Critical appraisal – Randomised controlled trial questions

Korpivaara, M., Laapas, K., Huhtinen, M., Schoning, B., Overall, K. (2017) Dexmedetomidine oromucosal gel for noise-associated acute anxiety and fear in dogs – a randomized, double-blind, placebo-controlled clinical study

Introduction	
Are the aims clearly stated?	Yes, "to evaluate the effect of dexmedetomidine oromucosal gel at subsedative dose in alleviation of noise-associated acute anxiety and fear in dogs."
Methods	
Is the study design suitable for the aims?	Yes, It was possible to assign the study population to two random groups where the only difference was the intervention, and then a predetermined outcome could be assessed to look for a difference.
Which population was studied?	Owned dogs recruited from 17 veterinary clinics in Germany and Finland. The dogs were > 2 years old, >2kg, had a history of suffering from acute anxiety and fear due to fireworks and were ASA status I or II.
Were the treatments randomly allocated? If yes, how was the randomisation done?	Yes. By and independent randomization specialist using computer software, balanced in each veterinary clinic in blocks of four.
Were the groups comparable prior to intervention?	The groups were well-balanced with respect to age, sex, weight and neuter status across the treatment groups. Information about previous behavioural history (NYE last year) was also similar between groups). Data was presented without statistical analysis.
Was the person who administered the interventions blinded?	Yes, the study personnel and owners did not know whether they were administering the dexmedetomidine gel or a placebo gel.

Is it clear what measurements were carried out in the study?	Yes, owner assessment of signs and extent of anxiety and fear: panting, trembling, vocalizing, pacing, seeking people, trying to hide, trying to escape, freezing, refusing to eat food/treats, inappropriate urinate, inappropriate defaecation and salivating. The behaviours were scaled subjectively from 0 to 4, in conjunction with a score of 1 to 4 on the extent of fireworks in the environment. The behavior assessments were made at baseline assessment 2 days before New Year's Eve and the effectiveness, safety and product usability on NYE. The assessments were made in comparison to the previous year without treatment. Local effects on the oral mucosa and alertness (on a scale of 1 to 4) were also observed. How many doses were given (up to five at ≥2 hour intervals) and usability of the product. Clinical success of treatment (alleviation of acute anxiety and fear without clinical sedation in the presence of fear-provoking stimuli) or failure (no or some treatment effect, increased reactions or had good treatment effect but were sedated) was also recorded.
Were the correct measurements chosen? Do they reflect (or are they strongly related to) the outcome of interest?	Yes. They are behavioural signs that indicate the emotional states of fear or anxiety. The alertness scale showed whether the doses used were sedative or not.
Were previously established validated methods used to make the measurements? (e.g. Glasgow pain score, International Units etc)	They behavioural signs were based on published behavioural studies (Overall and others 2006, Cracknell and Mills 2008, Sherman and Mills 2008). Functional alertness scale was modified from Jimenez and others (2012). All of these scales are subjective and whilst some

	have appeared in previous studies it is unclear if they have been validated except for Overall et al that has had some validation against behaviour testing
What outcomes were measured?	Treatment success was measured as a composite variable of the behavioural signs, sedative effect, in the presence of the fear-provoking stimuli compared to the dogs behaviour at the previous New Year.
Are the outcomes clinically relevant?	Yes, reduced signs of anxiety improve welfare of pets and owners. It is important for safety to know how sedating the medication is.
Were the outcomes assessed blind?	The assessors did not know whether the dog had had dexmedetomidine or a placebo.
Are the statistical methods described?	Yes.
Was the statistical significance level stated?	P = 0.05
Was the sample size justified?	Yes, a sample size of 65 dogs in each group was calculated to have a 95% power to detect a difference. 70 dogs were to be recruited to each group to allow for dropout.
Was ethical approval obtained?	Yes, it is stated the protocol was approved in both countries and the study was undertaken in accordance with good clinical practice
Are the methods described in enough detail that you could repeat them?	Yes. All of the scores were subjective which may mean whilst the methods are repeatable the results may not be.
Results	
Were the basic data adequately described?	No, no information was given about the intensity

	of the fireworks the dogs were exposed to. It just says all were exposed to fireworks.
Do the numbers add up? Are all subjects accounted for?	Yes. Yes. 188 dogs were screened, 187 were allocated to either treatment or placebo, five dogs did not receive the treatment, results are given for 182 dogs.
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, 9 events for 7 dogs given dexmedetomidine, 1 for placebo. Events were emesis, gastroenteritis, periorbital oedema, drowsiness and sedation. None were statistically significant between groups. Transient paleness of the oral mucosa was more commonly observed in the dexmedetomidine group compared to the placebo group
What were the main findings/key results?	There was a significant overall treatment effect, when compared to the previous year without treatment, for the dexmedetomidine when compared to the placebo group with odds ratio of 3.4 (95% CI 1.95-5.99, $p<0.0001$). A higher proportion of dogs in the dexmedetomidine group had some, good or excellent treatment effect compared to the placebo group (11, 55% and 17% in dexmedetomidine vs 39, 27% and 10%). When the dogs who had signs of treatment failure (dexmedetomidine 8, placebo 3) were removed from the analysis , there was a significant anxiolytic effect, when compared to last year without treatment, for the dexmedetomidine compared to the placebo group with an odds ratio of was 3.25 (95%CI, 1.84-5.74, $p<0.0001$).

	The behavioural scores were lower for the dexmedetomidine group compared to placebo, with an estimate difference over time of -2.16 (95% CI -3.87 to -0.45). When analysed at individual time points the behavioural scores were significantly lower after dexmedetomidine than the placebo group after the second dose only (p=0.0003). There was no significant difference between treatment groups in terms of alertness. Nine dogs were unable to stand up and walk when called, 7 in dexmedetomidine group and 2 in placebo. Twenty one dogs (7 on dexmedetomidine and 14 on placebo) were removed prematurely from the study mostly due to a lack of efficacy. It should be noted that no results were given to show the extent of exposure to fireworks.
Discussion and conclusion	
What do the main findings/key results mean?	Dexmedetomidine may reduce anxiety and fear due to noise phobia in some dogs. Most dogs don't get sedated or have side effects as a result of the use of this drug. The placebo effect in this study is very big which along with the likely recall bias (relating to comparing the effect of the drug to an episode 12 months previously) and the unknown level of exposure to noise means the repeatability and reliability of these results are uncertain!
Are the negative findings discussed? How are the negative findings interpreted?	The authors gloss over the extent of the placebo effect in the dogs receiving this intervention. This is not truly a negative finding but warranted more discussion.
Does the discussion reflect the results?	The discussion showed the drug in a very positive light. The extent of how recall bias, and the

	possible variation in exposure to fireworks may have affected the results were not really discussed. The significant effect of the placebo was not discussed fully.
Interpretation	
What are the clinical implications of this study? Are the subjects in the study similar to those in the BET/your own?	That dexmedetomidine may be used to reduce acute noise related anxiety. Yes.
General	
Who funded this study?	Orion corporation, manufacturer of Sileo dexmedetomidine gel.