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Caregiver Placebo Effect in Analgesic Clinical Trials for Painful Cats with Naturally-Occurring Degenerative Joint Disease

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Abstract

Methods—A literature review identified six placebo-controlled studies of analgesics in client-owned cats with degenerative joint disease-associated pain. Five studies with 96 cats had available data. Caregiver responses on a clinical metrology instrument, Client Specific Outcome Measure (CSOM), were compared to measured activity. Cats were categorized as 'successes' or 'failures' based on change in CSOM score and activity counts from baseline. Effect sizes based on CSOM score were calculated; factors that were associated with success/failure were analyzed using logistic regression.

Results—Effect sizes ranged from 0.97 – 1.93. The caregiver placebo effect was high, with 50–70% of placebo-treated cats classified as CSOM successes, compared to 10–50% of cats classified as successes based on objectively measured activity. 36% of CSOM successes were also activity successes, while 19% of CSOM failures were activity successes. No significant effects of cat age, weight, baseline activity, radiographic score, orthopedic pain score, or study type on CSOM success in the placebo groups were found.

Conclusions and relevance—The caregiver placebo effect across these clinical trials was remarkably high making demonstration of efficacy for an analgesic above a placebo difficult. Further work is needed to determine whether a potential placebo-by-proxy effect could benefit cats in clinical settings.

Keywords

placebo-by-proxy; dispositional optimism; feline; arthritis

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Introduction

The placebo effect has been extensively studied in humans (Hauser and others 2012; Rief and others 2009; Zhang and others 2008). This effect represents a beneficial response to an inert treatment that exists for reasons unrelated to the actual treatment given, but depends on the context in which the treatment is provided and the patient's experience and expectations (Benedetti 2013). Placebo effects on the patient are termed the placebo effect, while effects that alter the rating of outcomes provide by clinicians, caregivers, or the family are termed a caregiver placebo effect. Clinician and caregiver ratings often reflect a placebo effect, and observer ratings show an increased placebo effect size relative to patient self-report (Rief and others 2009). These caregiver ratings can directly influence the subject receiving the placebo, thereby enhancing the placebo effect – a phenomenon called the placebo-by-proxy effect (Grelotti and Kaptchuk 2011; Kossowsky and Kaptchuk 2015). Investigators must be careful to control the factors that may influence the magnitude of these placebo responses in their studies. In human clinical trials these factors can include trial design features, the type of treatment and route of administration, and the cost of the treatment (Espay and others 2015; Waber and others 2008), and patient-specific features such as baseline disease severity (Locher and others 2015) and an individual's dispositional optimism (Geers and others 2010; Hanssen and others 2014).

The placebo effect can improve self-ratings of pain and function in a substantial percentage of participants in human analgesia trials (Keltner and others 2006; Tuttle and others 2015). The placebo effect makes demonstrating analgesic efficacy above placebo difficult, thereby hindering analgesic development and approval (Tuttle and others 2015). The placebo effect becomes especially problematic when using proxy measures of pain or function, where the caregiver placebo effect could contribute to the approval of a medication that has lower efficacy than reported, or (in a trial setting) make it difficult for an efficacious medication to show superiority to placebo. In veterinary medicine, by necessity all subjective outcome assessments and clinical metrology instruments (questionnaires) are completed by a proxy.

The placebo effect in veterinary trials has been described in the past, particularly in discussing results of intervention trials (Cottam and Dodman 2009) but only a small number of papers directly report on this effect (Conzemius and Evans 2012; Malek and others 2012; Munana and others 2010). Munana and others (2010) raised the idea of the "perceived placebo effect" in studies of canine epilepsy, noting that time, better care (including increased compliance with baseline medication administration), and regression to the mean could all influence seizure frequency in dogs receiving a placebo as part of a clinical trial. They also raised a suggestion of what was later termed the caregiver placebo effect by Conzemius and Evans (2012). In this context, the caregiver placebo effect refers strictly to improved ratings of outcomes in companion animals in the absence of improvement in objective measures. The bases for this effect are likely multi-factorial, and include a desire for the trial to work, a wish to please the investigator, and the "better care" effect, where in this case, access to better health care and more follow-up can improve caregiver ratings on subjective measures. While it is yet to be studied in veterinary medicine, one could postulate that caregiver ratings could also be influenced by caregiver features including suggestibility, empathy toward animals, and optimism, among others. As an additional consideration to the

caregiver placebo effect, it is unknown in veterinary medicine whether there is a placebo-by-proxy effect on animals, where a caregiver's belief that the animal is receiving an effective medication alters their interaction with the animal and manifests as a real beneficial effect for the animal.

The objectives of the current study are to: (a) quantify the placebo effect in studies assessing therapies for degenerative joint disease or osteoarthritis (DJD/OA) associated pain in client-owned cats; (b) identify cat or owner features that affect the placebo response; (c) quantify the percentage of cats that show a potential placebo-by-proxy effect; and (d) to explore the effect of owner optimism on the caregiver placebo effect.

Materials and Methods

We reviewed five North Carolina State University (NCSU) studies that used client-owned cats and subjective and objective outcome measures (Table 1). These included a trial of a supplemented diet (Diet) (Lascelles and others 2010a), a nutraceutical (DQ), a study to evaluate a client metrology instrument (Feline Musculoskeletal Pain Index [FMPI]) (Benito and others 2013a; Benito and others 2013b), a study of a low-dose nonsteroidal anti-inflammatory drug (Low dose) (Gruen and others 2015), and a study of an anti-nerve growth factor antibody (Antibody) (Gruen and others 2016). A search for additional studies was performed on January 19, 2016 using Web of Science, CAB Abstracts, and PubMed and the following search terms and no time restriction: feline or cat, arthritis or osteoarthritis or degenerative joint disease, and placebo. One study met the inclusion criteria (the use of client-owned cats and subjective outcome measures in a placebo controlled trial) (Corbee and others 2012), however, our request for data sufficient to calculate an effect size in the placebo group was not fulfilled.

Across studies, similar physical, orthopedic, neurologic, and radiographic screening procedures and outcome assessment tools were used. These included:

1. Veterinary orthopedic examination to identify painful joints. A total pain score (TPain) was generated based on behavioral reactions during orthopedic exam palpation and manipulation (Gruen and others 2014).
2. Diagnosis of DJD/OA supported by radiography of painful joints. Radiographs of all appendicular joints and axial skeletal segments were used to generate a total radiographic DJD (TDJD) score (Lascelles and others 2010b) for the Antibody, Low-dose, and FMPI studies.
3. Owner rating of activity and mobility impairment. Owners rated their cat's ability to perform several individually tailored activities using a Client Specific Outcome Measure (CSOM) questionnaire (Lascelles and others 2007). Success was defined as determined for the individual studies, taking into account the way the CSOM was constructed and inclusion criteria.
    a. The Low-dose and Antibody studies' CSOM used 3 activities, each scored 0–4. The success criterion was defined as an improvement in total score of at least 2, representing an approximate 16% change in

total scale, or a 20–24% decrease in pain and impairment from baseline (Gruen and others 2014).

b. The Diet, DQ, and FMPI studies used a CSOM with 5 activities. The success criterion was defined as an improvement in total score of at least 4, representing a 20% change in total scale, or 28–30% decrease in pain and impairment from baseline.

4. Activity (accelerometry) data collected at 1-minute intervals using Actical® accelerometers (Lascelles and others 2008). Cats wore the same accelerometer throughout each study. Individual mean activity counts per-minute averaged over the baseline period and the treatment periods were calculated. A ≥ 10% increase in mean activity counts per-minute over baseline was used to define "success" with any decrease or increase <10% defined as a "failure" (Brown and others 2010; Gruen and others 2016).

The effect size is a way to standardize the magnitude of difference between the placebo and active treatment groups where an effect size of ≥ 0.8 is considered large (Cohen 1992; Dancey and others 2012). Effect sizes (as Cohen's *d*) were calculated for placebo and treatment arms for each outcome measure for the period following treatment versus baseline using the following equations:

- $$\text{Cohen's } d \text{ for treatment over placebo} = \frac{\Delta \text{ Mean}_{treatment} - \Delta \text{ Mean}_{placebo}}{\text{Pooled standard deviation}}$$
- $$\text{Cohen's } d \text{ for the treatment or placebo group} = \frac{Mean\ score_{treatment\ or\ placebo} - \ Mean\ score_{baseline}}{\text{Pooled standard deviation}}$$

For improvement and success/failure determinations, cats that had participated in more than one study were included only for the first study they participated in. Cats given placebo that were classified as CSOM successes, without having an increase in activity were considered to have "improved" due to the caregiver placebo effect. Cats that were given placebo and classified as CSOM and activity count successes were considered to have improved due to a placebo-by-proxy effect. Study populations were tested for uniformity of variance and compared using ANOVA with post-hoc testing when an overall effect was found. Factors associated with success/failure were analyzed using logistic regression to evaluate the distribution of CSOM success/failure against cat age, weight, study, baseline activity, TDJD score, and TPain score. Type of study and distributions of success/failure were investigated using Chi-square tests.

For the Antibody study, a pilot investigation of the effects of dispositional optimism of owners on proxy ratings of improvement was performed using the previously validated Life Orientation Test-Revised scale (Scheier and others 1994). Respondents indicate their level of agreement with 10 statements on a five-point scale, where the middle value is neutral. Responses were converted to numerical values (0–4) according to the published key (Scheier and others 1994). Higher scores indicate higher levels of optimism, though there is no published cut-off to discriminate "optimist" from "pessimist". The effect of dispositional optimism scores on CSOM success and on belief that their cat received active medication during the placebo period were evaluated using logistic regression. The relationship between dispositional optimism score and change in CSOM score over the placebo period was

analyzed using ANOVA. In all analyses, a probability $p < 0.05$ was considered statistically significant.

Results

Following removal of cats that participated in more than one study, a total of 96 cats were included in the analyses of effect size and success/failure, with one cat excluded from determination of activity success/failure due to a malfunction of the accelerometer. Cats in the placebo groups are further described in Table 2.

Study populations were not significantly different from each other for cats' age, weight, or sex, but were significantly different for baseline TPain score ($p < 0.001$) and baseline activity ($p = 0.01$). As expected, across all studies, male cats were heavier than female cats (one-sided t-test, $p < 0.001$). TPain scores across the study populations differed according to eligibility requirements, with the scores for the Diet and DQ studies being significantly lower than the scores for the Low-dose and Antibody studies ($p < 0.001$; Figure 1). Eligibility requirements were most rigorous for the Low-dose and Antibody studies, where two joints, rather than one, had to be affected on both orthopedic and radiographic examinations, and may have led to higher TPain scores in these studies. Orthopedic exams in the Diet and DQ studies were performed by one investigator (BDXL), FMPI study orthopedic exams were performed by a second, and Low-dose and Antibody orthopedic exams by a third (MEG), which also may contribute to study differences in TPain. Baseline activity was significantly different between the Diet and Low-dose studies (Figure 2A), with lower baseline activity in the Low-dose study (and correspondingly higher pain scores). Overall, the correlation between baseline activity and TPain score was −0.29 (Spearman ρ, $p=0.003$) (Figure 2B).

Effect Sizes

Effect sizes and 95% confidence intervals (CI) for each study are summarized in Table 3.

CSOM and Activity Successes During Placebo Treatment

Improved CSOM scores during placebo treatment were seen in all studies, with any improvement (a change in score toward improvement of at least one point) seen in 86.5% of cases, and the distribution of cases where CSOM score meeting success criteria shown in Table 4. CSOM scores meeting the success criteria (CSOM+) occurred in 54% to 74% of the cases. Some cats' activity improved during the placebo period (Table 4), with 10% to 63% of placebo-treated cats meeting the definition of activity success (Activity+). The distribution of cats meeting criteria for CSOM success (Overall CSOM+) was not different by study (χ^2, $p = 0.86$), unlike activity success, which did differ among studies (χ^2, $p=0.01$) with higher proportions of activity success seen in the DQ and FMPI studies. Overall, there was a non-significant trend for being defined as an activity success across CSOM conditions (Fisher's exact, $p = 0.15$, with $p = 0.07$ on a one-tailed analysis; Odds Ratio 2.34 [0.84–6.53]), with 36% of CSOM+ cats being Activity+, but only 19% of CSOM- cats being Activity+. Activity+ did not differ by sex, however CSOM+ did differ by sex, with spayed female cats having a lower proportion of CSOM+ outcomes than castrated male cats (58.9%

vs. 80.0%; p=0.03). No significant results for the effects of study, cat age, weight, baseline activity, TDJD score, or TPain score on CSOM success in the placebo groups were found. No significant result for study type (drug versus non-drug) by CSOM success in the placebo groups was found (χ^2 test, p = 0.37).

Dispositional optimism

For evaluation of dispositional optimism, 11 cats given placebo in the Antibody study were considered, regardless of previous study participation. Of the 11 cats in the Antibody study, 54.5% were considered CSOM+ at Day 36 while on placebo. Six cat owners (54.5%) also believed their cat received the active treatment, but concordance of these results was only 64%. Dispositional optimism scores ranged from 9 – 24 (possible range 0 – 24), however there was neither an effect of dispositional optimism score on CSOM success (p = 0.69), nor a relationship between dispositional optimism score and change in CSOM score (p = 0.55). Dispositional optimism score did not affect whether owners believed their cats received active medication during the placebo period (p = 0.64).

Discussion

Our study uncovered a profound placebo effect in caregiver ratings of improvement in mobility and activity in cats receiving therapies for DJD/OA associated pain. Approximately 50 – 70% of cats given the placebo in the studies we reviewed met criteria for success for improved ability to perform activities as determined by owner-completed questionnaires. There are, of course, limitations to the current investigation. We used previously determined or published criteria for success/failure for the CSOM completed by owners, while understanding that these criteria are based on one study, and further research is needed to understand whether or not these criteria represent a clinically meaningful response. An additional limitation is that all the studies we analyzed were performed at a single site (NCSU). Caregiver placebo effects have been demonstrated in client-owned cats in dermatology (King and others 2012), behavior (Gunn-Moore and Cameron 2004; Gunn-Moore and Shenoy 2004), and another DJD/OA study (Corbee and others 2012) performed elsewhere suggesting our observations are consistent with results seen in trials conducted at other veterinary medical centers. Two open-label trials of analgesics in client-owned cats with naturally occurring DJD/OA found that nearly 100% of owners reported that their cats improved at least slightly while receiving a non-steroidal anti-inflammatory drug (Bennett and Morton 2009; Clarke and Bennett 2006), with 75% reporting moderate to marked improvement in one study (Clarke and Bennett 2006). While improvement can be expected with an anti-inflammatory, our data suggest this level of response is unlikely due solely to the treatment.

Relative to other species, the caregiver placebo effect reported here is comparable to or higher than analgesic studies in dogs with osteoarthritis, while the overall placebo effect appears higher (Brown and others 2013; Brown and others 2010; Conzemius and Evans 2012; Malek and others 2012), and certainly is notably high when looking at any improvement in score, rather than meeting the success criteria. Multiple authors have noted the difficulty in evaluating pain and mobility impairment in cats (Klinck and others 2015).

Several putative factors contribute to the challenge of assessing DJD/OA associated pain in cats. Both veterinary and owner awareness of DJD/OA and associated pain in cats lags behind dogs, with the first descriptions of DJD/OA in cats appearing in the literature with a single citation in 1984 (Edmonds 1984), followed by characterization of the naturally occurring disease beginning in the mid-1990s (vs. the 1960s and 1970s for dogs). Interactions with cats in their homes are unquestionably different from interactions with dogs, and cats are not asked to perform the same daily tasks as dogs. Many cats with radiographic DJD/OA may not show clinically detectable lameness (Hardie 1997), and may be more likely to be perceived as just ‘slowing down’ or showing decreased mobility as part of normal ageing. General awareness of signs and prevalence of DJD/OA among cat owners is not known. The reason for the higher proportion of CSOM successes in male cats vs. female cats found in our study is unknown.Study designs were changed over time in an effort to combat the placebo effect, making direct comparisons over time inappropriate. For example, a two-week baseline period was included in the FMPI, Low-dose, and Antibody studies to facilitate data collection, provide a learning period for owners with the assessment tool, and minimize owner impact on the way behavior was perceived (i.e., Hawthorne effect) (McCarney and others 2007) thus improving confidence in their CSOM scores. Including an appropriate baseline period is important since CSOM scores collected on the first assessment day may be artificially worsened as owners might want to meet entry criteria. The DQ study design attempted to further mitigate the placebo effect on subsequent caregiver ratings by including an initial placebo period that owners were blinded to. In theory, this design allows the placebo effect to stabilize after the first two weeks of treatment, followed by further improvement only in the treatment group. Despite this study design modification we observed a significant placebo effect in this study, which may reflect the test article (supplement) and owners desire for it to be associated with efficacy. The treatment effect sizes shown in our study exemplify the difficulty with showing effectiveness of a treatment over a placebo when using owner completed clinical metrology instruments, but may also be reflective of a lack of efficacy of some of the tested treatments.

Several results point to dispositional optimism, or its converse, pessimism, as potential modulators of placebo responsiveness in analgesic trials in people, with dispositional optimism thought to be a putative resilience factor against the negative affective consequences of pain (Geers and others 2010). However, our pilot results from the Antibody study suggest that dispositional optimism is not an important source of caregiver placebo response in cat analgesic clinical trials. Further work is needed to confirm these preliminary findings and should investigate other owner characteristics that influence ratings on clinical metrology instruments, including empathy (Rae Westbury and Neumann 2008) and suggestibility scales. Likewise, further work should investigate the effect of treatment type on caregiver placebo effect.

Though these represent the minority of the CSOM successes, 36% of the CSOM successes were also activity successes, and the possibility that there could be some beneficial effect on the cat’s activity from the owner’s belief that the cat is on active treatment (placebo-by-proxy effect) bears further exploration. Overall, there was a trend for activity successes to increase in the cats that were defined as CSOM successes compared to those that were defined as CSOM failures. We adopted a definition of success for improvement in activity

counts that represents the response seen with medications that are considered effective in cats and other species. The observation that cats and dogs with DJD/OA appear to have increased activity counts when receiving an analgesic supports the application of this measure, although the actual threshold that is appropriate requires further investigation (Lascelles and others 2008). In addition, cats with DJD/OA have shown increased spontaneous activity counts when receiving an analgesic, independent of human intervention/interaction (i.e., measured at times when humans were absent) (Guillot and others 2012; Guillot and others 2013). Our finding of a trend for activity successes to increase in the cats that were defined as CSOM successes could certainly be interpreted as the CSOM working – owners were able to correctly identify the cats that had increased activity. Alternatively, this could be interpreted as a positive expectation or disposition having an impact on the cats' behavior - a placebo-by-proxy effect – because cats' activity would not be expected to increase with the administration of placebo. Owners may pay increased attention to their cats, engaging them more frequently in interactions and play, and thereby increasing both their total activity and the owner ratings of their abilities. Alternatively, owners may have an improved disposition – be more positive or happy, and this in its own right may alter the affect of the cats, perhaps reducing anxiety or improving positive feelings, and thus have the effect of decreasing pain and improving mobility. These are not mutually exclusive explanations. This hypothetical relationship is shown in Figures 3A and 3B.

The placebo-by-proxy effect is a relatively new concept (Grelotti and Kaptchuk 2011), and studies investigating this effect have a difficult time in differentiating the contributing components in adult populations. A study using a placebo (flower essence) in children with severe temper tantrums found that the number of tantrums decreased during the placebo treatment (Whalley and Hyland 2013). The study authors attributed this to altered interactions between the child and the parent that believes their child is being treated (Whalley and Hyland 2013). While interesting, these results must be considered with caution as no objective measures were included. In the context of cats with DJD/OA, we may use activity as an objective measure to explore the placebo-by-proxy effect, but greater understanding is needed of fluctuation of activity patterns over time in cats with DJD. This, accompanied by owner questionnaires targeting not only CSOM outcomes but also owner beliefs, would allow us to further understand the placebo-by-proxy phenomenon, and whether it would have clinical application. Clinicians could use the positive expectations of owners to encourage increased interactions, play, and exercise – all of which might increase a cat's activity, which in turn could be of benefit just as exercise has been shown to be of benefit in people with arthritis (Fransen and others 2002).

In conclusion, the overall and caregiver placebo effects are remarkably high in trials of putative analgesics for cats with DJD/OA. In reporting of clinical trials in veterinary medicine, the terms placebo effect and caregiver placebo effect have been used, sometimes without clarification, and readers are cautioned to understand what is being described. The caregiver placebo effect, as described by Conzemius et al., relates to owner ratings of improvement on an outcome measure, without improvement on an objective measure, while the overall placebo effect also includes cases where improvement on an objective may be seen during placebo treatment. These cases may simply represent fluctuation in the clinical

signs of the disease, however the possibility of a placebo-by-proxy effect in veterinary medicine exists and deserves further study. Understanding the mechanisms of the placebo effect may lead to advances in trial design or outcome assessments that mitigate these effects and allow for improved assessment of future therapies.

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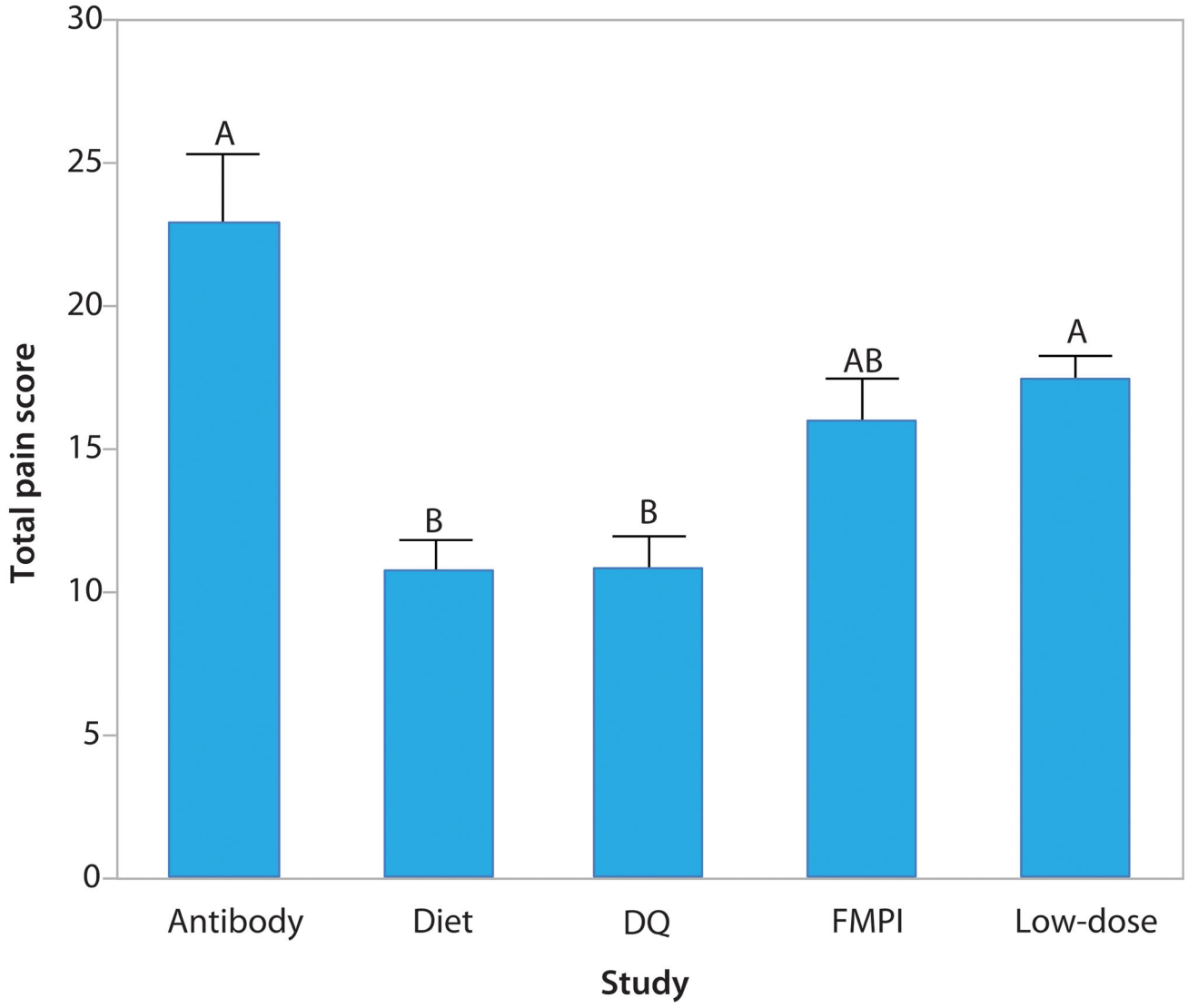

Figure 1.

Mean (± SE) total pain (TPain) score by study. The Diet and DQ studies had significantly ($p<0.001$) lower mean TPain scores when compared with either the Low-dose or Antibody studies. Studies not connected by the same letter are significantly different.

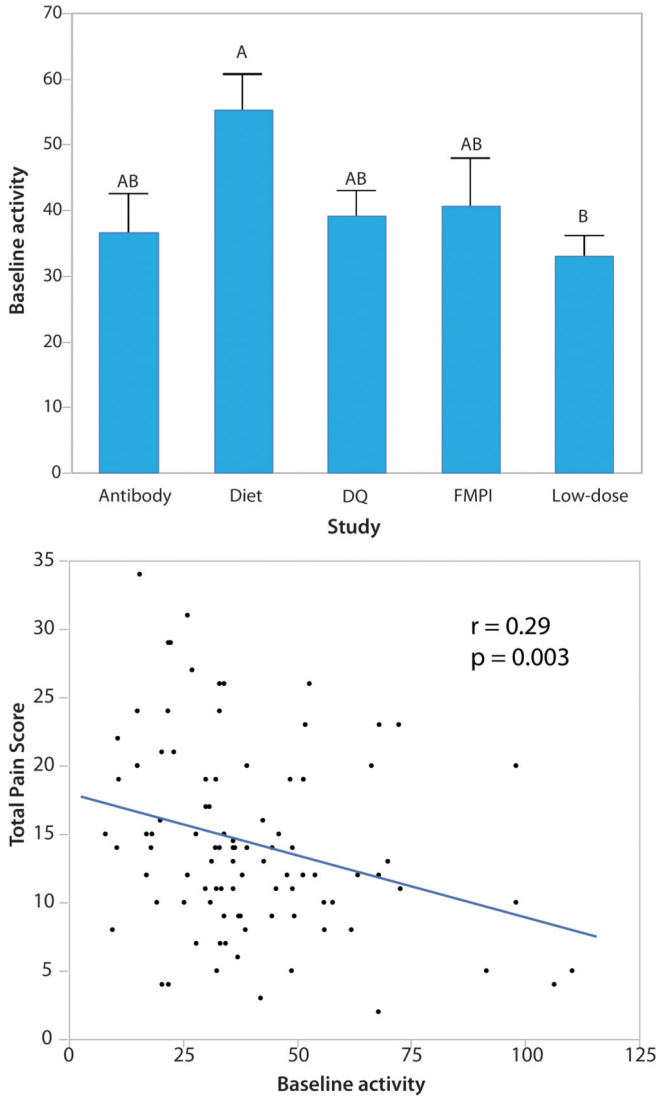

Figure 2.

(A) Baseline mean (± SE) activity counts by study. Mean activity counts were significantly different by study (p=0.01), with cats in the Low-dose study having significantly lower mean activity counts than cats in the Diet study. Studies not connected by the same letter are significantly different. (B) Baseline activity by TPain score.

Table 1

Key components of the reviewed NCSU studies.

Study identifier/year	Study type	Total number enrolled/ number in placebo group	Number of joints with pain and radiographic evidence of DJD	Qualifying baseline CSOM 'disability' score	Study design	Assessment time points	Comments
Diet (2009)	Non-drug; double blind	40/20	1	≥7 (of 20)	Diets transitioned over Days 1–7. Remained on study diets for 9 weeks	Days 0 and 70 (end of study)	Day 0 used because it was prior to transition to new diet and "treatment". Average activity counts over Days 0–7 = baseline. Activity counts during Days 63–70 was comparator.
DQ (2011)	Non-drug; double blind	59/30	1	≥7 (of 20)	Placebo given between days 0 and 14. Placebo or active treatment given for 6 weeks	Days 0 and 56 (end of study)	Day 0 was used since owners were blind to when treatment started. Average activity counts over Days 0–14 = baseline. Activity counts during Days 49–56 was comparator.
FMPI (2012)	Drug; double blind	25/13	1	≥7 (of 20)	2-week baseline. Placebo or active treatment given for 2 weeks. 2 week washout and crossover	Days 14 (baseline) and 28 (end of first treatment period)	Average activity counts over Days 2–13 = baseline. Activity counts during Days 16–27 was comparator.
Low-dose (2013)	Drug; double blind	58/29	2	≤5 (of 12)	2-week baseline. Placebo or active treatment given for 3 weeks. 3 week washout and crossover	Days 14 (baseline) and 35 (end of first treatment period)	Day 14 was the assessment just prior to the start of the treatment. Average activity counts over Days 0–14 = baseline. Activity counts during Days 38–35 was comparator.
Antibody (2014)	Drug; double blind	34/11	2	≤5 (of 12)	2-week baseline. Placebo or active treatment given for 9 weeks.	Days 14 and 35 (first assessment period following treatment)	Day 14 was the assessment just prior to the start of the treatment. Average activity counts over Days 0–14 = baseline. Activity counts during Days 28–35 was comparator.

Table 2

Demographic information on cats in the placebo groups. No significant differences in distribution between the studies were found for cat age, weight, or sex.

Study	Number of cats	Age (mean ± SD), years	Weight (mean ± SD), kg	Sex Ratio%FS/%MC
Diet	19	10.8 ± 2.7	6.1 ± 2.2	42/58
DQ	28	12.3 ± 4.3	5.3 ± 1.4	64/36
FMPI	11	12.4 ± 3.4	5.4 ± 1.2	82/18
Low-dose	29	12.2 ± 3.2	5.6 ± 1.8	52/48
Antibody	9	12.9 ± 1.5	5.3 ± 0.9	67/33

Table 3

Effect sizes for the placebo period, treatment period, and treatment over placebo by study.

	Effect size (95% CI)		
Study	**Placebo**	**Treatment**	**Treatment over placebo**
Diet	1.93 (1.16–2.70)	1.33 (0.65–2.02)	−0.35 (−0.98–0.28)
DQ	1.71 (1.12–2.30)	1.40 (0.81–1.96)	−0.35 (−0.87–0.16)
FMPI	0.97 (0.16–1.78)	1.40 (0.42–2.37)	0.35 (−0.48–1.18)
Low-dose	1.05 (0.50–1.60)	1.09 (0.53–1.64)	0.09 (−0.43–0.60)
Antibody	1.20 (0.25–2.16)	2.06 (1.34–2.77)	0.74 (−0.02–1.50)

Table 4

Summary of proportion of overall CSOM success during placebo treatment (CSOM+) as well as breakdown of CSOM and activity (Activity+) successes and failures (CSOM− and Activity−) by study.

Study	N	Overall CSOM+	CSOM+/Activity+	CSOM+/Activity−	CSOM−/Activity+	CSOM−/Activity−
Diet	19	0.74	0.11	0.63	0.00	0.26
DQ[1]	28	0.70	0.33	0.37	0.11	0.19
FMPI	11	0.54	0.45	0.09	0.18	0.27
Low-dose	29	0.66	0.21	0.45	0.03	0.31
Antibody	9	0.67	0.11	0.56	0.00	0.33
Overall	96[1]	0.68	0.24	0.43	0.06	0.26

[1]One cat excluded due to accelerometer malfunction; n=96 for overall CSOM, n=95 for CSOM/Activity.