes - blinded, placebo controlled randomised controlled trial (RCT) Cohort would have also been appropriate.
Which population was studied?	Dogs in Colorado with epilepsy treated with minimum of 1 AED which met the International Epilepsy Task Force Tier II criteria for a diagnosis of idiopathic epilepsy (still having at least 2 seizures per month). Also needed to have therapeutic levels of potassium bromide (KBr) or phenobarbital or be on labeled dose of zonisamide or levetiracetam.
Were the treatments randomly allocated? If yes, how was the randomisation done?	Yes Computer-based random number generator
Were the groups comparable prior to intervention?	Yes in terms of age, reproductive status, weight and seizure type. Concurrent anti-epilepsy drug use and seizure frequency are not clearly reported by group.
Was the person who administered the interventions blinded?	Yes - vets and owners
Is it clear what measurements were carried out in	Yes

the study?	
Were the correct measurements chosen? Do they reflect (or are they strongly related to) the outcome of interest?	Yes although measurement of individual seizure frequency (if >1 seizure per 24 hours, it was counted as 1 seizure) over time (on a continuous scale) would likely have been better than analysing monthly values, especially given the small sample size. Yes
Were previously established validated methods used to make the measurements? (e.g. Glasgow pain score, International Units etc)	C-BARQ is validated behaviour questionnaire Biochemistry, complete blood count (CBC), AED concentration and CBD concentration all validated methods Method of owner evaluation of seizure frequency not validated
What outcomes were measured?	• Mean monthly seizure frequency from 16 weeks before study and the 12 weeks of the study • Response to treatment defined as ≥50% reduction in mean monthly seizures • Serum AED, biochemistry and CBC at weeks 0 and 12 • Plasma CBD at 4, 8 and 12 weeks • Adverse drug effects and change in anxiety-related behaviour using C-BARQ at weeks 0 and 12
Are the outcomes clinically relevant?	Yes
Were the outcomes assessed blind?	Yes
Are the statistical methods described?	Yes
Was the statistical significance level stated?	Yes
Was the sample size justified?	No and had 90% exclusion at enrollment, only 65% completed taking numbers down

	to 9 in CBD group, 7 in placebo
Was ethical approval obtained?	Not stated
Are the methods described in enough detail that you could repeat them?	Yes
Results	
Were the basic data adequately described?	Yes, but it would be useful to have had a full list of AEDs for each dog rather than just the number on each AED type, and to have had clear details of the baseline seizure frequency for each dog. Data reporting the main outcome of interest are very sparse in the main text, with further details available online in the supplementary materials. However, the seizure frequency data are presented only in very summarised form.
Do the numbers add up? Are all subjects accounted for?	Yes Yes
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?	Yes 3 in the CBD group were withdrawn from the study (status epilepticus in 1, ataxia in 2) Increased ALP in all of CBD group comparing week 0 and week 12
What were the main findings/key results?	Eight of the nine dogs in the CBD arm showed a reduction in mean monthly seizure frequency compared to 16 weeks prior to treatment. Three of the seven dogs receiving placebo treatment also had a reduction in mean monthly seizure frequency. This is also reported as a 33% decrease in group median for mean monthly seizure frequency in CBD group

	compared to no change in group median in the placebo group. 2 dogs in each of CBD and placebo groups were considered responders (≥50% decrease in mean monthly seizure frequency). No significant adverse clinicopathological events were reported in either group during the study. No behavioural differences were detected by owner assessment using C-BARQ questionnaire.
Discussion and conclusion	
What do the main findings/key results mean?	The significance of these data are difficult to interpret. Only a small number of dogs were included in each arm of this 12 week study. Data were grouped into mean monthly seizure frequency counts where any amount of seizure activity in a 24 hour period is counted as one unit. It is therefore not possible to be certain that dogs did not have an increase in cluster seizure frequency whilst receiving CBD. A standard error is not presented for each mean, neither is the actual seizure frequency per month so the mean data may mask significant variation.
Are the negative findings discussed? How are the negative findings interpreted?	Yes ALP changes - liver induction, poly pharmacy They suggest the dose given may have been too low to see an adequate response Are aware the sample size is a significant limitation Did not discuss: 1) impact of high (90%) exclusion on enrollment and losses during study, 2) why no change observed in C-BARQ assessment
Does the discussion reflect the results?	Yes, broadly

Interpretation	
What are the clinical implications of this study?	This study tested a specific CBD oil. These results cannot be extrapolated to other oils available, or its use at other dosage levels. Whilst eight of the nine dogs in the CBD group did show some reduction in seizure frequency whilst receiving this CBD product, it is not clear how the CBD and placebo groups compare with respect to seizure frequency, or what the actual number of seizures was for each dog. There was no difference in the number of dogs that showed a >50% reduction in seizure frequency between CBD and placebo arms, so there is no evidence that this treatment provides a significant improvement in epilepsy control versus placebo for dogs concurrently being treated with conventional AEDs. In addition, the trial was for only three months, so it is not possible to determine how sustained any change might be. This specific product appears relatively safe to use in dogs, but owners should be warned of the potential increase in ataxia.
Are the subjects in the study similar to those in the BET/your own?	The majority of dogs in this study were on two or three anti-epilepsy drugs, so it is possible that these dogs had more severe epilepsy than dogs typically managed in a general practice setting.
General	
Who funded this study?	Applied Basic Science Corporation, the company that produces the CBD oil that was evaluated in the study. It was stated that the company had no role in study design, data collection and analysis or preparation of manuscript. One author has a 5% share in the company.