Caregiver placebo effect for dogs with lameness from osteoarthritis

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Objective—To document the caregiver placebo effect in owners and veterinarians of dogs with lameness from osteoarthritis.

Design—Prospective, randomized, double-blinded, placebo-controlled, multicenter clinical trial.

Animals—58 dogs with lameness secondary to osteoarthritis.

Procedures—Dogs enrolled in the placebo arm of an FDA-approved study were evaluated to determine the relationship between subjective (caregiver responses) and objective (force platform gait analysis) patient outcome measures.

Results—A caregiver placebo effect for owners evaluating their dog's lameness occurred 39.7% of the time. A caregiver placebo effect occurred 44.8% of the time when veterinarians examined dogs for lameness at a walk, 44.8% of the time when veterinarians examined dogs for lameness at a trot, and 43.1% of the time when veterinarians evaluated dogs for signs of pain on palpation of the joint. This effect was significantly enhanced with time. Mean ground reaction forces (GRFs) remained unchanged for dogs during treatment with the placebo. Individually, of 58 dogs, 5 had GRFs that worsened by ≥ 5% over 42 days, 7 had GRFs that improved by ≥ 5% over 42 days, and 46 had GRFs that remained unchanged.

Conclusions and Clinical Relevance—A caregiver placebo effect was common in the evaluation of patient response to treatment for osteoarthritis by both pet owners and veterinarians. Force platform gait analysis was an unbiased outcome measure for dogs with lameness from osteoarthritis. A caregiver placebo effect should be considered when interpreting owner and veterinary reports of patient response to treatment. (*J Am Vet Med Assoc* 2012;241:1314–1319)

Many clinical veterinary orthopedic studies assess patient outcomes with subjective measures such as owner questionnaires or veterinarian lameness scores. Although many subjective measures are validated for dogs with osteoarthritis and owner input is undoubtedly useful, these methods of assessing subjects have an additional source of bias: the assessors (owner and veterinarian). A placebo effect is a change in a patient's illness attributable to the symbolic import of a sham treatment perceived by the patient rather than a specific pharmacological or physiologic property.[1,2] In situations where patients have no understanding of the efficacy of a treatment given to them by a caregiver, a caregiver placebo effect can develop. A reasonable definition of the caregiver placebo effect for veterinary medicine is a sham medical intervention that causes pet caregivers (owners or veterinarians) to believe the treatment they provided to the pet improved the pet's condition. The caregiver placebo effect may have its greatest influence during evaluation of a single patient and when interpreting results of an uncontrolled study or case series. In these situations, the bias created can artificially inflate the perceived effect of treatment, thereby causing unwarranted changes in clinical practice.

Abbreviations

GFR	Ground reaction force
PVF	Peak vertical force
VI	Vertical impulse

The caregiver placebo effect has been documented in veterinary medicine for the treatment of osteoarthritis for dogs. Review of FDA Freedom of Information summaries of NSAIDs shows that pet owners and veterinarians consistently report improvement in dogs treated with a placebo (reported improvement in dogs treated with the drug was significantly greater than the improvement reported for placebo-treated dogs). In deracoxib[a] and carprofen[b] summaries,[3,4] the reported percentage of dogs with osteoarthritis treated with placebo that were perceived to improve ranged from 34.1% to 42.1%, depending upon the question asked, the time of the interview (eg, day 14 vs 42 of a study), and who was asked (owner or veterinarian). However, these summaries do not provide all of the necessary information to measure the true caregiver placebo effect because they incompletely describe the questions asked, grading scales, range of responses, and how the caregiver responses compared with an objective measure of patient disease status (eg, limb function measured by force platform gait analysis). These summaries tend to

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focus on the percentage of caregivers stating the patient was improved and do not mention whether caregivers reported their dog as unchanged when it had actually gotten worse. This would also be evidence of a caregiver placebo effect. In these 2 clinical trials,[3,4] when limb function was measured objectively by means of force platform gait analysis and GRFs, a treatment effect was documented when dogs were treated with the active drug but no placebo response was found via measurement of GRFs.

A treatment effect in dogs with lameness from osteoarthritis that received only placebo has been consistently documented in the past.[5–12] For example, in an investigation of the safety and efficacy of meloxicam,[c] both owners and veterinarians reported that, on average, placebo-treated dogs improved.[5] During the Liverpool Osteoarthritis in Dogs (elbow) owner questionnaire validation study for dogs with osteoarthritis, Hercock et al[6] found that, on average, owners reported their dog's lameness as improved even when treated only with placebo. There was no improvement in lameness when the same placebo-treated dogs were evaluated by use of GRFs. Moreau et al[7] reported that veterinarians graded placebo-treated dogs as improved when gait analysis showed no change. In a randomized, double-blinded, placebo-controlled study, Innes et al[8] found that mean function in placebo-treated dogs improved when rated by both owners and veterinarians. Again, no change in the mean GRF of these dogs occurred. Similar to FDA Freedom of Information summaries, these papers simply address when the caregiver reported the patient as improved and do not address when a caregiver might have reported the patient as unchanged when it had in fact worsened. In addition, none reported how caregivers' opinions compared with an objective outcome measure of the patient.

Osteoarthritis is a chronic debilitating disease that affects millions of dogs each year. The efficacy of nonsurgical and surgical interventions for the treatment of osteoarthritis is commonly determined on the basis of owner interview and examination by a veterinarian. Veterinary patients cannot verbally communicate the effect of an intervention or treatment, so these simple and subjective outcome measures are necessary for routine veterinary care and clinical research. However, correct interpretation of a scientific manuscript, an interview with an owner, or even a veterinary physical examination would be improved with a better understanding of how often caregivers (owners and veterinarians) overestimate or underestimate the efficacy of a potential intervention for osteoarthritis. The objective of the study reported here was to document the caregiver placebo effect in owners and veterinarians in evaluation of dogs with lameness from osteoarthritis.

Materials and Methods

The study included only dogs that were in the placebo arm of a larger prospective, randomized, double-blinded, placebo-controlled, multicenter clinical trial to evaluate the safety and efficacy of an orally administered NSAID (deracoxib[a]) for the treatment of lameness secondary to osteoarthritis in dogs. All 7 institutional sites that contributed cases for this study were located in the United States, and the experimental protocol was approved by the institutional animal care and use committee at each institution. The duration of the study was 50 days, including a 7-day pretreatment period and 42 treatment days. Dogs were randomly assigned, and randomization schedules were specific for each institution. Both pet owners and veterinarians (all caregivers) were blinded to which dogs were receiving the experimental drug and which were receiving the placebo. The placebo pill was identical to the treatment tablet with the exception that the active ingredient was not in the placebo, and the dosing schedule (orally, once daily) was the same.

Inclusion criteria for dogs entering the general NSAID study included informed owner consent, body weight > 6.35 kg (13.97 lb); skeletal maturity; good health as determined by physical examination and evaluation of CBC, buccal bleeding time, and serum biochemistry analysis results; at least a grade 2 of 4 lameness (**Appendix 1**) on both days –7 and 0 of the study; and lameness secondary to radiographically evident osteoarthritis in at least 1 joint (dogs could have osteoarthritis in > 1 joint, but on days –7 and 0 of the study, 1 leg had to consistently have the greatest lameness). Dogs could be of any breed or sex. In addition, dogs must have been in the placebo arm of the study and completed force platform gait analysis at each visit.

Dogs were excluded from the study if they were pregnant, had surgery within 180 days prior to the study, received an intra-articular injection within 90 days prior to the study, had arthrocentesis within 30 days prior to the study, or were receiving treatment with topical or systemic pharmaceuticals or biologics (other than routine parasiticides) within 14 days prior to the study. Finally, dogs were not enrolled that received injectable depot corticosteroids or the administration of polysulfated glycosaminoglycans, glucosamine, or chondroitin sulfate nutritional supplements within the 30 days prior to enrollment.

For the dogs evaluated in this study, force platform gait analysis was required at all evaluation times (days –7, 0, 14, 28, and 42). The first 5 valid trials (passage by a dog over the force platform in which only the forepaw contacted the surface of the plate and was only followed by contact of the ipsilateral hind paw) in the affected limb were evaluated for the GRFs, PVF, and VI with the dog at a trot (1.7 to 2.0 m/s). All sites used similar force platforms from the same manufacturer[d] and the same data acquisition system,[e] and all trials were performed by a designated technician or by an investigator with technical assistance. All data were normalized to percentage of body weight, and the force platform system at each site was verified prior to the onset of the study and a minimum of once each month throughout the study. Ground reaction forces (PVF and VI) were used as the standard for a dog's limb function throughout the study. Dog limb function was measured twice before inclusion into the study to document that there was a presence of lameness in the limb being evaluated (both PVF and VI were lower in the affected limb than the opposite normal limb on both occasions) and that disease was stable going into the trial (the difference between the 2 trials was < 5%). Given that the GRFs were stable between days –7 and 0, each dog's limb function at the beginning

of the study was quantified by calculating the mean data from days –7 and 0. Lameness was defined as improved if both PVF and VI increased or worse if both decreased by ≥ 5% on at least 2 of 3 postintervention examinations (days 14, 28, and 42); dogs that did not achieve this cutoff were considered unchanged. Although the ≥ 5% cutoff was used for comparison with subjective outcome measures, limb function was also evaluated with a ≥ 10% change in GRF to document the frequency that dogs with lameness from osteoarthritis have large variations in their limb function.

Owners completed a questionnaire on day 0 of the study that asked whether the dog's degree of lameness was none, mild, moderate, or severe. Explanations for each degree of lameness were on the questionnaire (Appendix 1). Owners completed a follow-up questionnaire on days 14, 28, and 42 of the study that asked whether the dog's degree of lameness (compared with day 0) was greatly improved, was somewhat improved, appeared unchanged, or appeared worse.

Owners received $500 for full participation in study (attendance at all appointments, completion of medication diary, and completion of all surveys). An owner response to the follow-up question addressing their dog's degree of lameness was used for comparison with the other outcome measures.

A single veterinarian (all were diplomates of the American College of Veterinary Surgeons [ie, board-certified surgeons]) was identified at each site to perform all physical and orthopedic examinations. A lameness examination was performed on days –7, 0, 14, 28, and 42 of the study. During each examination, the veterinarian documented the dog's posture (graded 0 to 3), lameness at a walk (graded 0 to 4), lameness at a trot (graded 0 to 4), willingness to raise the contralateral limb (graded 0 to 4), and at the conclusion of each examination, signs of pain in response to palpation (graded 0 to 3; **Appendix 2**). For all parameters, a grade of 0 was normal and degrees of abnormality increased with an increasing grade or number. Changes (positive or negative) in the veterinarian's responses to questions addressing the dog's lameness at a walk, lameness at a trot, and signs of pain in response to palpation were documented and used for comparison with the other outcome measures.

The subjective outcome measures, owner follow-up questions (lameness), and veterinary examination (lameness at walk, lameness at trot, and signs of pain on palpation) were compared with the objective outcome measure (change in GRF). The GRF was used as a gold standard for objectivity, not lameness. A dog's gait was considered improved if the GRF increased by ≥ 5% of its body weight and deteriorated if the GRF decreased by ≥ 5%. Otherwise, the gait was considered unchanged.

Caregivers (owners or veterinarians) had a correct response if their response regarding patient status correctly matched the changes in GRF (improved, deteriorated, or unchanged). Caregivers underestimated improvement if their response was worse than the changes in GRF (eg, owner stated dog was worse when the GRF remained unchanged or had improved or owner stated the dog was unchanged when the dog had improved). Caregiver placebo effect was identified when the caregiver overestimated improvement (eg, overstated that the dog had improved when GRF remained unchanged or worsened by at least 5% or stated there was no change when the GRF had worsened).

To evaluate the caregiver placebo effect, the data were tested in several ways. First, internal agreements over time between methods of assessment of lameness (owner, veterinarian, and force platform) were calculated via Cronbach α,[f] a standard measure of rater reliability. Values near 0 represent poor reliability, and values near 1 represent good reliability. Second, correlations between assessments of lameness were made (Kendall)[f] to see whether a significant relationship existed between day 0 (prior to intervention) and days 14, 28, and 42 (after intervention). Third, to measure whether any caregiver placebo effect was enhanced or attenuated with time, a matched pairs Wilcoxon signed rank test[g] was performed on measures of limb function. Fourth, to estimate the frequency (%) of a caregiver placebo effect, we evaluated each dog's change in GRF to the mean response from its caregiver. Thus, each dog generated a single data point (improved, no change, or worsened) for each type of evaluation (response feature analysis)[18,19] and the caregiver response was compared with the change in GRFs for each dog. Finally, to test whether any caregiver placebo effect was significant ($P < 0.05$), we used a Clopper-Pearson exact binomial test.[g]

We chose these methods because these data present several statistical challenges that preclude many typical data comparison techniques. Those challenges include that although each dog was evaluated during the intervention period (day 1 to 42) several times, the evaluations (eg, owner questionnaires) were not independent of each other. Some of the data were generated subjectively (eg, owner questionnaire) and created ordinal data and other data were objective (GRFs) and created continuous data, and not all dogs were evaluated by the same evaluators (ie, the force platform evaluated all dogs, but each owner only evaluated their own dog).

Results

Fifty-eight dogs, the placebo arm of the original NSAID study, were included in this study. When a change in GRF of ≥ 5% was used, most dogs had a status in limb function that did not change over the 42-day evaluation period. Improvement in limb function was documented by GRF in 7 of 58 (12.1%) dogs, and limb function had worsened in 5 (8.6%). When a change in GRF of ≥ 10% was used, only 1 of 58 (1.7%) dogs improved and 1 (1.7%) worsened. The agreement in lameness over time between various methods of assessments found a strong agreement for VI (0.96) and PVF (0.97) but poor agreement in the assessment of lameness over time for veterinarian assessment of lameness at a walk (0.18), veterinarian assessment of lameness at a trot (0.33), and owner assessment of lameness (0.37).

Correlations between objective measures of lameness were strong and significant. For example, for PVF, the Kendall τ for days 0 to 14, 0 to 28, and 0 to 42 was 0.83, 0.79, and 0.80, respectively ($P < 0.001$ at each time point). In contrast, correlations were low for subjective measures of lameness and were not significant. For owner assessment of lameness, Kendall τ for days 0 to 14, 0 to 28, and 0 to 42 was 0.19, 0.24, and 0.23, respectively ($P < 0.05$ at each time point). These

findings suggest a change in the assessment of lameness for owners and veterinarians. We found that this change in response was enhanced with time. Caregiver (both owners and veterinarians) responses significantly changed over time as they scored lameness even more improved on day 42, compared with day 14 or 28. The mean scores for the assessment of lameness over time for PVF and owners is shown graphically (**Figure 1**).

For the owner question addressing degree of lameness, 29 of 58 (50%) owners stated their dog was improved, 6 (10.3%) stated their dog's limb function had worsened, and the remainder stated their dog's limb function was unchanged. The caregiver placebo effect for owners evaluating their dog's lameness occurred 56.9% of the time (owner responded the dog had improved when the dog's GRFs were unchanged or had worsened, and owner responded the dog was unchanged when GRF had worsened).

For veterinarians examining the dog's lameness at a walk, 26 of 58 (44.8%) graded the dog as improved or less lame and 8 (13.8%) as worse or more lame during the intervention period, compared with days –7 and 0. When veterinarians examined the dog's lameness at a trot, 28 of 58 (48.3%) graded the dog as improved and 8 (13.8%) as worse. When veterinarians evaluated dogs for signs of pain on palpation, 26 of 58 (44.8%) graded the dog as having less signs of pain and 8 (13.8%) as having more signs of pain on palpation of the joint. For evaluation of dog posture, 10 of 58 (17.2%) were graded as improved and 5 (8.6%) were graded as worse. For willingness to raise the contralateral limb, 16 of 58 (27.6%) were graded as improved and 18 (31.0%) were graded as worse.

The caregiver placebo effect for veterinarians examining the dog at a walk occurred 39.7% of the time, whereas the frequency was 44.8% when examining the dog at a trot, 43.1% when examining the dog for signs of pain on palpation of the joint, 25.9% when evaluating the dog's posture, and 31.0% when examining the dog's willingness to raise the contralateral limb. The caregiver placebo effect for both owners and veterinarians was significant ($P < 0.001$) at all postintervention time points. Caregiver responses suggested patient improvement from day 0 at all time points, which demonstrates a caregiver placebo effect.

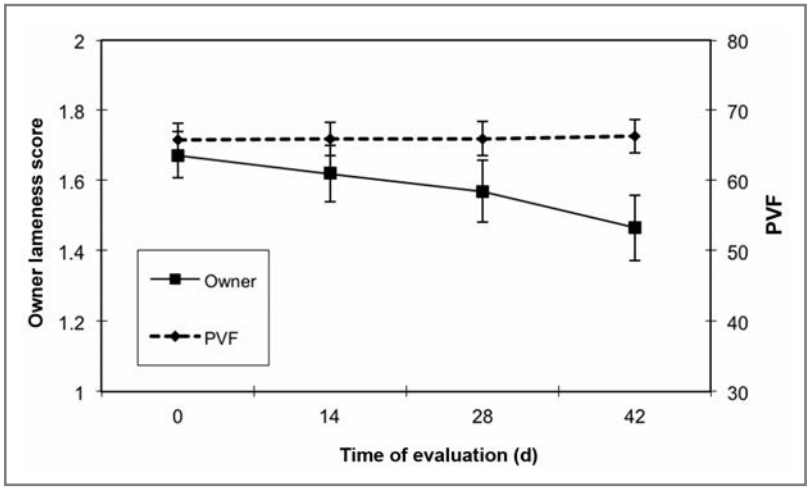

Figure 1—Mean ± SE lameness evaluation score for 58 dogs with lameness secondary to osteoarthritis evaluated over time as generated by owners and force platform (PVF). These data were not normally distributed.

Discussion

In the present study, a caregiver placebo effect was common in the evaluation of response to treatment for osteoarthritis in both pet owners and veterinarians. Force platform gait analysis allowed an objective outcome measure for evaluation of lameness in dogs with osteoarthritis. Quantifying the caregiver placebo effect is important because treatments may be perceived as more effective than they are. In fact, if we accept the presence of a caregiver placebo effect, it may be that the success rates of many interventions for osteoarthritis in dogs are overstated. This is because a medication effect can be defined as the response after administration of a drug minus the placebo response.[13] This may not be routinely considered when reporting the success rate of an intervention to a student, pet owner, or colleague. In view of our results, a caregiver placebo effect should be considered when interpreting owner and veterinary reports of patient response to treatment. Overlooking a caregiver placebo response can lead to increased patient morbidity and increased financial and time burden on the caregiver, and it diverts resources away from treatments that may benefit the patient.

We present data to estimate this effect for osteoarthritis in dogs; it might be different if different questions were asked or for other disease processes. However, the caregiver placebo effect we found is similar to that reported for caregivers of children with attention-deficit hyperactivity disorder, for which it has been reported that 58% of parents and 46% of teachers are subject to a caregiver placebo effect.[14]

The data of the present study arguably underestimate the caregiver placebo effect for owners and veterinarians, considering that caregivers did not have to match limb function exactly and were aware of the fact that 50% of all dogs would be in a placebo-treated group. Another potential contribution to our data being an underestimate of the caregiver placebo effect for owners is that owners received a financial incentive ($500) to participate in this study. If they had actually paid for a treatment, it is possible they could have experienced cognitive dissonance. Cognitive dissonance is an uncomfortable feeling caused by holding 2 contradictory ideas simultaneously. People try to reduce this disagreement in their mind by justifying or rationalizing their attitudes, beliefs, and behaviors. This could occur if an owner had to pay for a treatment and was told that the treatment would be effective. The owner may believe their dog should get better and ultimately dismiss evidence that the treatment was ineffective or not as effective as they had believed.

In the present study, we used GRFs as the gold standard for limb function because it has been shown to be an ob-

jective and sensitive measure of limb use in dogs.[15] The GRF data remained very consistent from the preintervention through all postintervention time points. However, this does not necessarily mean that GRFs accurately tell us how much a patient's joint hurts or how much it affects the patient's quality of life. This is why we would suggest that when designing clinical investigations, it is important to consider including both subjective and objective outcome measures. To achieve our study objective, information gathered from the owner via questionnaire had to be compared with some objective measure of limb function. Given the objective and sensitive nature of measuring GRFs via force platform gait analysis, it seemed like a reasonable choice. Use of a pedometer or accelerometer would have been another objective measure of patient function that could have been used and may have yielded different results.[16] We used an increase in both PVF and VI to document a change in limb function because these GRFs are inversely dependent on patient velocity. For example, if velocity were increased in a trial, PVF would generally increase but VI would generally decrease. In this study, there was an allowable velocity range (1.7 to 2.0 m/s), so a small difference in PVF or VI between evaluation periods could simply be from a difference in trial velocity within the allowable range. Requiring that both PVF and VI change in the same direction to define a change in limb function provides a greater assurance that the change in GRFs was associated with a change in patient function. This could also be controlled by normalizing the GRFs to stance time.

Changes of 5% and 10% were selected as cutoffs because in several clinical investigations documenting the efficacy of an oral intervention for dogs with lameness from osteoarthritis, an improvement in function of 5% to 10% was noted.[3,4,12] We decided the GRFs had to increase during at least 2 of 3 postintervention time points to define improvement because one would expect an effective intervention for osteoarthritis to be effective at least 50% of the time. For the 5% and 10% cutoffs, we found that limb function changed in 20.7% and 3.4% of the cases, respectively. This suggests that the clinical sign of lameness from osteoarthritis over a 50-day period certainly can change, but a dramatic improvement or worsening should be considered unusual. These findings could be translated to the clinic. It seems we need to be cautiously optimistic if a patient's GRF changes by only 5% because the results show this occurs naturally. However, interventions that make a ≥ 10% change appear to be the most desirable because this an unusual natural change. To our surprise, it was very hard to find data where the degree of change in GRFs[17] (ie, degree of treatment response) was reported. In general, studies for osteoarthritis reported only mean change after intervention. With our findings in mind, it seems important to know the percentage of dogs that had GRFs improve by ≥ 5% and ≥ 10%. This would be similar to longitudinal studies for cancer treatments, where it is important to document that the intervention was, on average, better than placebo but also what was the probability of survival at 1 or 2 years.

A report of a placebo response by a caregiver of a dog with osteoarthritis is common.[5–12] The caregiver placebo response may be an explanation of why in some studies, pet owners and veterinarians underestimate lameness in dogs or there is a mismatch between the owner's report of their pet's performance and that of an objective outcome measure. For example, in a case series addressing lameness in dogs from a fragmented coronoid process, it was reported that caregivers stated the dog had improved more than what was found when measuring GRFs.[18] Change in caregiver response can also be credited to regression to the mean, where relatively high or low reports are followed by less extreme reports.[11] This phenomenon was well described by Brown et al[11] when they investigated the canine brief pain inventory to validate its ability to detect a response in dogs with lameness from osteoarthritis.

Studies with control groups help mitigate the caregiver placebo effect. Controls are needed to eliminate alternate explanations of experimental results. For example, a noncontrolled study may suggest that an intervention helped dogs with lameness from osteoarthritis. However, it may be that owners who were willing to have their pet participate in the clinical trial were more motivated to exercise their dogs once the study began. Thus, it is unknown whether the intervention helped the dogs or motivated owners changed the lifestyle of dogs once they entered the study. A controlled trial would balance the number of owners who exercised their dogs, thus removing this confounding variable. Scoring systems for ranking the strength of scientific evidence severely penalize studies without control groups.

The point of this study is not to suggest that measurement of GRF is the best or only way to document an effect when studying an intervention for patients with lameness from osteoarthritis. Several other outcome measures can be successfully used alone or in combination with GRF to document a treatment difference between groups. For example, a validated owner assessment tool could be used. However, more subjective assessment tools will include a caregiver placebo effect, so they will likely require the study of a larger number of animals. Owner and veterinary assessment tools are of particular importance when behaviors other than patient lameness are being considered.

The caregiver placebo effect for dogs with osteoarthritis appears to be approximately 57% for owners and 40% to 45% for veterinarians when they are questioned (owners) or visually evaluate (veterinarians) a dog's lameness. This caregiver placebo effect was enhanced with time. Veterinarians need to consider the caregiver placebo effect and all of the things that may influence it when interpreting owner responses, veterinary examination findings, and clinical research reports. In addition, findings from clinical trials that do not include a control group should be carefully translated to clinical practice.

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d. Advanced Mechanical Technology Inc, Watertown, Mass.
e. Sharon Software Inc, Dewitt, Mich.
f. JMP, version 9.0.0, SAS Institute Inc, Cary, NC.
g. R, version 2.8.1., R Foundation for Statistical Computing, Vienna, Austria. Available at: www.r-project.org/. Accessed Jul 8, 2009.

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Appendix 1

Descriptions provided to pet owners to assist them in grading of their pets' degree of lameness in a study of the caregiver placebo effect in evaluation of dogs with lameness from osteoarthritis.

Category	Description
Normal	No lameness
Mild	Slight stiffness and occasional lameness when walking; minimal licking of the affected joint; does not whimper or cry upon voluntary joint movement; rises from resting position with minimal difficulty; climbs steps or jumps up near normally; mild signs of pain when joint is moved (looking at joint and pulling away of limb)
Moderate	Increased stiffness or noticeable limping when walking; shortened steps; some licking of affected joint; occasional whimpering or yelp upon voluntary joint movement; slow to rise from resting position; sitting preferred over standing; reluctant to climb steps or jumps up; increased signs of pain when joint is moved (looking at joint and pulling away of limb)
Severe	Will not bear weight (carries affected leg); frequent licking of the affected joint; frequent whimpering or yelp upon voluntary joint movement; increased difficulty in rising from resting position; cannot climb steps or jumps up; will not allow person to handle joint (biting, growling, and pulling away of limb)

Appendix 2

Lameness scoring and criteria used for each grade of lameness.

Lameness grade	Definition
0	Normal
1	Mild subtle lameness with partial weight bearing
2	Obvious lameness with partial weight bearing
3	Obvious lameness with intermittent weight bearing
4	Full non–weight bearing