Review
J Vet Intern Med 2013;27:1011–1019

Systematic Review of Nonsteroidal Anti-Inflammatory Drug-Induced Adverse Effects in Dogs

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The aim of this systematic review was to identify, assess, and critically evaluate the quality of evidence of nonsteroidal anti-inflammatory drug (NSAID)-induced adverse effects in dogs. Original prospective studies published in peer-reviewed journals in English (1990–2012) that reported data on the safety of NSAIDs administration in dogs were searched. For each study, design type (I, II, III, or IV) and assessment of quality (+, Ø, −) were rated. For each drug, quantity and consistency rating (***, **, *) and strength of evidence (high, moderate, low, or extremely low) were identified and evaluated. The strength of evidence was defined in terms of how applicable and relevant the conclusions were to the target population. Sixty-four studies met the inclusion criteria. Thirty-five (55%) research studies and 29 (45%) clinical trials were identified. A high strength of evidence existed for carprofen, firocoxib, and meloxicam; moderate for deracoxib, ketoprofen, and robenacoxib; and low for etodolac. Quality and consistency rating were as follows: carprofen (***/***), deracoxib (**/***), etodolac (*/unable to rate), firocoxib (***/**), ketoprofen (**/***), meloxicam (***/***), and robenacoxib (**/**), respectively. Adverse effects were detected in 35 studies (55%) and commonly included vomiting, diarrhea, and anorexia. Three studies (5%) reported a power analysis related to adverse effects of ≥80%. In randomized, placebo-controlled, blinded studies (n = 25, 39%), the incidence of adverse effects was not statistically different between treated and control dogs. Finally, most studies were not appropriately designed to determine the safety of NSAIDs, and involved a healthy nongeriatric population of research dogs.

Key words: Analgesia; Canine; Evidence-based medicine; Osteoarthritis; Pain.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesics in veterinary medicine.[1] After the introduction of preferential and selective cyclooxygenase (COX)-2 inhibitors, these drugs became even more popular for their anti-inflammatory, analgesic, and antipyretic effects.[1,2] NSAIDs are crucial in the treatment of acute pain, such as in the perioperative period, and are the cornerstone in the treatment of osteoarthritis (OA) and other chronic painful conditions.[3]

NSAIDs are associated with different levels of inhibition of both COX-isoforms, and for this reason, they might induce adverse effects that include gastric irritation, development of protein-losing enteropathy, renal damage, and prolongation of bleeding time.[4–9] Preferential and selective COX-2 inhibitor veterinary approved NSAIDs are thought to maintain important levels of constitutive COX-1 activity (COX-1-sparing effect) and have been postulated to be associated with fewer adverse events. However, this theory has not been proved in veterinary medicine and these newer drugs can still produce gastrointestinal (GI) adverse drug experience in dogs.[1,6,7,10] Indeed, the true incidence of adverse effects after NSAID administration in dogs remains unknown.[11]

Abbreviations:

APTT	activated partial thromboplastin time
BMBT	buccal mucosal bleeding time
COX	cyclooxygenase
FDA	Food and Drug Administration
GI	gastrointestinal
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
PT	prothrombin time
RPCB	randomized placebo-controlled blinded

The clinical relevance of adverse effects associated with NSAID administration in small animal clinical practice is of utmost importance because of their high level of usage, and the growing interest in pain management in veterinary medicine. Evidence-based medicine aims to help clinicians on the decision-making process with basis on robust publications.[12] Systematic reviews of the literature are instrumental for bridging research to health care practice by attempting to synthesize all the empirical evidence that meets prespecified eligibility criteria to answer a given research question.[13]

The aims of this systematic review were to (1) identify and critically evaluate the quality of evidence of NSAIDs-induced adverse effects in dogs through a systematic review by use of the Food and Drug Administration (FDA) ranking system for scientific data and (2) compare the incidence of adverse-related events between NSAID- and placebo-treated dogs in prospec-

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Submitted October 31, 2012; Revised April 8, 2013; Accepted May 14, 2013.

10.1111/jvim.12127

tive randomized placebo-controlled blinded (RPCB) studies.

Materials and Methods

A literature search was performed using the CAB abstracts, Google Scholar, and Pubmed online platforms. Search terms included the following in an "OR" or "AND" combination where deemed applicable: adverse effects; adverse events; analgesia; canine; carprofen; deracoxib; dog; etodolac; firocoxib; flunixin meglumine; GI; ketoprofen; ketorolac; meloxicam; NSAIDs; NSAIDs-induced; pain; robenacoxib; safety; tepoxalin; tolfenamic acid; toxicity; and vedaprofen. In addition, references of book sections and review articles on the use of NSAIDs in dogs were evaluated for relevant citations.

Prospective studies that evaluated, even as only part of the study design, the safety of NSAIDs administration in dogs, in the acute or chronic setting, published in the English language, and in peer-reviewed journals between 1990 and 2012 were included in the systematic review. Studies that evaluated the administration of NSAIDs alone, in association with other drugs, or both were included. Clinical trials that exclusively evaluated the efficacy/analgesic effects of these drugs, and that did not report adverse drug experiences, were not included.

The evaluation criteria were adapted from previously reported systematic reviews.[3,14] This system was based on the ranking system for scientific data produced by the US FDA, which in turn was modeled according to the Institute for Clinical Systems Improvement (adapted by the American Dietetic Association).[15] Detailed description of rating of study design type and assessment of quality of each study is provided in Table 1. Table 2 describes the criteria used for quantity and consistency ratings of each drug; and Table 3 shows the criteria used to assess the strength of evidence of each drug.

In addition, for assessment of quality, it was decided that only randomized controlled blinded studies would be classified as "+." Studies with questionable bias, or no control group, were classified as "Ø" (Table 1). The quantity ratings were based on the number of studies and the number of animals tested with a specific NSAID. Preferentially, a higher rating was given to clinical trials rather than research studies, indicating a greater ability to generalize and extrapolate the results to the target population. To classify consistency rating, consistent results were defined as the frequency with which outwardly detectable adverse effects occurred in a population. Outwardly detectable adverse effects were usually assessed by observational monitoring, physical examination, and noninvasive procedures. Consistency was not classified ("Unable to rate") when there were 3 or fewer studies available for that specific NSAID (Table 2). The strength of evidence was defined in terms of how applicable and relevant the conclusions of the entire body of evidence were to the target population (Table 3).

Overall, each paper was individually and independently rated by 1 observer (BPMS) for study design type and assessment of quality after critical examination of reported population, randomization, control group, and blinded evaluation of results.

Table 1. Criteria used for rating of study design type and assessment of quality of each study.

Study Design Type	Criteria
I	Randomized controlled blinded clinical trials
II	Randomized controlled intervention trials or prospective observational cohort studies
III	Nonrandomized intervention trials with concurrent/historical controls, case-control studies, or experimental data
IV	Cross-sectional studies, analyses of secondary endpoints in intervention trials or case series
Assessment of Quality	**Criteria**
+	Adequately considered factors affecting scientific quality, such as inclusion/exclusion, bias, ability to generalize, and data collection and analysis
Ø	Some uncertainties relating to whether the report adequately considered the above factors
–	Not adequately addressed the above factors

Corrections made after online publication June 19, 2013: Table 1 Criteria have been updated.

Table 2. Criteria used for quantity and consistency rating of studies using the same NSAID.

Quantity Rating	Criteria
***	Number of studies and number of animals tested in the studies of design types I and II that are of high quality (+) are sufficiently large to generalize the results to the target population
**	Number of studies and number of animals tested in the studies of design types I, II, and III of at least moderate quality (Ø) are adequate, but it is uncertain whether the results can be generalized to the target population
*	Number of studies and number of animals tested are too small for the target population
Consistency Rating	**Criteria**
***	Sufficient studies of design types I and II that are of high quality (+) and have consistent results; any inconsistencies are explained satisfactorily
**	Moderate consistency across all study levels
*	Results of the studies are inconsistent

Table 3. Criteria used to assess the strength of evidence produced by all studies using the same NSAID.

Strength	Criteria
High	Studies are relevant, high quality, type I and II, incorporating sufficient animals, and giving results that are relevant to the target population
Moderate	Studies are relevant, high-to-moderate quality, type III and higher, incorporating sufficient animals, and giving results that could be extrapolated to the target population with some confidence
Low	Studies are moderate-to-low quality, of study design type III, with insufficient animals. Results can be extrapolated to the target population only with low confidence
Extremely low	Studies are moderate-to-low quality, of study design type III, with insufficient animals. Results can be extrapolated to the target population only with extremely low confidence

Thereafter, the study was categorized by drug, meaning that studies evaluating multiple NSAIDs were distributed repeatedly across the different NSAIDs. After this, all papers related to each NSAID were classified for quantity and consistency rating to determine the collective strength of evidence of that specific NSAID. Quantity and consistency rating, and strength of evidence were classified by agreement between 2 observers (BPMS and PVMS). In case of disagreements, the 2 evaluators reviewed all the ratings for that drug until an agreement was reached. In addition, studies were searched for power analyses report; however, no posthoc power calculations were performed. The doses and duration of treatment in each study was recorded and taken into account for consistency rating.

A subgroup restricted to prospective RPCB studies was identified to compare if the incidence of adverse drug experiences between NSAID- and placebo-treated dogs was statistically significant.

Results

Sixty-four studies met the inclusion criteria and 14 NSAIDs were evaluated in this systematic review. Table 4 summarizes the results of study design type, assessment of quality, quantity and consistency rating, and strength of evidence for each NSAID. Using the classification system, a high strength of evidence existed for carprofen, firocoxib, and meloxicam; moderate for deracoxib, ketoprofen, and robenacoxib; and low for etodolac, respectively. Flunixin meglumine, ketorolac, licofelone, rofecoxib, tepoxalin, tolfenamic acid, and vedaprofen revealed an extremely low strength of evidence. In this systematic review, "adverse effects," "adverse events" and "adverse drug experience" were used interchangeably and were defined as any undesirable experience associated with the use of NSAIDs in a dog.

Overall, 35 (55%) research studies and 29 (45%) clinical trials were identified. Across all studies, outwardly detectable adverse effects in dogs treated with NSAIDs were reported in 35 (55%) of 64 studies and most commonly included vomiting (30), diarrhea (23), anorexia (11), lethargy (5), and melena (6). Less commonly, fecal blood (4), bleeding (3), colitis (3), abdominal pain (2), aggressiveness or behavior change (2), hypersalivation (2), polydipsia (3), polyuria (3), adipsia (1), constipation (1), icterus (1), skin reactions (1), and weight loss (1) were reported. The number in brackets represents the number of studies for which each clinical sign was observed at least once. The number of dogs involved was not reported consistently, and so estimates of the frequency of individual adverse drug experience in the treated population could not be ascertained. Sixty-two percent and 38% of the clinical and research trials, respectively, reported adverse events. The frequency at which adverse effects were recorded in each clinical trial is described in Table 5. Twenty-one research studies were identified where no

Table 4. Summary of the results of the review.

NSAID	Study Design Type	Assessment of Quality	Quantity Rating	Consistency Rating	Strength of Evidence	References
Carprofen	8 studies: type I 15 studies type II 1 study: type III 4 studies: type IV	17 studies: + 9 studies: Ø 2 studies: −	***	***	High	4,7,8,16–40
Deracoxib	1 study: type I 8 studies: type II 1 study: type IV	7 studies: + 3 studies: Ø	**	***	Moderate	9,17,20,21,23,24,41–44
Etodolac	3 studies: type II	2 studies: + 1 study: +	*	Unable to rate	Low	4,7,45
Firocoxib	2 studies: type I 5 studies: type II 3 studies: type IV	6 studies: + 4 studies: Ø	***	**	High	26,42,46–53
Flunixin meglumine	1 study: type II 2 studies: type III	1 study: + 1 study: Ø 1 study: −	*	Unable to rate	Extremely low	7,54,55
Ketoprofen	2 studies: type I 9 studies: type II 1 study: type III	7 studies: + 5 studies: Ø	**	***	Moderate	5,7,30,35,37,38,56–61
Ketorolac	1 study: type III	1 study: Ø	*	Unable to rate	Extremely low	37
Licofelone	1 study: type II	1 study: +	*	Unable to rate	Extremely low	10
Meloxicam	4 studies: type I 15 studies: type II 1 study: type III 1 study: type IV	15 studies: + 6 studies: Ø	***	***	High	7,17,20,23,29,31,38,42,50,56,59,60,62–70
Rofecoxib	1 study: type II	1 study: +	*	Unable to rate	Extremely low	10
Robenacoxib	3 studies: type I 1 study: type II	3 studies: + 1 study: Ø	**	**	Moderate	16,18,63,71
Tepoxalin	3 studies: type I	3 studies: +	*	Unable to rate	Extremely low	48,50,72
Tolfenamic acid	1 study: type I	1 study: +	*	Unable to rate	Extremely low	73
Vedaprofen	1 study: type IV	1 study: Ø	*	Unable to rate	Extremely low	69

Table 5. Prospective clinical investigations and reported incidence of dogs treated with an NSAID that developed at least 1 adverse drug experience.

NSAID Administered	Percentage of Dogs That Developed Outwardly Detectable Adverse Effects[†]	Total Number of Treated Dogs	Duration of NSAID Treatment (days)	Age of Dogs (range in years)	Reference
Firocoxib	2.9%	1002	40	0.5–16	53
Carprofen	3.8%	805	84	Adults[*]	8
Firocoxib or etodolac	2.4%	249	29	0.9–20	52
Firocoxib or carprofen	4.6%	218	30	0.6–19	26
Vedaprofen or meloxicam	16.8%	214	Up to 56	Unclear[*]	69
Robenacoxib or meloxicam	24.3%	140	15	0.5–7.5	63
Carprofen	4.5%	110	120	Mean of 9.3[*]	22
Carprofen or meloxicam	2.8%	71	60	1.5–12	31
Carprofen	8.6%	70	14	2.1–8.9	39
Meloxicam or ketoprofen	5%	60	1	0.3–12	59
Meloxicam	3.4%	59	84	6.3–12.6	62
Tolfenamic acid	0%	58	1	0.5–10	73
Carprofen or ketoprofen	0%	46	21	0.4–6.4	30
Firocoxib	36.6%	41	90	Elderly[*]	49
Meloxicam	25%	40	28	5.9–12.5	70
Ketorolac, ketoprofen or carprofen	0%	40	1	0.5–10	37
Meloxicam	0%	38	1–6	0.6–13	67
Deracoxib	23.5%	34	3	0.4–16	41
Robenacoxib or carprofen	9.4%	32	28	5.9–14.4	16
Carprofen or ketoprofen	0%	30	1	0.5–8	35
Carprofen	0%	26	5	0.25–13.5	28
Carprofen	18.2%	22	60	1–11	27
Ketoprofen	0%	22	1	0.5–3	5
Firocoxib	37.5%	16	90	Elderly[*]	47
Carprofen, deracoxib or meloxicam	0%	8	10	4–13	23
Carprofen	0%	6	30	0.6–12	33

*The range of the age was not specified.

[†]This percentage was calculated based on the available data retrieved from the papers. Therefore, bias might have been introduced attributable to any misinterpretation or unclear reporting of the results.

outwardly detectable adverse effects were reported,[19–21,24,29,32,36,40,42,61,64,66,68,72] including when NSAID administration occurred for ≥28 days.[10,38,43,45,51,57,58]

In all the studies included in the systematic review, 2 GI perforations were recorded. One occurred after accidental administration of a 2-fold recommended dosage of firocoxib,[46] while the 2nd case was recorded in a dog that was given a systemic NSAID and also being treated with a topical steroid during a clinical trial.[62] In addition, a retrospective study[6] (n = 29) and a case report[74] (n = 3) reported GI perforation in dogs after deracoxib administration.

Table 6 describes the number of animals treated with each NSAID in the clinical and research setting. Power analysis related to adverse effects was mentioned in 7 studies (5 research and 2 clinical studies), and deemed to be sufficient (≥80%) in 3 of them.[29,65,66] Insufficient power analysis (<80%) was reported in 4 studies.[17,23,32,62]

Twenty-five studies (39%) were included in the RPCB subgroup (16 studies [64%] research; 9 studies [36%] clinical trials). This subgroup was selected to compare the incidence of adverse-related events between NSAID- and placebo-treated dogs. Carprofen and meloxicam were investigated in 10 RPCB studies, followed by deracoxib and ketoprofen (6), firocoxib (4), tepoxalin (3), and etodolac (2), respectively. Flunixin meglumine, licofelone, rofecoxib, and tolfenamic acid were evaluated each in 1 RPCB study.

A statistically significant difference between treated and placebo groups based on objective outcome measures was detected in 5 of 25 RPCB studies (20%). GI lesions' scores were greater,[10,24,48] platelet aggregation was decreased,[5] and food consumption and body weight were both decreased[43] in NSAID-treated dogs when compared with placebo-treated dogs. Whether there was a significant difference between these groups by means of assessing outwardly adverse drug experiences was not explicitly reported in any study. A cross-over design was used in 8 of these RPCB studies in the research setting.

Discussion

The administration of NSAIDs and the potential for the development of adverse effects in dogs are well accepted. Our study found, however, that the strength of evidence regarding adverse drug experience was highly variable among published studies and individual NSAIDs. For example, a high strength of evidence was found to exist for carprofen, firocoxib, and meloxicam, meaning that the conclusions of the entire

Table 6. Number of dogs treated with each NSAID in the clinical and research setting and their respective number of dogs used in the placebo group.

	Treatment			Placebo		
NSAID	Client-Owned Dogs (n)	Research Dogs (n)	Total	Client-Owned Dogs (n)	Research Dogs (n)	Total
Carprofen	1165	125	1279	76	78	154
Deracoxib	51	66	117	17	58	75
Etodolac	121	21	142	0	16	16
Firocoxib	1336	28	1364	0	28	28
Flunixin meglumine	0	21	21	0	6	6
Ketoprofen	67	58	125	26	57	83
Ketorolac	10	0	10	0	0	0
Licofelone	0	7	7	0	7	7
Meloxicam	277	134	390	104	78	182
Rofecoxib	0	7	7	0	7	7
Robenacoxib	222	58	280	0	16	16
Tepoxalin	0	42	42	0	32	32
Tolfenamic acid	27	0	27	31	0	31
Vedaprofen	105	0	105	0	0	0

body of evidence for these drugs appear relevant and applicable to the target population. Carprofen was administered to a large population of dogs in the clinical setting in several studies that received high ratings. Firocoxib was investigated in fewer studies, but cumulatively, it had the largest clinical population sample. Meloxicam has not been systematically evaluated in clinical trials in comparison with carprofen and firocoxib; however, most of the studies involving this drug received high ratings. Indeed, meloxicam was evaluated in large placebo-controlled studies, which strengthened its evidence. Even though the trials that involved deracoxib and ketoprofen received high ratings, a moderate strength of evidence was determined to both drugs attributable to the small population of animals reported to have been administered the drug.

Robenacoxib is a relatively new selective COX-2 inhibitor that has been approved for use in dogs in several countries in Europe. The safety of robenacoxib and, therefore, its adverse effects have only been reported in 4 studies. These manuscripts received high ratings and were performed in a large population of dogs that were consistent with a moderate ranking of classification. The current results were considered to be promising, and further studies and clinical trials will potentially strength its current evidence. Etodolac received a low-level ranking because of a small population sample and small number of studies with high ratings. Flunixin meglumine, ketorolac, licofelone, rofecoxib, tepoxalin, tolfenamic acid, and vedaprofen were ranked as extremely low strength of evidence because of limited number of high rating studies, as well as a small population sample that would prevent the results to be extrapolated to the target population. At this point, further studies using these latter drugs are warranted to provide better scientific evidence of their adverse effects profile in dogs.

The occurrence of at least 1 adverse event recorded at least once per study was communicated in 55% of the studies. However, the number and frequency of affected dogs in relation to treated dogs were not explicitly reported, and therefore incidence of adverse effects resulting from NSAID ingestion in dogs remains unknown.[11] Data from the American Society for the Prevention of Cruelty to Animals, Animal Poison Control Center electronic medical record database, revealed that the dog was the most commonly reported species with adverse drug experience resulting from NSAID ingestion.[11] Data from this source are biased to nonapproved NSAIDs, however, and do not provide accurate incidence data for approved NSAIDs. Interestingly, we found that the administration of NSAIDs alone rarely induced adverse effects in the research setting,[17,34,48,50,65] unless if administered "off-label," at higher doses than recommended or for prolonged periods of time,[7,43,44,71] or in combination with corticosteroids or a 2nd NSAID.[54,55,57]

Adverse clinical signs appeared to be more commonly recorded in clinical trials when compared with research studies (62% versus 38%, respectively). For most part, research studies enrolled young healthy animals that did not undergo medical or surgical interventions because of a specific disease process, and might not reflect the population that is more likely to be administered NSAIDs such as older dogs with naturally occurring disease.

Across all studies, vomiting and diarrhea were the most commonly observed clinical signs. Other outwardly detectable adverse drug experiences related to the GI system included melena, fecal blood, colitis, abdominal pain, and icterus. GI ulceration and perforation are thought to occur primarily as a result of NSAID-induced depression of normal cytoprotective effects in the gastric mucosa including suppression of bicarbonate secretion and mucus production.[6,75] Indeed, NSAID treatment is considered to be the most common predisposing factor for GI ulceration in dogs that might require emergency intervention.[6,76–82] How-

ever, what is not known, and our study could not answer, is what the incidence of GI ulceration is, and the incidence of GI perforation.

Monitoring of serum activity of liver-derived enzymes did not detect significant changes during or after the long-term (≥28 days) administration of NSAIDs in dogs.[7,22,26,27,38,51–53,70] However, the need for intensive treatment was reported in 1 dog with liver toxicosis out of a population of 805 animals that were administered carprofen for 84 days in 1 clinical study.[8] In another clinical study, serious liver adverse effects were recorded with an incidence of 1.6% of dogs that were administered robenacoxib or carprofen for up to 84 days out of a population of 188 dogs.[18] In these cases, however, all 3 dogs had evidence of pre-existing hepatic disease.[18] In general, authors agree that hepatic adverse drug experience secondary to NSAID administration is more likely to be an idiosyncratic reaction unique to specific drugs rather than intrinsic (or inherent) hepatotoxicity.[1,8,18] By contrast, kidney injury and GI adverse effects can be dose-dependent.

When the renal effects of NSAID were investigated by means of clinical pathology evaluation in prospective randomized controlled studies, no differences in the incidence of renal adverse drug experience among various NSAIDs, or between treated and control groups, were detected.[7,27,51,60] Renal function tests failed to detect renal adverse effects after NSAIDs administration in dogs undergoing general anesthesia[25,49] and submitted to hypovolemic, hypotensive stress, or both.[29,32,36,65] Outwardly detectable adverse drug experiences that could have been directly attributable to renal effects were observed in 4 studies and included polyuria alone,[49] polyuria and polydipsia,[47,55] and polydispsia and adpsia.[26] A direct association of the aforementioned clinical signs and renal adverse effects cannot be concluded with the exception of 1 study[55] where a well-known nephrotoxic agent was administered. Large clinical trials associated with better specific diagnostic tools may elucidate the incidence of renal adverse drug experience in dogs after NSAID administration. Indeed, the lack of information on the incidence of renal adverse effects might be caused by the presence of GI adverse effects before clinical signs of renal failure are evident.

With the exception of aspirin, studies have not demonstrated a significant association between the use of NSAIDs and clinically significant bleeding disorders. These effects were evaluated by means of 1 or more of buccal mucosal bleeding time (BMBT), platelet-function analyzer and aggregation, thrombelastography, cuticle bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT), or fibrinogen concentration among others, both in the acute and chronic settings.[7,34,35,38,43,51,57,58,60,66,67] In a population of 8 dogs with OA, platelet aggregation was decreased after the administration of aspirin and carprofen. Treatment with carprofen also decreased clot strength, suggesting hypocoagulability.[23] Nevertheless, values were within reference range and the clinical relevance of these findings might be questionable. In another study with 10 research dogs,[20] no effects on platelet function after aspirin, carprofen, and meloxicam were observed. In the latter study, deracoxib caused a mild decrease in platelet aggregation while all NSAID treatments did not affect platelet number, PT or APTT, and thromboxane B2.[20] Controversially, the preoperative administration of ketoprofen to healthy dogs undergoing ovariohysterectomy in the clinical setting has revealed a significant decrease in platelet aggregation, when compared with saline-treated dogs. Nevertheless, BMBT did not differ between groups.[5]

The power of a study is directly proportional to the sample size and contributes to the detection of statistical significance of a treatment's evaluation.[83] Power analyses were rarely reported in the studies that were reviewed herein, which suggests either a possible deficiency of the studies or a lack of standardized data reporting. In this review, 29 of 64 studies (45%) were clinical trials, and only 14 (21.8%) of them were randomized, controlled, and blinded reports. Although randomized controlled trials are considered at the top of hierarchy of evidence among clinical studies, they require considerable resources.[84] In addition, in a clinical trial, it may not be possible to have a control group without the administration of analgesics. When RPCB studies were evaluated, a statistically significant difference in the incidence of outwardly detectable adverse effects between treated and placebo control group was not observed. These results might suggest either that the incidence of adverse drug experiences of NSAIDs in dogs is not as frequent as previously believed, but most likely that the current literature has not produced robust data that are representative of a clinical scenario.

The authors might have introduced a language and selection bias by only selecting papers that were published in English after 1990. There might also have existed observational bias because reviewers were not blinded to the studies' authors. Nevertheless, bias could have been minimized by explicit, systematic methods of evaluation such as the one herein.[13]

A single investigator (BPMS) was responsible for rating of the study design type and assessment of quality, and 2 investigators (BPMS and PVMS), by agreement, performed the ratings of quantity and consistency as well as the final ranking of each NSAID. Differences in the classification of a same study among systematic reviews have been observed.[3,14] Guidelines for the standardization of systematic reviews are warranted and have been recently suggested to limit heterogeneity of results and ensure fair comparisons between studies.[85]

Conclusions

This systematic review provides evidence-based evaluation of the data on the adverse effects affecting dogs after the use of the most contemporary NSAIDs. Few studies were designed in a randomized, controlled, and blinded manner using a clinical population of dogs. Most studies did not report power analysis and there-

fore it is difficult to discern if a significant difference truly exists between NSAIDs regarding safety. In general, studies involved a healthy nongeriatric population of research dogs in the absence of naturally occurring disease. The incidence of outwardly detectable clinical signs of NSAID-related adverse effects was not different between treated and placebo groups when only the highest quality studies were included. The overall incidence of adverse drug experiences cannot be calculated from the data in the literature, although estimates for the most serious adverse effects suggest that they occur at a very low frequency.

Acknowledgment

Conflicts of Interest: Authors disclose no conflict of interest.

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