Topics in Drug Therapy

Systematic review of clinical trials of treatments for osteoarthritis in dogs

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Objective—To identify and critically evaluate the quality of evidence of the most commonly used pharmacologic, nutraceutical, and purported slow-acting drugs of osteoarthritis for the management of osteoarthritis in dogs by use of the FDA's evidence-based medicine scoring system.

Design—Systematic review.

Sample Population—16 clinical trials.

Procedures—A broad bibliographic search was performed prior to May 2006. Inclusion criteria focused on prospective trials evaluating commonly used medical treatment interventions for the management of osteoarthritis in dogs and published in peer-reviewed journals. The analysis consisted of the following: study design rating, quality factor rating, quantity rating, consistency rating, relevance to disease risk reduction rating, and cumulative strength of evidence ranking.

Results—4 trials evaluating meloxicam were rated as type I. Three trials evaluating carprofen were rated as type I, and 2 trials were rated as type III. One trial evaluating each of the following agents was rated as type 1: etodolac; P54FP; polysulfated glycosaminoglycan; and a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate. Two trials evaluating pentosan polysulphate and 2 trails evaluating green-lipped mussels were rated as type I. One trial evaluating hyaluronan was rated as type III.

Conclusions and Clinical Relevance—A high level of comfort exists for meloxicam that the claimed relationship is scientifically valid and that its use is clinically efficacious for the treatment of osteoarthritis in dogs. A moderate level of comfort exists for carprofen; etodolac; pentosan polysulphate; green-lipped mussels; P54FP; polysulfated glycosaminoglycans; and a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate. An extremely low level of comfort exists for hyaluronan. (*J Am Vet Med Assoc* 2007;230:514–521)

Osteoarthritis in dogs is a slowly progressive, degenerative, and dynamic disease, which can cause notable signs of pain, lameness, and disability. Reportedly, 20% of the canine population > 1 year old have some degree of osteoarthritis.[1,2] Multiple etiologies have been suspected of contributing to the formation of osteoarthritis, including defective articular cartilage structure and biosynthesis, joint trauma, joint instability, congenital and developmental abnormalities, and inflammatory conditions.[2,3] Management of osteoarthritis typically involves a multimodal approach, which can include 1 or more of the following: activity control; weight management; nutritional support; physical therapy; and administration of nonsteroidal anti-inflammatory drugs, analgesic medications, nutraceuticals, and purported SADOAs. The SADOAs are subdivided into symptomatic, slow-acting drugs for treatment of osteoarthritis and DMOADs.[4,5] Surgical management may be an option for treatment of osteoarthritis in certain cases by treating the underlying condition or acting as a salvage procedure, such as with a total hip replacement.

Abbreviations

SADOA	Slow-acting drug of osteoarthritis
DMOAD	Disease-modifying osteoarthritic drug
EBM	Evidence-based medicine
RDRR	Relevance to disease risk reduction

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During the past decade, numerous therapeutic agents have been introduced and used for the treatment of osteoarthritis in dogs with various levels of effectiveness.[4,6-21] To complicate matters, these therapeutic agents vary widely regarding their documented efficacy and safety.[4,22] This discrepancy creates a difficult situation for clinicians who want to make an informed clinical decision with their clients and for their patients. The establishment of peer-reviewed, quality evidence regarding these interventions is desired. Appropriate assessment of clinical trials is an important element when grading evidence. Proper outcome assessment of clinical trials for the management of osteoarthritis in small animals is beyond the scope of our study but has been reported.[4]

The purpose of the systematic review reported here was to identify and critically evaluate the quality of evidence of the most commonly used pharmacologic, nutraceutical, and purported SADOAs for the management of osteoarthritis in dogs by use of the FDA's EBM scoring system.

Materials and Methods

Search strategy

A broad bibliographic search was performed prior to May 2006 through multiple online databases (Cab Abstracts, Medline, PubMed, and Veterinary Information Network). Search terms included the following and, if applicable, included both common and trade names: carprofen[a]; ketoprofen[b]; etodolac[c]; meloxicam[d]; tepoxalin[e]; deracoxib[f]; aspirin[g]; piroxicam[h]; firocoxib[i]; glucosamine; chondroitin sulfate; a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate[j]; green-lipped mussel[k]; polysulfated glycosaminoglycan[l]; pentosan polysulphate[m]; hyaluronan[n]; P54FP[o] (an extract of Indian and Javanese turmeric [*Curcuma domestica* and *Curcuma xanthorrhiza*, respectively]); diacerhein; nutraceutical; disease modifying; canines; dogs; and osteoarthritis. Additionally, bibliographies of book sections and articles that reviewed and discussed the management of osteoarthritis in dogs were evaluated for relevant citations.

Inclusion criteria

Prospective clinical trials in dogs that evaluated the use of the aforementioned medical interventions for the management of osteoarthritis published in peer-reviewed journals were used in the systematic analysis. Abstracts were not included in the analysis. Only studies published in English were reviewed. The focus of our evaluation was on the management of osteoarthritis in dogs by evaluating the subjective and objective clinical outcome measures and excluded other intended uses of these medical interventions such as pre- or postoperative pain management and effects on gross or histologic evaluation. Clinical trials evaluating concentrations of inflammatory mediators as response variables were not included in the systematic evaluation because presently, an association between these agents and clinical signs of osteoarthritis has not been detected. Clinical trials that met the inclusion criteria were reviewed by the authors and assessed for study design, medical interventions used, outcome measures, and subjective and objective responses of patients.

Reporting of quality assessment and qualitative results

The FDA's evidence-based ranking system for scientific data was adapted and used for study rating and ranking.[23] This ranking system is a science-based systematic evaluation of the strength of the evidence behind a statement and is based on the Institute for Clinical Systems Improvement as adapted by the American Dietetic Association.[23] This evidence-based classification model has also been reviewed by the Agency for Healthcare Research and Quality.

Briefly, 3 ratings are used for study evaluation as follows: a rating for study design, a rating for study quality, and a group agent rating for the strength of the entire body of evidence. A final rank of the scientific evidence is decided on the basis of classifications from the 3 rating systems.[23] This system does not use the terms rate and rank interchangeably.

Study design rating—Each study is initially classified or rated according to the type of experimental design, which is independent of study quality. The FDA's 4-component rating is as follows: randomized, controlled intervention trials (study design type I); prospective observational cohort studies (study design type II); nonrandomized intervention trials with concurrent or historical controls or case-control studies (study design type III); and cross-sectional studies or analyses of secondary disease endpoints in intervention trials or case series (study design type IV).

Quality factor rating—A quality factor rating (+, ∅, or –) is then assigned. A rating of + indicates that the study has adequately addressed the issues of scientific quality relating to data collection, analysis, inclusion and exclusion, bias, and generalizability. A rating of ∅ indicates that some uncertainties exist relating to the scientific quality. A rating of – indicates that the study has not adequately addressed issues of scientific quality.

Total body of evidence rating—Studies are further rated on 3 factors according to their total body of evidence and ranked according to quantity, consistency, and RDRR.

Quantity rating (***, **, or *) considers the number of studies and the total number of individuals studied to arrive at a conclusion as to the generalizability of the findings to the target population. A quantity rating of *** indicates that the number of studies (type I, type II, and + only) and individuals tested are sufficiently large enough to comfortably generalize to the target population. A quantity rating of ** indicates that there is a sufficient number of studies and individuals but uncertainties remain regarding generalizing. A quantity rating of * indicates that the number of studies and individuals are insufficient for generalization.

Consistency rating (***, **, or *) considers whether studies with both similar and different designs report similar findings. A consistency rating of *** indicates that a sufficient number of studies of high quality (+) that are type I or II studies have consistent results. A consistency rating of ** indicates that there is a moderate consistency across all study types, and a consistency rating of * indicates that the results are inconsistent.

An RDRR in the target subgroup rating is assigned (***, **, or *). An RDRR rating of *** indicates that the magnitude of the effect observed in the studies (type I, type II, and + only) is physiologically meaningful and achievable. An RDRR rating of ** indicates that there is some suggestion that the effect will be physiologically meaningful and achievable, and an RDRR rating of * indicates that the magnitude of the effect in the studies is not likely to be physiologically meaningful or achievable.

Strength of evidence ranking—Ranking the strength of evidence of a particular study requires evaluation of each individual rating. The 4 predominant ranking levels used for the purposes of our study include high level of comfort, moderate level of comfort, low level of comfort, and extremely low level of comfort.

A high level of comfort ranking indicates that qualified scientists agree that a specific claim is scientifically valid. This highest level of ranking indicates an extremely low level of probability that new scientific data will overturn the conclusion that the relationship in question is valid or significant. This rank is based on relevant, high-quality studies of study design types I and II with sufficient numbers of individuals, resulting in a high degree of confidence that the results are relevant to the target population.

A moderate level of comfort ranking describes a relationship as promising but not definitive. The claim is based on relevant, high- to moderate-quality studies of study design type III and higher and sufficient numbers, resulting in a moderate degree of confidence that the results could be extrapolated to the target population.

A low level of comfort ranking indicates a low consistency. The relationship is based on moderate- to low-quality studies of study design type III and has insufficient numbers of individuals tested, resulting in a low degree of confidence that the results could be extrapolated. Uncertainties would also exist as to whether the proposed benefits would be physiologically meaningful and achievable.

An extremely low level of comfort ranking has extremely low consistency and is based on moderate- to low-quality studies of design type III and insufficient numbers, resulting in an extremely low degree of confidence that the results could be extrapolated.

Power analysis

After the evidence-based ranking scoring was completed, all studies were evaluated for the incorporation of a power analysis component. If this was absent, an attempt to perform post hoc power analyses from the reported data was made by use of a previously reported method.[24] Studies that provided a mean and SD were included in the power analysis. If median and interquartile ranges were reported, the mean was taken as the median and the SD was calculated by use of the following formula: (upper quartile – lower quartile)/1.35. Power (1 – beta) was calculated at a 20%, 50%, and 80% treatment effect. This was performed by calculating a 20%, 50%, or 80% change (decrease or increase) from baseline in the primary outcome variable (such as visual analog score or peak vertical ground reaction force). Additionally, the number of dogs needed to achieve a power ≥ 0.80 with a 20%, 50%, or 80% treatment effect was determined (Table 1).

Table 1—Power (1 – beta) at a 20%, 50%, and 80% treatment effect and the number of dogs required to achieve ≥ 0.80 power with a 20%, 50%, or 80% treatment effect (Nreq) calculated for 15 prospective clinical trials evaluating the use of pharmacologic and nutraceutical agents for treatment of osteoarthritis in dogs.

Clinical trial	Clinical trial endpoint	Power at 20% treatment effect (Nreq)	Power at 50% treatment effect (Nreq)	Power at 80% treatment effect (Nreq)
Moreau et al[6]	Subjective and force plate (objective)	0.13 (152)	0.998 (41)	1 (13)
Brandt et al[20]	Force plate (objective)	ID	ID	ID
Lipscomb et al[10]	Subjective and force plate (objective)	ID	ID	ID
Schneider et al[11]	Force plate (objective)	ID	ID	ID
Holtsinger et al[12]	Subjective	0.93 (65)	1 (13)	1 (14)
Innes et al[15]	Subjective	ID	ID	ID
Vasseur et al[13]	Subjective and force plate (objective)	0.42 (85)	0.998 (12)	0.998 (12)
Budsberg et al[14]	Subjective and force plate (objective)	ID	ID	ID
Peterson and Keefe[7]	Subjective	ID	ID	ID
Doig et al[8]	Subjective	ID	ID	ID
Bierer and Bui[18]	Subjective	1 (< 7)	1 (< 7)	1 (< 7)
Bui and Bierer[17]	Subjective	0.19 (82)	0.8 (14)	0.99 (6)
de Haan et al[19]	Subjective	ID	ID	ID
Read et al[16]	Subjective	0.22 (76)	0.95 (22)	1 (8)
Nell et al[9]	Subjective	0.55 (64)	0.99 (11)	1 (5)

ID = Insufficient data.

Results

The literature search was concluded prior to May of 2006. Three hundred eighty-one references were identified, of which only 16 clinical trials met the inclusion criteria. The 16 clinical trials covered 9 pharmacologic or nutraceutical agents and reported data on 1,367 dogs.[6-21] There were 13 prospective, randomized trials[6-9,12-19,21] and 3 prospective, nonrandomized trials.[10,11,20] Results of 13 studies[6-14,16-19] indicated a positive effect with treatment using 1 or more of the described agents, results of 2 studies[15,20] indicated no effect with treatment, and results of 1 study[21] indicated a positive treatment effect subjectively but not objectively. No clinical trials that met the inclusion criteria were identified for firocoxib,[i] tepoxalin,[e] deracoxib,[f] piroxicam,[h] ketoprofen,[b] aspirin,[g] or diacerhein. The total body of evidence rating for each medical intervention is summarized (Table 2). If the consistency rating was not able to be determined, it was because only 1 study was evaluated.

Four trials[6-9] included information on 270 dogs regarding the use of meloxicam[d] to treat osteoarthritis (Table 2). All 4 studies were prospectively designed, randomized, and rated as type I studies. Results of all 4 studies indicated a positive effect subjectively alone[7-9] or objectively and subjectively.[6] Quality factor ratings for all 4 studies were +.

Five trials[6,10-13] included information on 163 dogs regarding the use of carprofen[a] to treat osteoarthritis. All 5 trials were prospectively designed, but only 3 were randomized.[6,12,13] Results of all 5 studies indicated a positive effect either subjectively alone,[12] objectively alone,[11] or both subjectively and objectively.[6,10,13] Three studies[6,12,13] were rated as type I studies and 2 studies[10,11] were rated as type III studies. A quality factor rating of + was given to 3 studies,[6,12,13] and a quality factor rating of ∅ was given to 2 studies.[10,11]

One trial[14] included information on 66 dogs regarding treatment of osteoarthritis with etodolac.[c] That study was prospective, randomized, rated as a type I study, and given a quality factor rating of +. A positive effect was identified both subjectively and objectively.

Two clinical trials[15,16] describing 47 dogs were identified relating to the use of the proposed DMOAD pentosan polysulphate.[m] Both studies were prospective in design, were randomized, and received a type I rating. Additionally, both studies received a quality factor rating of ∅. Subjective results of 1 study[16] indicated a positive effect, and subjective results of the other study[15] indicated no positive effect.

Two clinical trials[17,18] included information on 62 dogs regarding the use of green-lipped mussels[k] (*Perna canaliculus*) for the treatment of osteoarthritis. Both studies were prospective and randomized in design and received a type I rating. Additionally, results of both studies subjectively indicated a positive effect, and a quality factor rating of ∅ was given to both studies.

One trial included information on 54 dogs regarding the use of P54FP[o] to treat osteoarthritis.[21] That study was prospective in design, randomized, and rated as a type I study. A quality factor rating of + was given, and a positive treatment effect was achieved subjectively but not objectively.

Table 2—Results of a systematic review of clinical trials evaluating various pharmacologic and nutraceutical agents for treatment of osteoarthritis in dogs by use of the FDA's EBM scoring system.

Agent rating	Study design rating	Quality factor rating	Quantity rating	Consistency rating	RDRR ranking	Strength of evidence
Meloxicam[d]	4 studies: type I	4 studies: +	***	***	***	High level of comfort
Carprofen[a]	3 studies: type I 2 studies: type III	3 studies: + 2 studies: ∅	**	**	**	Moderate level of comfort
Etodolac[c]	1 study: type I	1 study: +	*	Unable to rate	***	Moderate level of comfort
Pentosan polysulphate[m]	2 studies: type I	2 studies: ∅	*	*	**	Moderate level of comfort
Green-lipped mussels[k]	2 studies: type I	2 studies: ∅	*	**	**	Moderate level of comfort
P54FP[o]	1 study: type I	1 study: +	*	Unable to rate	**	Moderate level of comfort
Polysulfated glycosaminoglycan[l]	1 study: type I	1 study: ∅	*	Unable to rate	**	Moderate level of comfort
Chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate[j]	1 study: type I	1 study: +	*	Unable to rate	**	Moderate level of comfort
Hyaluronan[n]	1 study: type III	1 study: –	*	Unable to rate	*	Extremely low level of comfort

Scoring system classifies evidence within trials on the basis of multiple rating scores and a final ranking score. Study design is rated as follows: randomized, controlled intervention trials (type I); prospective observational cohort studies (type II); nonrandomized intervention trials with concurrent or historical controls or case-control studies (type III); and cross-sectional studies, analyses of secondary disease endpoints in intervention trials, or case series (type IV). Quality is rated as follows: + = the study has adequately addressed the issues of scientific quality relating to data collection, analysis, inclusion and exclusion, bias, and generalizability; ∅ = some uncertainties exist relating to the scientific quality; and – = the study has not adequately addressed issues of scientific quality. Quantity is rated as follows: *** = the number of studies (type I, type II, and + only) and individuals tested is sufficiently large enough to comfortably generalize to the target population; ** = there is a sufficient number of studies and individuals, but uncertainties remain regarding generalizing; and * = the number of studies and individuals is insufficient for generalization. Consistency is rated as follows: *** = a sufficient number of studies of high quality (+) that are type I or II have consistent results; ** = there is a moderate consistency across all study types; and * = the results are inconsistent. Relevance to disease risk reduction is rated as follow: *** = the magnitude of the effect observed in studies (type I, type II, and + only) is physiologically meaningful and achievable; ** = there is some suggestion that the effect will be physiologically meaningful and achievable; and * = the magnitude of the effect in the studies is not likely to be physiologically meaningful or achievable. A high level of comfort ranking is based on relevant, high-quality studies of study design types I and II with sufficient numbers of individuals, resulting in a high degree of confidence that the results are relevant to the target population. A moderate level of comfort is based on relevant, high- to moderate-quality studies of study design type III and higher and sufficient numbers, resulting in a moderate degree of confidence that the results could be extrapolated to the target population. A low level of comfort is based on moderate- to low-quality studies of study design type III and has insufficient numbers of individuals tested, resulting in a low degree of confidence that the results could be extrapolated. An extremely low level of comfort ranking is based on moderate- to low-quality studies of study design type III and insufficient numbers, resulting in an extremely low degree of confidence that the results could be extrapolated.

Unable to rate = Only 1 study was evaluated.

One trial[19] was identified that provided information on the treatment of osteoarthritis in 63 dogs by use of polysulfated glycosaminoglycan.[l] The study was prospective and randomized in design and received a type I rating. Results of the study subjectively indicated a positive effect, and a quality factor rating of ∅ was given.

One trial[6] describing 19 dogs was identified on the use of a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate[j] for the proposed use of improving clinical signs associated with osteoarthritis and preventing the degenerative process. The study design was prospective, randomized, and received a type I rating. Additionally, results of the study indicated no improvement subjectively or objectively. A + quality factor rating was given.

One trial was identified describing 20 dogs addressing intra-articular hyaluronan[n] injections and its effect on the progression of osteoarthritis.[20] This prospective, nonrandomized study was rated as a type III study and was given a quality factor rating of –. No clinical improvement or preventative effects were identified subjectively.

Two[12,18] of 7 studies for which a post hoc power analysis was performed achieved > 0.80 power at a 20% treatment effect (Table 1). All studies[6,9,12,13,16-18] for which a post hoc power analysis was performed achieved > 0.80 power at 50% and 80% treatment effects. Power analyses could be performed in 2[6,9] of 4 studies involving meloxicam.[d] Three[6,12,13] of the 5 studies for carprofen[a] permitted power analyses of data. For the etodolacc study, there were inadequate data to calculate power. For pentosan polysulphate,[m] 1[16] of the 2 studies provided adequate data to perform a power analysis. Both studies[17,18] involving green-lipped mussels[k] provided sufficient data to calculate power. One study,[21] evaluating P54FP,[o] included a power analysis component of data and therefore was not subject to post hoc power analysis. The study[19] evaluating polysulfated glycosaminoglycans[l] provided insufficient data to calculate power. The study[6] evaluating a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate[j] provided sufficient data to calculate power. Lastly, the study[20] evaluating intra-articular hyaluronann provided insufficient data to calculate power.

Discussion

As the treatment options for osteoarthritis in dogs evolve and expand, the need to critically evaluate the research associated with these options becomes increasingly important. Evidence-based medicine can assist the clinician with the decision-making process.[25] The systematic evaluation of 16 clinical trials[6-21] involving 9 pharmacologic and nutraceutical interventions addressing osteoarthritis in dogs was performed. The overall limited number of studies made it difficult with some interventions to evaluate and rate the total body of evidence, particularly when a final ranking of evidence was assigned where only 1 study was identified. Within each treatment category, the studies were divided on the basis of whether the authors detected a subjective or objective positive effect or no effect. Of the 16 clinical trials, 13 trials[6-14,16-19] reported a positive treatment effect, 2 trials[15,20] reported no treatment effect, and 1 trial[21] reported a positive treatment effect subjectively but not objectively. The 2 clinical trials in which no treatment effect was detected provided insufficient data to calculate power.

The FDA's EBM classification scheme does not segregate between clinical trials that use various endpoints of evaluation. For example, clinical trials that evaluated only subjective measures and clinical trials that exclusively evaluated objective measures were compared similarly with clinical trials that measured both subjective and objective outcomes. The decision was made by the authors not to modify this attribute for the simple reason of not adding to the intricacy of an already detailed evaluation system. When describing whether an agent has a high, moderate, low, or extremely low level of comfort, the recommendation is directed at the comfort of the confidence and scientific validity in the study or studies' results. Additionally, the comfort level was determined on the basis of a vote-counting method of meta-analysis because of the overall limited number of studies.

In our systematic review, 4 studies on use of meloxicam[d] received a first-level rank, suggesting that a high level of comfort exists that the claimed relationship is scientifically valid and can reduce the clinical signs of osteoarthritis. All 4 studies were type I studies, received the highest rating scores, and reported a positive effect subjectively[6] or both subjectively and objectively.[6-9] Current reported adverse effects are low and predominantly include gastrointestinal tract disturbances.[6,8,9,26] Presently, a high level of comfort exists for meloxicam[d] that the claimed relationship is scientifically valid and that its clinical use to treat osteoarthritis in dogs can be efficacious.

Regarding carprofen,[a] a second-level rank of scientific evidence was determined such that a moderate level of comfort exists supporting that the substance and disease relationship is scientifically valid and carprofen[a] can relieve the clinical signs of osteoarthritis. Cumulatively, the carprofen[a] group in comparison had the highest number of studies[6,10,11,13] that were objectively evaluated, although 2[10,11] of those studies were type III studies. Clinically, use of carprofen[a] in dogs has one of the longest track records in the United States, predominantly attributable to the duration it has been on the market. Reported adverse effects have been few with the most common being gastrointestinal tract disturbances.[11,12,27-29] Although in 1 study,[30] idiosyncratic hepatocellular toxicosis was detected, most dogs in that report recovered after discontinuation of carprofen[a] and administration of supportive care. By use of the EBM approach, a moderate level of comfort exists for carprofen[a] that the claimed relationship is scientifically valid and that its use can be clinically efficacious for the treatment of osteoarthritis in dogs.

Only 1 or 2 clinical trials met the inclusion criteria for the following medical interventions used for the treatment of osteoarthritis in dogs: etodolac[c]; pentosan polysulphate[m]; green-lipped mussels[k]; polysulfated glycosaminoglycan[l]; hyaluronan[n]; and a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate.[j] The limited number of studies

made use of these agents difficult to evaluate; however, the same evaluation standards were applied to all studies.

In evaluating the clinical evidence for etodolac,[c] 1 study was identified. That study was ranked as a type I study and results objectively and subjectively indicated a positive effect. Clinically, use of etodolac[c] in dogs is similar to carprofen[a] regarding the duration on the market. Although only 1 study was detected, etodolac[c] received a second-level ranking. Presently, a moderate level of comfort exists for etodolac[c] that the claimed relationship is scientifically valid and that its use can be clinically efficacious for the treatment of osteoarthritis in dogs. Additional controlled clinical trials are necessary to provide a more comprehensive assessment of etodolac[c] in the treatment of osteoarthritis in dogs.

Two clinical trials were identified describing the use of the proposed DMOAD, pentosan polysulphate,[m] for the treatment of osteoarthritis in dogs. The oral formulation of pentosan polysulphate[m] can be combined with a sodium salt or a calcium salt. The calcium formulation was developed to assist with absorption.[31] Results of studies in multiple species are promising, from enhancing the synthesis of hyaluronan[32] to assisting with reducing the loss of proteoglycans from articular cartilage.[33] Neither study reported any adverse affects. Both studies in our review were rated as type I studies, although results of the 2 studies were contradictory with results of 1 study[16] indicating a favorably positive effect subjectively and results of the other study[15] indicating no positive effect subjectively. Presently, a moderate level of comfort exists for pentosan polysulphate[m] that the claimed relationship is scientifically valid. With the contradiction of results and the low number of controlled clinical trials, additional studies are necessary to construct a scientifically sound recommendation.

Another substance in the DMOAD category, green-lipped mussels[k] administered as an oral formulation, has been proposed to alleviate and improve signs of osteoarthritis in dogs.[17] New Zealand green-lipped mussels have a quantitative composition of glycosaminoglycans, omega-3 fatty acids, amino acids, vitamins, and minerals.[17] Additionally, it has been suggested that the combination of these nutrients may act synergistically to reduce inflammation, limit cartilage breakdown, and support the regeneration of cartilage.[17,18] Two clinical trials were identified by use of green-lipped mussels[k] to treat osteoarthritis in dogs. Both clinical trials were scored as type I studies and received a second-level quality factor (∅) rating. Additionally, both studies reported a subjectively positive outcome. Adverse effects were not mentioned in either study. Presently, a moderate level of comfort exists for green-lipped mussels[k] that the claimed relationship is scientifically valid or is efficacious for clinical use to treat osteoarthritis in dogs. The limited number of controlled clinical trails and the lack of objective data make it difficult to make a definitive recommendation at this time.

The evaluation of P54FP[o] for the treatment of dogs with osteoarthritis was identified in 1 study. An extract of Indian and Javanese turmeric, P54FP[o] contains a number of ingredients including curcuminoids and essential oils.[21] The purported DMOAD has been documented to have antioxidant and anti-inflammatory properties.[34,35] The only adverse effect detected in 19 dogs treated with P54FP[o] was a malodor from the skin, urine, and feces. The study was rated as a type I study and received a + quality factor rating. Subjectively, a positive response was identified, but objectively, significance was not reached. Presently, a moderate level of comfort exists for P54FP[o] that the claimed relationship is scientifically valid. Although the study design in the trial was appropriate, additional studies are needed to make any accurate recommendations.

One clinical trial was found describing the use of a semisynthetic polysulfated glycosaminoglycan[l] (given IM), another proposed DMOAD, for the prevention and treatment of osteoarthritis in dogs. The study was rated as a type I study, had a second-level (∅) quality factor rating, and was subjectively evaluated. A slight clinical improvement was detected in dogs receiving polysulfated glycosaminoglycan,[l] compared with dogs receiving a placebo; however, the differences were not significant. No adverse effects were detected during the study. A moderate level of comfort exists for polysulfated glycosaminoglycan[l] that the claimed relationship is scientifically valid. The limited number of controlled clinical trails and lack of supportive data make it difficult to recommend at this time.

One study was identified describing the use of a combination of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate,[j] which is another proposed DMOAD, to reduce clinical signs and prevent the degenerative process of osteoarthritis in dogs. The study was rated as a type I study and had a quality factor rating of +. Subjectively and objectively, dogs receiving this agent had no significant improvement, compared with dogs receiving placebo. No adverse effects were reported. A moderate level of comfort exists that the claimed relationship is scientifically valid. The lack of response and the limited number of controlled clinical trials make it difficult to formulate any recommendations at this time.

One clinical trial was identified describing the treatment of osteoarthritis in dogs with intra-articular injections of hyaluronan.[n] No positive effects of treatment were identified objectively. This clinical trial was rated as a type III study and received the lowest level ranking. Adverse effects were not discussed in the study. On the basis of the current evidence, an extremely low level of comfort exists for hyaluronan[n] that the claimed relationship is scientifically valid or its clinical use to treat osteoarthritis in dogs is of any benefit. The limited number of controlled clinical trails and the current evidence make it difficult to recommend use of intra-articular injections of hyaluronan[n] to help treat osteoarthritis in dogs.

Greater than half of the publications did not report data in a way that would allow a retrospective power analysis to be performed. This suggests a lack of standardized data reporting and a possible deficiency in regard to data reporting. Readers who have access to summarized data may be more able to critically evaluate the published information. According to one author, a 20% effect can be loosely defined as one typically of interest in clinical studies, a 50% effect as one visible to the

naked eye, and an 80% effect as so stark that the study is probably unnecessary.[36] Unfortunately, studies that reported no significant difference among groups did not report data in such a way as to subject it to power analysis, making it difficult to determine whether there was truly no difference or whether a possible difference was missed because of poor power. Although the other publications did report a significant difference among groups, calculating power may be of benefit for future study planning and as a surrogate to evaluate the accuracy of the data. Some statisticians argue that power should not be calculated retrospectively.[37] However, a retrospective analysis can provide information for future study planning and also provide a perspective on the value of publications as a conglomerate and has been used successfully in other publications.[38,39]

Limitations of our study could include several biases (publication, selection, language, observation, detection, and attrition), thereby reducing the validity of the target publications or our systematic review. Selection bias can be a factor if studies are included that are not properly randomized or if studies that qualify are not included. This is somewhat unlikely in the study reported here because 13[6-9,12-19,21] of the 16 studies were appropriately randomized. The lack of incorporation of foreign written studies introduced a language bias in our study. Observational bias may play a role because some would argue that the scoring systems are subjective and it is impossible to blind reviewers. Detection bias can influence a study if the outcome assessors (investigators or owners) are not unaware of the treatment. Results of our study may have been influenced by detection bias because only 9[6,12-19] of 15 studies were appropriately blinded. Additionally, deviations from protocol, patient withdrawal, or loss to follow-up can introduce attrition bias. Only 1 study[15] included information regarding client compliance. Therefore, deviations from protocol could not be identified, although most studies reported patients that were withdrawn or lost to follow-up.

During the past 2 decades, numerous treatment options have become available to the clinician for the management of osteoarthritis in dogs. Ultimately, the decision is based on a multiple-treatment approach, controlled clinical data, clinical experience, patient response, and client factors such as cost and willingness to medicate. The cost-benefit ratio for some clients is a huge factor regarding the use of medical interventions. This ratio was beyond the scope of our study, but some decisions are simply made on the basis that if giving the treatment does not hurt a patient, finances are not a limiting factor, compliance can be ensured, and the treatment may work, then the decision to use a certain treatment is performed. Follow-up of efficacy with these cases is strictly subjective, being that evaluation is performed by the owners at home or by a veterinarian during examination.

Presently, the strongest evidence available for the medical treatment of clinical signs associated with osteoarthritis in dogs is mostly limited to nonsteroidal anti-inflammatory drugs. Additional controlled studies in all groups of medical treatments are needed especially in the group of SADOAs. Management of osteoarthritis in dogs is a lifetime commitment, involves a multimodal approach, and is aimed at reducing pain and improving mobility and quality of life. By increasing our understanding of osteoarthritis and the ever-developing medical treatments, we as a profession will be able to provide multiple options for our patients and clients aimed at the ultimate goal, a good quality of life.

a. Carprofen, Pfizer Animal Health, Exton, Pa.
b. Ketoprofen, Fort Dodge Animal Health, Fort Dodge, Iowa.
c. Etodolac, Fort Dodge Animal Health, Fort Dodge, Iowa.
d. Meloxicam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
e. Tepoxalin, Schering-Plough Animal Health Corp, Union, NJ.
f. Deracoxib, Novartis Animal Health US Inc, Greensboro, NC.
g. Aspirin, Bayer Corp, Myerstown, Pa.
h. Piroxicam, EGIS Pharmaceuticals Ltd, Budapest, Hungary.
i. Firocoxib, Merial Ltd, Mississauga, ON.
j. Cosequin DS, Nutramax Laboratories Inc, Edgewood, Md.
k. Glycoflex, Vetri-Science Laboratories of Vermont, Essex Junction, Vt.
l. Adequan, Luitpold Pharmaceuticals Inc, Shirley, NY.
m. Cartrophen Vet, Biopharm Australia Pty Ltd, Bondi Junction, New South Wales, Australia.
n. Hyaluronan, Advanced Medical Optics Uppsala AB, Uppsala, Sweden.
o. P54FP, Phytopharm plc, Godmanchester, Cambridgeshire, United Kingdom.

References

1. Johnson SA. Osteoarthritis: joint anatomy, physiology, and pathobiology. *Vet Clin North Am Small Anim Pract* 1997;27:699–723.
2. Roush JK, McLaughlin RM, Radlinsky MG. Understanding the pathophysiology of osteoarthritis. *Vet Med* 2002;97:108–117.
3. McLaughlin RM. Management of chronic osteoarthritic pain. *Vet Clin North Am Small Anim Pract* 2000;30:933–949.
4. Budsberg SC. Outcome assessment in clinical trials involving medical management of osteoarthritis in small animals. *Vet Clin North Am Small Anim Pract* 1997;27:815–823.
5. Lequesne M, Altman R, Bellamy N, et al. Guidelines for testing slow acting drugs in OA (SASOA). *J Rheumatol* 1994;21:65–71.
6. Moreau M, Dupuis J, Bonneau NH, et al. Clinical evaluation of a nutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *Vet Rec* 2003;152:323–329.
7. Peterson KD, Keefe TJ. Effects of meloxicam on severity of lameness and other clinical signs of osteoarthritis in dogs. *J Am Vet Med Assoc* 2004;225:1056–1060.
8. Doig PA, Purbrick KA, Hare JE, et al. Clinical efficacy and tolerance of meloxicam in dogs with chronic osteoarthritis. *Can Vet J* 2000;41:296–300.
9. Nell T, Bergman J, Hoeijmakers M, et al. Comparison of vedaprofen and meloxicam in dogs with musculoskeletal pain and inflammation. *J Small Anim Pract* 2002;43:208–212.
10. Lipscomb VJ, AliAbadi FS, Lees P, et al. Clinical efficacy and pharmacokinetics of carprofen in the treatment of dogs with osteoarthritis. *Vet Rec* 2002;150:684–689.
11. Schneider TA, Budsberg SC. Plasma and synovial concentrations of carprofen in dogs with chronic osteoarthritis. *Vet Comp Orthop Traumatol* 2001;14:19–24.
12. Holtsinger RH, Parker RB, Beale BS, et al. The therapeutic efficacy of carprofen (Rimadyl-v™) in 209 clinical cases of canine degenerative joint disease. *Vet Comp Orthop Traumatol* 1992;5:140–144.
13. Vasseur PB, Johnson AL, Budsberg SC, et al. Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal anti-inflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc* 1995;206:807–811.
14. Budsberg SC, Johnston SA, Schwarz PD, et al. Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. *J Am Vet Med Assoc* 1999;214:206–210.
15. Innes JF, Barr RS, Sharif BM. Efficacy of oral calcium pentosan

polysulphate for the treatment of osteoarthritis of the canine stifle joint secondary to cranial cruciate ligament deficiency. *Vet Rec* 2000;146:433–437.
16. Read RA, Cullis-Hill D, Jones MP. Systemic use of pentosan polysulphate in the treatment of osteoarthritis. *J Small Anim Pract* 1996;37:108–114.
17. Bui LM, Bierer TL. Influence of green lipped mussels (*Perna canaliculus*) in alleviating signs of arthritis in dogs. *Vet Ther* 2003; 4:397–407.
18. Bierer TL, Bui LM. Improvement of arthritic signs in dogs fed green-lipped mussel (*Perna canaliculus*). *Am Soc Nutr Sci* 2002; 132:1634S–1636S.
19. de Haan JJ, Goring RL, Beale BS. Evaluation of polysulfated glycosaminoglycan for the treatment of hip dysplasia in dogs. *Vet Surg* 1994;23:177–181.
20. Brandt KD, Smith GN, Myers SL. Hyaluronan injection affects neither osteoarthritis progression nor loading of the OA knee in dogs. *Biorheology* 2004;41:493–502.
21. Innes JF, Fuller CJ, Grover ER, et al. Randomised, double-blind, placebo-controlled parallel group study of P54FP for the treatment of dogs with osteoarthritis. *Vet Rec* 2003;152:457–460.
22. Boothe DM. Nutraceuticals in veterinary medicine. Part II. Safety and efficacy. *Compend Contin Educ Pract Vet* 1998;20:15–21.
23. US FDA Web site. Interim evidence-based ranking system for scientific data. Available at: www.cfsan.fda.gov/~dms/hclmgui4.html. Accessed May 16, 2005.
24. Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990;11:116–128.
25. Aragon CL, Budsberg SC. Applications of evidence-based medicine: cranial cruciate ligament injury repair in the dog. *Vet Surg* 2005;34:93–98.
26. Forsyth SF, Guilford WG, Haslett SJ, et al. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. *J Small Anim Pract* 1998;39:421–424.
27. Fox SM, Johnson SA. Use of carprofen for the treatment of pain and inflammation in dogs. *J Am Vet Med Assoc* 1997;210: 1493–1498.
28. Jenkins CC, Kanara EW. First-year clinical experience with Rimadyl (carprofen): assessment of product safety. *Pfizer Animal Health Technical Bulletin*, May 1998.
29. Fox SM, Campbell S. Update: two years (1997–1998) clinical experience with Rimadyl (carprofen). *Pfizer Animal Health Technical Bulletin*, August 1999.
30. MacPhail CM, Lappin MR, Meyer DJ, et al. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *J Am Vet Med Assoc* 1998;212:1895–1901.
31. Ghosh P. The pathobiology of osteoarthritis and the rationale for the use of pentosan polysulfate for its treatment. *Semin Arthritis Rheum* 1999;28:211–267.
32. Francis DJ, Hutadilok N, Kongtawelert P, et al. Pentosan polysulphate and glycosaminoglycan polysulphate stimulates the synthesis of hyaluronan in vivo. *Rheumatol Int* 1993;13:61–64.
33. Golding JC, Ghosh P. Drugs for osteoarthritis. The effects of pentosan polysulfate (SP54) on the degradation and loss of proteoglycans from articular cartilage in a model of osteoarthrosis induced in the rabbit knee joint by immobilation. *Curr Ther Res Clin Exp* 1983;33:173–184.
34. Ammon HPT, Wahl MA. Pharmacology of curcuma-longa. *Planta Medica* 1991;57:1–7.
35. Miquel J, Bernd A, Sempere JM, et al. The curcuma antioxidants: pharmacological effects and prospects for future clinical use. A review. *Arch Gerontol Geriatr* 2002;34:37–46.
36. Cohen J. *Statistical power analysis for the behavioral sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1998.
37. Levine M, Ensom MHH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy* 2001;21:405–409.
38. Maggard MA, O'Connel JB, Liu JH, et al. Sample size calculations in surgery: are they done correctly? *Surgery* 2003;134:275–279.
39. Freedman KB, Back S, Bernstein J. Sample size and statistical power of randomized, controlled trials in orthopedics. *J Bone Joint Surg Br* 2001;83-B:397–402.