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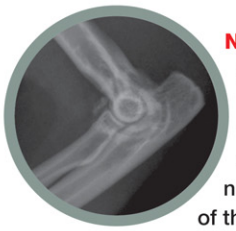
SPECIAL ARTICLE

ISFM AND AAFP CONSENSUS GUIDELINES
Long-term use of NSAIDs in cats



NSAIDs and cats Non-steroidal anti-inflammatory drugs (NSAIDs) are an important class of drug in feline medicine, having analgesic, anti-inflammatory and antipyretic activity. While most published data on their use in this species relate to short-term (often perioperative) therapy, there is increasing evidence of the value of these drugs in treating chronic pain in cats (for example, that associated with degenerative joint disease), and some NSAIDs have now become licensed for long-term use in cats in some geographies. Most of our knowledge of therapeutic mechanisms or adverse drug reactions associated with NSAIDs is extrapolated from work in other species, and there is a paucity of published data relating to cats.

Guidelines These guidelines have been drawn together by an expert panel, which have reviewed the current literature on long-term NSAID use in cats and other species, and developed guidance on their use based on this information. The aim is to provide practical information for veterinarians to encourage appropriate NSAID therapy whenever cats will benefit from the use of these drugs.

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Introduction

Pain in cats has many negative effects, both physiological and emotional.[1,2] It is now accepted that there is no such thing as 'good pain' following surgery and during treatment for trauma or disease – eg, pain that inhibits potentially deleterious movement after surgery. Pain delays recovery, impacts negatively on a patient's wellbeing, and disturbs the bond with its owner and also the veterinary team.[1,3]

Studies have looked at the use of non-steroidal anti-inflammatory drugs (NSAIDs) for acute, especially perioperative, pain in cats.[4–7] Surveys have shown clinicians were more likely to treat pain in dogs than cats,[8,9] as a result of difficulties in recognising pain, lack of knowledge concerning the use of analgesics, and fear of drug side effects in cats. Less has been published on the management of chronic pain in cats, but it is recognised that signs may be subtle and include withdrawing from attention, decreased mobility, reduced interactions with humans and other animals, poor appetite and aggression.[10–12]

Chronic pain can be regarded as pain that has persisted for more than 2–3 weeks, often persists months or years, and may continue beyond the anticipated healing time. Importantly, chronic pain can become dissociated from the inciting cause and be maladaptive, such that the degree of pain does not necessarily correlate with the pathology observed or perceived by the individual, and is not associated with healing.[12] Multimodal analgesia is commonly advocated, but it is becoming evident that NSAIDs will play a key role in managing chronic feline pain, especially musculoskeletal pain, just as they do in humans and dogs.[10,13–16] Until quite recently, while many NSAIDs have been available to treat dogs with degenerative joint disease (DJD),[17] only a restricted range has been licensed for short-term (up to a few days) use in cats. At the time of writing, at least one NSAID – meloxicam – has been licensed for long-term use in cats in many regions of the world, transforming our ability to manage pain in this species, and a second – robenacoxib – has been licensed for up

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to 6 days of therapy in cats (see Table 1, page 529). There is little doubt that others will become licensed for long-term use in the future, due to the recognition of the need and value for such NSAID therapy in this species.[10,11,13–15,18]

Clinicians are aware of their duty to promote animal welfare and relieve suffering, but are also often reminded of Hippocrates' advice to 'first do no harm'. This is often rightly used to question whether an intervention will actually do more harm than good, and to withhold that intervention when doubts exist. However, we need also to recognise that withholding treatments such as analgesics can sometimes cause the greater harm, because we are no longer addressing the pain and suffering the animal is enduring. In drawing up these guidelines, the international panel of experts' purpose has been to review the current literature on long-term NSAID use in cats, and to provide practical guidance on their use. The overarching aim is to encourage more widespread and appropriate NSAID therapy, when cats will benefit from the use of these drugs. However, most of our knowledge of therapeutic mechanisms or adverse drug reactions is extrapolated from work in other species, as there is a paucity of published data relating to cats.

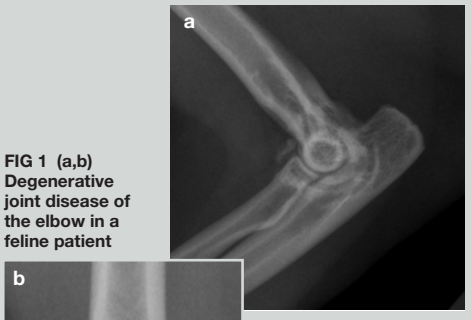


FIG 1 (a,b) Degenerative joint disease of the elbow in a feline patient

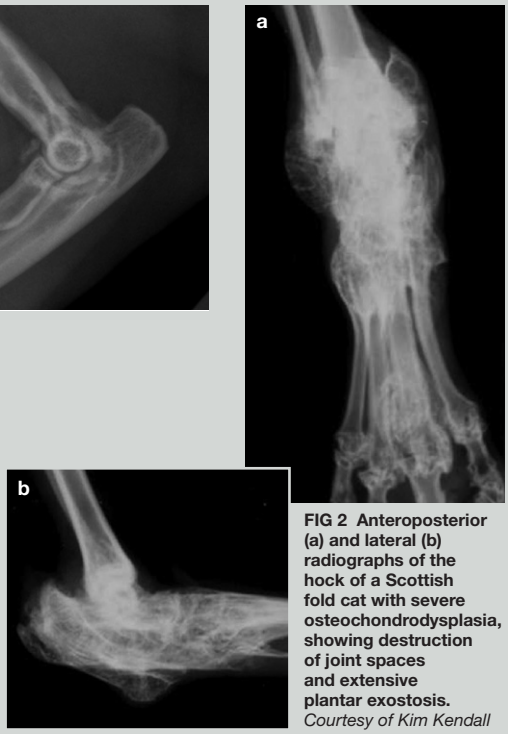


FIG 2 Anteroposterior (a) and lateral (b) radiographs of the hock of a Scottish fold cat with severe osteochondrodysplasia, showing destruction of joint spaces and extensive plantar exostosis. *Courtesy of Kim Kendall*

FIG 3 Watson, a DJD sufferer, enjoying the benefits of daily NSAID treatment

Common causes of chronic pain and inflammation in cats

One of the difficulties in managing pain in cats is its initial recognition. It is important, therefore, to be aware of common causes of pain and to have a high index of suspicion for signs and behaviours potentially related to pain. If something is painful to us, it is likely to be painful to a cat.

Degenerative joint disease

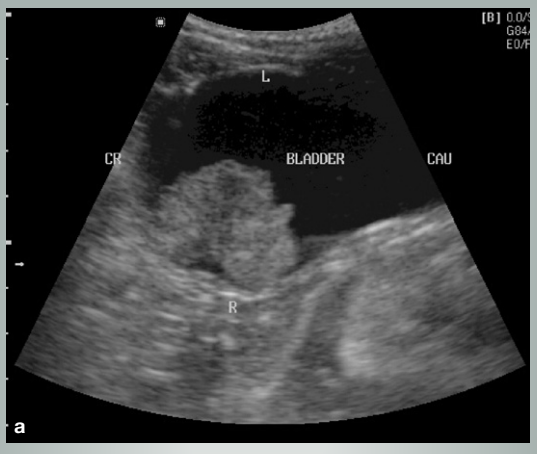
The most common cause of chronic feline pain is thought to be DJD, and this has been the subject of a number of important studies in the past 10 years.[11,15,16,18–24] From these studies, it is clear that DJD is very common, with radiographic changes affecting up to 60–90% of cats (Figs 1 and 2),[18,24] that it affects both the spine and the appendicular joints, and that it occurs especially commonly in older patients.[18,24] The hips, stifle, shoulder, elbow, tarsus and spine are the most common sites affected, although other joints can also be involved. Studies based on radiographic findings have limitations, though, as the changes observed do not necessarily correspond to clinical disease, or the severity of clinical disease and pain. Nevertheless, where clinical disease is present many owners may simply assume a cat is 'getting old', and even educated and attentive owners may not necessarily appreciate suffering associated with DJD without veterinary observation and insight.

In the absence of medical intervention, many cats with DJD suffer pain and discomfort for years, greatly affecting their quality of life and the human/feline bond. It is vital that examinations of the older feline patient should specifically address whether DJD is present, through history and physical examination and, where necessary, radiology and therapeutic trials. Control of bodyweight, exercise and environmental modifications may help cats with DJD, as may other medical therapies. However, the dramatic responses reported to NSAIDs[13,21,23] indicate that there is a huge scope for safe, effective long-term NSAID therapy in the large cohort of aged cats with DJD (Fig 3).

Other diseases

There are many other feline diseases where control of protracted inflammation and pain is important. These include various cancers (Fig 4a), particularly where definitive treatment is not possible, or in some cases for the antineoplastic effect NSAIDs may offer.[25–28] Other common conditions associated with chronic pain where NSAIDs may form part of therapy include trauma, lymphoplasmacytic gingivostomatitis (Fig 5),[29] idiopathic cystitis,[30,31] skin disease and uveitis (Fig 6). In the last, both topical and/or systemic NSAID therapy may be valuable.[32] Through their antipyretic effect, control of fever with NSAIDs may also be valuable in some situations. A short therapeutic trial of an NSAID without a definitive diagnosis may sometimes be appropriate, using the response to treatment as a guide to diagnosis and further therapy. Informed client consent and close monitoring of the patient is mandatory, especially in such cases.

If something is painful to us, it is likely to be painful to a cat.



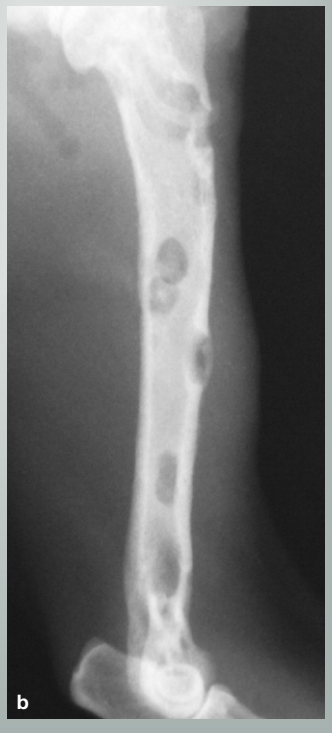
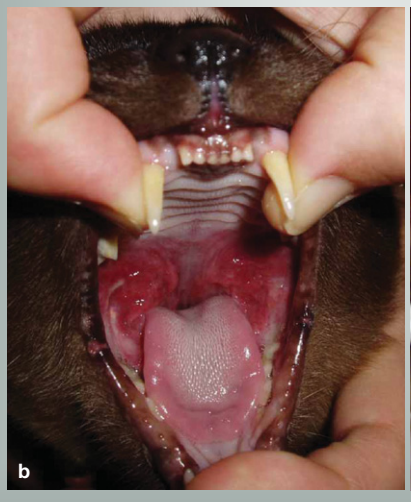


FIG 4 Transitional carcinoma of the bladder (a) and multifocal osteomyelitic bone lesions (b) in two feline patients. The tumour in the first cat was debulked surgically and the cat then received piroxicam; the second cat was given meloxicam in addition to antibiotics. *Courtesy of Randolph Baral (a) and Emma Hughes (b)*



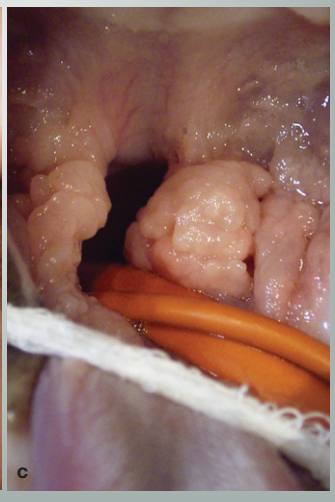


FIG 5 (a–c) Severe and painful ulcerative and proliferative gingivostomatitis in three cats. *(c) Courtesy of Alberto Barneto*

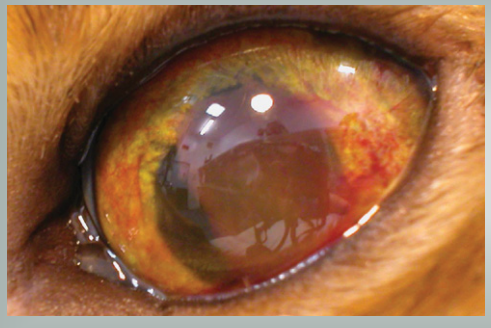


FIG 6 Uveitis in a cat with toxoplasmosis. *Courtesy of Carolyn O'Brien*

NSAIDs and cyclo-oxygenase/ lipoxygenase inhibition

The therapeutic benefits of NSAIDs include their antipyretic, analgesic and anti-inflammatory actions. They exert these effects mostly through inhibiting the production of prostaglandins (PGs) and leukotrienes (LTs) by the cyclo-oxygenase (COX) and 5-lipoxygenase (5-LOX) enzymes, respectively.[33–35] Most NSAIDs primarily inhibit the activity of COX enzymes. Although some also inhibit LOX enzymes, for currently licensed feline drugs this is generally short-lived in comparison with COX inhibition, and evidence of additional clinical efficacy from this is lacking. More effective dual COX/LOX inhibitors may become available in the future.[36–38]

Two distinct COX isoforms (COX-1 and COX-2) have been identified as being responsible for the production of prostaglandins (Fig 7).[35] A third isoform has also been identified, initially known as COX-3, now described as a splice-variant of COX-1, which seems to have a role in the central control of pain.[38] Phospholipase A_2 is the rate-limiting enzyme that initiates the COX pathway by liberating arachidonic acid (AA) from membrane-bound phospholipids. Both COX isoforms are then responsible for converting AA to PGG_2 and PGH_2 via identical enzymatic reactions. Following these initial steps, PGH_2 functions as an intermediate substrate for the biosynthesis, by specific synthases and isomerases, of prostaglandins, prostacyclin and thromboxanes. COX-1 converts AA to a range of molecules, including thromboxanes (TX), such as thromboxane A_2 (TXA_2), and prostaglandins, such as PGD_2, PGE_2 and PGF_2, and prostacyclin (PGI_2). COX-2 activity produces a narrower spectrum of prostaglandins, specifically PGE_2 and prostacyclin.

The prostaglandins play a major role in many aspects of normal physiology, including vascular homeostasis, gastroprotection, renal development and blood flow, blood clotting, reproduction, bone metabolism, wound healing, nerve development and growth, and immune responses. They are also involved in pathophysiological processes, including pain and inflammation, and cancer progression. However, much of our knowledge is extrapolated from other species, as there is a paucity of feline-specific data.

Expression of COX enzymes

Both COX-1 and COX-2 are enzymes that are constitutively expressed (normally present in tissues and at fairly constant concentrations), as well as induced (appear and/or increase in concentration in response to an inciting factor, often associated with inflammation). COX-1 is considered as predominantly constitutive, being expressed in almost all tissues, and involved in the production of prostaglandins responsible for 'house-keeping' functions, such as the cytoprotective effects in the gastric mucosa, normal platelet function and maintenance of renal perfusion.[39] Constitutive expression of COX-2 appears to be more

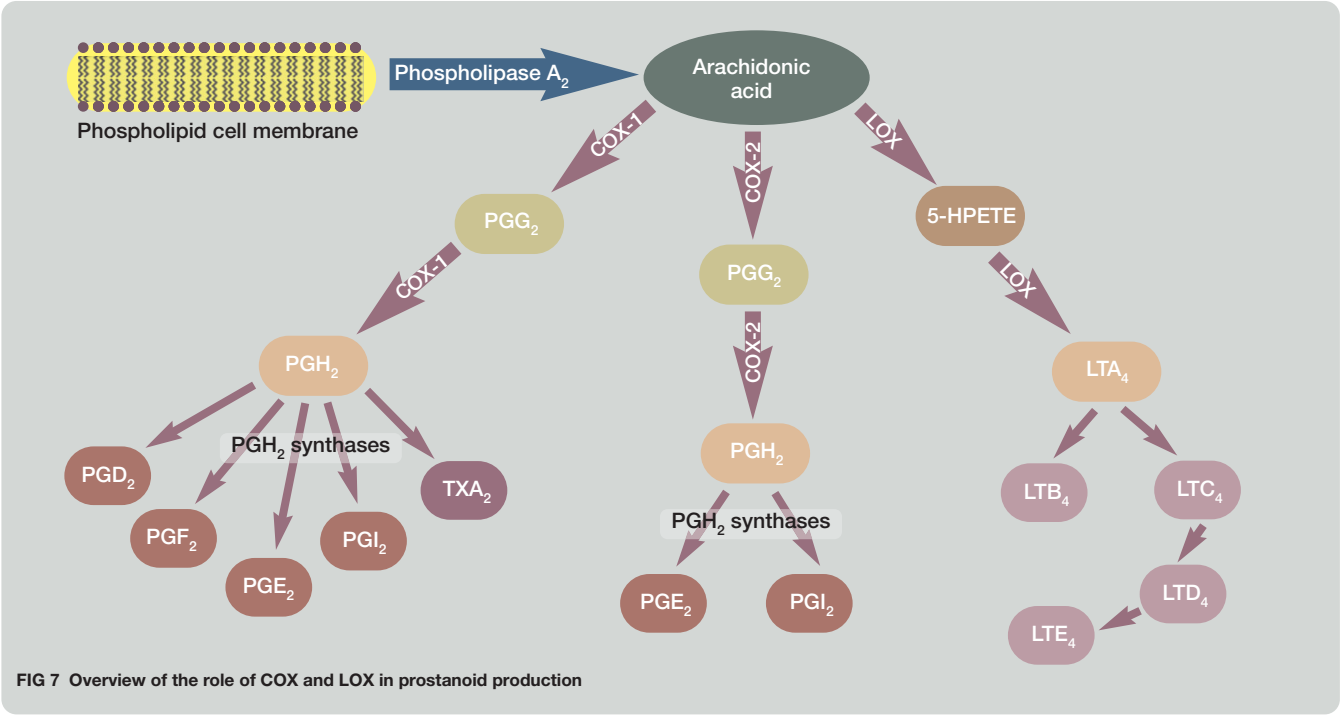


FIG 7 Overview of the role of COX and LOX in prostanoid production

restricted,[39,40] although it is present, along with COX-1, in the central nervous system, kidney, vascular endothelium, reproductive tract and gastrointestinal (GI) tract – sites where COX-2 activity contributes to homeostatic functions.[35,41] It appears that COX-2 has an important role in healing damaged mucosa in the GI tract, and although COX-2 has been shown to be constitutively expressed in the canine GI tract,[42,43] information on cats is lacking.

While COX-1 is the predominant constitutively produced enzyme, COX-2 is predominantly inducible and its production is dramatically upregulated during inflammation, in which it plays a central role.[44] The expression of COX-2 may also be upregulated in certain neoplasms, and in cats variable expression has been reported in transitional cell carcinomas, squamous cell carcinomas, mammary carcinomas and pancreatic carcinomas.[25–28,45–47] However, just as COX-2 has some constitutive expression, COX-1 expression also has a role to play in the inflammatory response.[39,40]

COX and LOX selectivity, and NSAID adverse effects

Inhibition of COX-1, the enzyme predominantly associated with homeostatic functions, is reported to be the cause of most NSAID-induced side effects such as gastric ulcers and blood dyscrasias. In an attempt to avoid this, NSAIDs with a greater propensity to suppress COX-2 than COX-1, so-called 'COX-2 preferential' (or 'COX-1 sparing') NSAIDs, have been developed. Drugs that have negligible effect on COX-1 have been termed 'COX-2 selective' rather than 'preferential', although there is no recognised precise definition of these terms.[48]

However, it rapidly became evident from human studies that COX-2 preferential or selective NSAIDs, while reducing some of the side effects classically associated with COX-1 inhibition, still caused adverse events such as acute renal failure, thromboembolic disease and gastric ulceration,[49,50] consistent with a physiological role for COX-2 in a number of tissues. For example, both COX-1 and COX-2 are expressed in mammalian kidneys. They are found within different cells of the kidney (macula densa, cortical ascending tubule, medullary interstitial cells), and play different roles, but both are important to preserve renal function during hypovolaemia.[50] Additionally, the inhibition of COX has been postulated to be associated with an increase in LOX activity, which can result in adverse effects on the GI mucosa. Furthermore, it has been suggested that dual inhibitors may be associated with fewer GI adverse effects than COX-1 or COX-2 inhibitors.

Although the COX/LOX selectivity of an NSAID may be important, this does not negate all potential side effects, and indeed evaluation of COX/LOX selectivity is not the only factor to consider when trying to predict the safety of an NSAID.

There are several other issues to consider. Firstly, the risks of adverse events can be affected by tissue concentrations of the drug – where the extracellular fluid is of a lower pH than the intracellular fluid, 'ion trapping' of weakly acidic drugs, such as most NSAIDs, can occur with accumulation of the drug within cells (eg, the gastric mucosa).[51] The extent to which this occurs will vary between drugs but this local accumulation can affect the prevalence of side effects.

Secondly, differences are recognised between species in both the expression and distribution of the COX enzymes.[52–55] Very little feline-specific data are available, but there could be differences in susceptibility to adverse events as a result of such differences in cats.

Thirdly, there are substantial variations in the reported COX selectivity of an NSAID based on the type of in vitro assay used to measure COX-1 and COX-2 activity. These results vary depending on the species used to source the material for the assay; and, even when the assay is performed in tissue from the target species, different assays yield different results.[36,38,56] Additionally, differences in metabolism of drugs between species can result in differing selectivity. In the dog, tepoxalin is a dual inhibitor for a short period of time only; but, in the cat, tepoxalin pharmacokinetics indicate it is potentially a balanced COX and LOX inhibitor throughout its kinetic profile.[38]

Other factors also affect the risk of adverse events – for example, age. Older humans are recognised to be at greatest risk of GI ulceration; and in human medicine pre-existing renal insufficiency, cardiovascular disease and hepatic disease are all relative contraindications for use of NSAIDs. However, management of pain in the geriatric patient becomes critical to quality of life. Therefore, careful selection of NSAIDs and their dose, and the use of adjunctive therapies (such as proton pump inhibitors to assist gastroprotection, other analgesics to modulate other parts of the pain pathway and reduce the required NSAID dose, and fluid therapy to minimise effects of hypovolaemia), must be considered rather than simply avoiding addressing pain in both humans[57–60] and veterinary species.[61] Patient selection, dose titration and ongoing monitoring for the early signs of toxicity are essential.[62,63]

Panel recommendations

COX-2 selectivity

- In keeping with other species, studies of NSAIDs in cats suggest no difference in anti-inflammatory or analgesic efficacy between COX non-selective drugs and variably COX-2 selective inhibitors.
- It is presumed, as in other species, that using drugs with a greater COX-2 selectivity in cats will help avoid some of the potential adverse effects associated with COX-1 suppression, such as GI irritation/ulceration and platelet inhibition. However, selective COX-2 inhibition will not completely negate the possibility of adverse effects and may not confer any renoprotective effect in comparison with a non-selective inhibitor.
- It is presumed that dual inhibition of COX and LOX may be associated with reduced GI adverse effects over COX inhibition alone. However, it is unlikely that dual inhibition will completely negate the possibility of adverse effects.

What does this mean for cats?

Because of species differences in expression of COX enzymes and in the in vitro COX selectivity assays, it is imprudent to generalise results from any single study.[64] With all these variables, it is not surprising that there is no simple answer to the question of whether a COX selective or a dual COX/LOX inhibitor is better, and indeed what the 'ideal' COX/LOX selectivity and profile of an NSAID is in the cat. It may indeed depend on the disease process and the individual being treated. Despite these caveats, and given the paucity of feline-specific data at present, we can only cautiously extrapolate knowledge based on data from other species.

Practical NSAID therapy in cats

Beyond the question of COX selectivity, many other factors are also important in choosing and using NSAIDs for long-term therapy in cats.

Compliance

Administering medication to cats can be challenging for owners, yet adequate therapy relies on good owner compliance. Along with NSAIDs, many cats will be receiving other medications and the 'administration burden' may be daunting for owners, leading to inconsistent dosing. To help long-term use, a drug should ideally be highly palatable and taken voluntarily by the cat – for example, in food or as a treat – and veterinary pharmaceutical companies undertake much research into this.[65] Published studies suggest meloxicam liquid is highly palatable in cats,[13,16] with one study suggesting it was significantly more palatable than ketoprofen tablets.[16] Other drugs may be compounded in specific flavours that are appealing to individual cats. However, it is important to follow all regulations and compliance policies for drug compounding,[66] which are different throughout the world, and to consider the potential effect of compounding on bioavailability and stability/shelf-life.

Additionally, owners must be consistent and remember to administer the drug. Based on the long duration of action of many NSAIDs in cats, this should be at a set time on treatment days. Creative reminder systems may help ensure cats receive medication on the correct day(s), at the correct time(s) and at the correct dose. Giving medication along with a daily food ration (which should also be done for safety) can provide a built-in reminder system for owners, and encourage owner involvement in the monitoring process.

Dosing – intervals, frequency, timing and the 'lowest effective dose'

Short-term pharmacokinetic data are available for a number of NSAIDs in cats, which form a basis for dosing intervals. While many NSAIDs are metabolised via glucuronidation in the liver, and the relative deficiency of glucuronyl transferase enzymes in cats may lead to a prolonged half-life for some of these drugs,[37,56] others, such as piroxicam and meloxicam,[56,67] are metabolised by oxidation. Single doses of many approved/licensed NSAIDs for acute pain in cats seem to have a duration of action of around 18–20 h.[56] However, it is not known if such prolonged pharmacokinetics are necessary for appropriate efficacy. For example, meloxicam and robenacoxib have a serum half-life of approximately 24 and 2 h, respectively,[68,69] yet both have been shown to be effective for daily treatment of musculoskeletal pain in cats by virtue of their European licences.

For most of the NSAIDs used in cats, it is not known if repeated long-term dosing alters the pharmacokinetics or pharmacodynamics of the drug. In one study, the administration of flunixin daily for 7 days appeared to result in more rapid metabolism of the drug after 7 days and decreased pharmacodynamic effects,[70] although the same did not appear to be evident during daily administration of meloxicam for 7 days.[68] Additionally, information on the apparent efficacy of daily versus every-other-day or less frequent dosing is anecdotal, with no controlled studies yet published. Daily dosing of meloxicam at less than the labelled dose for a mean of 5.8 months was considered to be clinically effective and associated with minimal adverse effects in one non-blinded study,[13] although efficacy was not measured objectively or with a validated assessment system. However, due to the inter-cat variability of pharmacokinetics with administration of a variety of NSAIDs, it is likely that daily dosing may be appropriate for some cats, while longer intervals might be appropriate for others.

Unfortunately there is no practical way to determine which cats might be 'fast' metabolisers and which slower. Additionally, probably as a result of their high protein-binding, which may enable NSAIDs to persist in inflamed tissue sites for longer than in plasma, the anti-inflammatory and analgesic activity of these drugs often persists longer than would be predicted from their serum half-life. This may enable daily dosing even for drugs with a relatively short half-life.[38,69] Indeed persistence at the site of inflammation has been demonstrated in an experimental study of robenacoxib in cats.[67] It is, therefore, unlikely that a set mg/kg dose and dosing schedule will work equally well for all cats; furthermore, variations in the level of pain may alter the cat's needs over time.

Very little attention has been given to the best time of day to administer NSAIDs to cats to achieve the most beneficial effect, a concept termed chronotherapy.[71] Theoretically, long-term dosing may result in a pharmacokinetic and pharmacodynamic steady-state. However, 'peaks and troughs' may still occur. If the peak beneficial effect on lameness occurs at say 5 h after dosing, treatment may be tailored to achieve maximum clinical effect when the cat is most active. The timing, therefore, may depend on a cat's lifestyle. Alternatively, an owner may find that at 'peak effect' the cat is more comfortable, it rests for longer and may choose to administer the drug to promote resting and sleeping at the most suitable time for the household.

Panel recommendations

Dosing frequency

- To avoid potential side effects, owners should be encouraged to work on titrating to the 'lowest effective dose' that works for their cat, with the understanding that this may change over time. This dose may often be less than the labelled dose.[13,14,21]
- In overweight or obese cats, it is prudent to calculate initial doses for NSAIDs according to their lean or ideal bodyweight.
- When attempting to reduce the overall dose of an NSAID, it would seem prudent to reduce the label dose but maintain the label frequency, where possible.
- The panel recognise that intermittent therapy, for example 2–3 times weekly rather than daily, is better than no therapy at all, and anecdotally appears efficacious in some cats. However, there may be a risk of significant periods of time when no effective therapy, or suboptimal therapy, is being achieved.
- Intermittent drug withdrawal, a reduced frequency of dosing, or a reduction of the dose may all help owners to assess drug efficacy.
- The panel see little rationale for pulse therapy with NSAIDs unless the underlying disease process varies sufficiently in severity that it does not require consistent analgesic/anti-inflammatory therapy.

Dosing – accuracy

Dosing accuracy will depend on the formulation of the drug. Liquids are more easily measured, and can be delivered in small volumes. Thus incremental increases or decreases in dose are potentially more readily achieved. However, differing dispensing methods can potentially result in wide variations in doses. Tablets or caplets are not

Treatment may be tailored to achieve maximum clinical effect when the cat is most active. Alternatively, an owner may choose to administer the drug to promote resting and sleeping at the most suitable time for the household.

Panel recommendations

Dosing accuracy

- Liquid formulations will provide for the most accurate dosing and dose adjustment of NSAIDs in cats; and manufacturers are encouraged to explore this route of delivery.
- The use of a dedicated and clearly marked syringe for administration of the liquid (Fig 8) should be encouraged to prevent accidental administration of excess drug when it is administered directly from a storage container.

always easy to divide and therefore delivering a small dose may be problematic and inaccurate. Intact tablets will provide a different dose to cats of different weights, which may not be a problem when the drug is licensed for a dose range, as for example robenacoxib, but may be a problem if a very precise target dose is required. Repeat subcutaneous injections may be another option in some cats and with some owners, although no NSAIDs are currently licensed for long-term use by this route.

Dosing – switching drugs

There is little objective data available on the best way to transition therapy from one NSAID to another, and feline-specific information is lacking. There is concern about changing from aspirin to another NSAID in other species due to COX-2 dependent adaptive mechanisms that may occur during therapy.[38,61] However, there is uncertainty about the need for or timing of any 'washout' period with other NSAIDs.[38,61]

FIG 8 Use of a dedicated dosing syringe is advisable

Panel recommendations

Switching between NSAIDs

- As a precaution, a 'washout' period of approximately 7–10 days should be used when switching from aspirin to another NSAID.
- A sensible precaution may be to allow a washout period of 3–5 days when switching between other NSAIDs, and potentially longer if the previous NSAID had a prolonged half-life. Additional adjuvant therapy with other analgesics should be considered if required during this time.

Monitoring efficacy

There is no validated assessment tool for acute or chronic feline pain, although studies are ongoing.[72] In studies evaluating the efficacy of NSAIDs in cats with musculoskeletal pain, improved mobility, and in particular the willingness to jump and the height of the jump, have been the most obvious signs of improvement,[13,21] and another study found increases in mobility with administration of an NSAID.[15] One key feature of chronic pain assessment is owner involvement and observation, especially as pain may manifest in different ways in individual cats.[56,73] It has been postulated that four behavioural domains – mobility, activity, grooming and temperament – are particularly useful to both clinicians and owners in assessing chronic musculoskeletal pain and monitoring the response to therapy.[23]

When treating animals with long-term diseases, an overall assessment of 'quality of life' may be beneficial; this includes, but is not limited to, pain. An assessment tool may need to be individually designed since what is important to each patient will be different: can the cat climb trees, hunt, play with other pets in the household, and so on?[15] This was the thinking behind the use of client-specific outcome measures in a recent study.[15] Owners should keep a regular journal or diary of the cat's activities, as changes in mobility and behaviour may be subtle and occur slowly. The owner is the best person to judge and track the cat's behaviour and demeanour. It may only be obvious from consulting the 'diary' that a change in treatment is needed.

A key feature of chronic pain assessment is owner involvement and observation.

TABLE 1 NSAIDs licensed for systemic use in cats
(NB not all drugs are licensed in all regions and veterinarians should refer to local information and regulations)

NSAID	COX selectivity*	Formulation	Dose	Route	Frequency	Licensing indications	Duration
Carprofen	COX-2 preferential	Injection, 50 mg/ml	4 mg/kg (= 0.08 ml/kg)	SC, IV	Once	Postsurgical pain	Once only
Ketoprofen	None	Injection, 10 mg/ml	2 mg/kg (= 0.2 ml/kg)	SC	q24h	Relief of acute pain and inflammation associated with musculoskeletal and other painful disorders	Up to 3 days
		Tablets, 5 mg	1 mg/kg (= 1 tablet/5 kg)	PO	q24h		Up to 5 days, ± can use injection instead on day 1
Meloxicam	COX-2 preferential	Injection, 5 mg/ml	0.3 mg/kg (= 0.06 ml/kg)	SC	Once	Postoperative analgesia following ovariohysterectomy and minor soft tissue surgery	Once only
		Injection, 2 mg/ml	0.2 mg/kg (= 0.1 ml/kg)	SC	Once	Mild to moderate postsurgical pain	Can be followed by 0.05 mg/kg q24h PO for 4 days
		Oral suspension, 0.5 mg/ml	0.1 mg/kg (= 0.2 ml/kg) day 1, then 0.05 mg/kg (= 0.1 ml/kg)	PO	q24h	Inflammation and pain in chronic musculoskeletal conditions	Indefinite
Robenacoxib	COX-2 selective	Tablets, 6 mg	1 mg/kg (= 1 tablet/6 kg)	PO	q24h	Pain and inflammation associated with musculoskeletal disorders	Up to 6 days
		Injection, 20 mg/ml	2 mg/kg (= 1 ml/10 kg)	SC	Once	Pain and inflammation associated with soft tissue surgery	Once only
Tolfenamic acid	None?	Tablets, 6 mg	4 mg/kg (= 1 tablet/1.5 kg)	PO	q24h	Treatment of febrile syndromes	3 days
		Injection, 40 mg/ml	4 mg/kg (= 0.1 ml/kg)	SC	q24h	Adjuvant treatment of upper respiratory tract disease	2 days, or once, followed by tablets (above)
***Acetylsalicylic acid*†**	*None*	*Tablets/caplets*	*1–25 mg/kg*	*PO*	*q72h*	*n/a*	*Indefinite*

†Aspirin is NOT licensed for use in cats, but is included here as it has commonly been recommended for use in cats as an antithrombotic agent to help prevent thromboembolism, particularly associated with cardiomyopathy. Wide ranging doses have been recommended (usually in the region of 5–75 mg/cat every 3 days) and its efficacy remains unproven

*COX-2 preferential = greater suppression of COX-2 than COX-1; COX-2 selective = virtually no COX-1 suppression at therapeutic doses

A variety of other (off-licence) dose regimens have been advocated for a number of NSAIDs in cats, in addition to dose regimens for other analgesic agents – for recent overviews see references 10,11 and 57

NSAIDs and concomitant disease

Renal disease

Prostaglandins play an important role in mammalian renal physiology, helping to autoregulate vascular tone, glomerular filtration rate (GFR), renin production and sodium/water balance. When renal haemodynamics are normal, prostaglandins appear to have a minimal role. In keeping with this, a recent study evaluating the effect of 5-day therapy with meloxicam in healthy adult cats showed no alteration in GFR based on iohexol clearance studies,[74] and similarly in healthy cats undergoing anaesthesia there is evidence of its safety when standard care is taken to avoid hypovolaemia and hypotension.[5] Under conditions of low effective renal blood flow, however, prostaglandins become crucial in maintaining renal function and GFR. Prostaglandin inhibition by NSAIDs may reduce renal blood flow and GFR and can result in the potential complication of acute kidney failure (AKF) in humans.[75]

Both COX-1 and COX-2 enzymes appear to be important in maintaining renal function, but their relative importance and physiological role may differ between species;[56,74] for example, a recent immunohistochemistry study demonstrated greater COX-2 expression in the kidneys of dogs with chronic renal disease than in cats.[55] These observations suggest that the propensity for NSAIDs to cause AKF may vary between species. In humans, the risk of AKF is regarded as low, and can occur with both non-selective and COX-2 selective NSAIDs, although the risk may vary between individual agents.[50,75–79] In general, the risks for NSAID-induced AKF in humans are higher with conditions causing renal hypoperfusion (eg, dehydration, hypovolaemia, congestive heart failure), with old age (occult renal disease) and pre-existing renal disease, with concomitant drug therapy (eg, diuretics, angiotensin converting enzyme inhibitors [ACEIs]) and with higher doses of NSAIDs. The resultant AKF is usually reversible, provided it is detected in time.[50,63,76,77,79–81] The use of NSAIDs also carries a small risk of inducing hyperkalaemia in human patients, which is higher in those with existing renal disease and those on potassium supplements.[50,57,75]

In human medicine, the role of NSAIDs in chronic kidney disease (CKD) is much less clear. While some studies have suggested that NSAIDs may be a risk factor for developing CKD (so-called 'analgesic nephropathy'),[82–84] or in the progression of existing CKD,[85] others have found no evidence of a causal association,[86,87] and the difficulties in interpreting trial data have been highlighted.[88] Where studies have suggested a link between CKD and NSAID use, the risk appears to be low, and may be exacerbated by heavy use of one or more NSAIDs.[85,88,89]

Two retrospective studies evaluated the safety of NSAIDs in a total of 76 older cats, including some cats with stable CKD. In both studies, cats received oral meloxicam (approximately 0.02 mg/kg/day) on a long-term basis for osteoarthritis. One study included three cats with International Renal Interest Society (IRIS) stage 3 CKD[90] and an additional 10 cats without CKD that had serum creatinine concentrations monitored,[13] and the other included 22 cats with IRIS stage 1–3 CKD.[14] Neither study showed any significant difference in the development or progression of renal dysfunction in treated cats, compared with age- and disease-matched controls, over an average period of 6 months[13] or more than 1 year.[14] Another study evaluated 73 cats that received oral piroxicam at an average dose of 0.2–0.3 mg/kg/day for between 1 and 38 months. In that study, no significant changes were seen in serum renal or hepatic parameters within the first month of therapy in 43 cats that had follow-up samples collected.[91] During prolonged therapy, five cases of renal insufficiency were detected in 58 cats receiv-

Panel recommendations

Renal disease

- Based on data from cats and other species, the risk of AKF developing during appropriate therapeutic NSAID use in cats is low and not abrogated by the use of COX-selective agents.
- Monitoring serum renal analytes and urine parameters before and after commencement of NSAID therapy is highly recommended as a precaution, in an attempt to recognise AKF at an early stage should it occur (see section on monitoring).
- Risk factors for renal toxicity in humans are presumed to apply to cats. Where an increased risk of renal toxicity is anticipated the lowest effective dose should always be administered (which may be facilitated by the use of adjuvant analgesic therapy) and increased monitoring is prudent.
- NSAIDs should be administered with food, and therapy withheld if food is not eaten – see recommendations for GI disease. In cats predisposed to dehydration, such as with CKD, using a wet rather than dry diet is a sensible precaution to optimise water intake.
- Specific risk factors, such as dehydration and hypovolaemia, should always be addressed before therapy is administered, and if analgesia is required in the interim period an alternative such as an opioid can be utilised. Care should be taken to ensure good renal perfusion is also maintained if anaesthesia is required during therapy.
- Current data suggest that at least some NSAIDs can be used safely in cats with stable CKD at judicious doses, and that this should not be a reason for withholding analgesic therapy when it is indicated. Further data, particularly in cats with advanced renal disease, would be valuable and such pharmacovigilance studies are vital.
- The combination of cardiac disease and renal disease is problematic – care is urged with the use of NSAIDs in this situation due to the increased risks of AKF. The exploration of analgesic options other than NSAIDs may be prudent, but the potential risks of exacerbating these diseases should not restrict the use of analgesic therapy where it is needed.
- As there is a risk of hyperkalaemia developing during NSAID therapy in other species, especially in the face of renal failure or potassium supplementation, potassium monitoring is recommended during therapy.

ing piroxicam, but as other therapies were being received, as the cats had underlying neoplasia, and as they were an older population without any controls, it was impossible to know if any of these were related directly to piroxicam therapy.[91] It has been demonstrated that cats with CKD have higher circulating levels of gastrin[92] and, as such, these cats may be at increased risk of GI adverse effects when NSAIDs are used.

Gastrointestinal disease

Because of the physiological role of COX in maintaining the normal gastric mucosal barrier, upper GI bleeding has been the most common serious complication associated with NSAID use in humans. Indeed, the GI tract has been considered the major site for NSAID toxicity in both humans and animals, including cats.[13,16,21,48,57,93] In one study of the long-term use of piroxicam in 73 cats with neoplasia,[91] vomiting was the most commonly reported adverse effect (occurring in 16% in the first month), although there was evidence that other therapies (eg, chemotherapeutic agents) contributed to the reported prevalence. During long-term use of oral meloxicam at a dose of 0.1 mg/cat, vomiting was reported in 2/46 cats (4%).[14] Direct topical injury to the GI mucosa may also occur and contribute to adverse GI effects.[38,59] Although studies in cats are lacking, in humans and other species, COX-1 has a major role in maintaining the mucosal integrity. However, COX-2 expression is also thought to be important, especially for repair of injured mucosa.[48,49,94,95]

Factors that have been recognised as increasing the risks of GI adverse events in humans include higher doses of NSAIDs, the specific NSAID used, increased age, previous NSAID-associated GI disease, liver disease, pre-existing GI ulcers, and concurrent anticoagulant or glucocorticoid use.[57,59,63,77] Some of these risk factors have also been noted in dogs.[38] In humans, the two main strategies to prevent GI adverse events with NSAIDs are to use COX-1 sparing drugs, and/or a combination of an NSAID and a mucosal protectant such as a prostaglandin analogue (eg, misoprostol) or a proton-pump inhibitor (eg, omeprazole).[49,57,59,62,63,77] In cats, NSAID-associated gastric and intestinal ulceration and perforation is recognised and, in the current absence of species-specific studies, data from humans are considered relevant.[56]

Panel recommendations

Gastrointestinal disease

- It is assumed that, as in other species, COX-1 sparing NSAIDs may have a better safety profile than non-selective agents. As GI pain and discomfort may be difficult to detect clinically, the panel recommend the routine use of COX-1 sparing NSAIDs for long-term therapy in cats.
- NSAIDs should routinely be given with, or after, food in cats. Inappetence or anorexia may be an early sign of adverse GI events; hence withholding therapy in an inappetent patient is prudent. Furthermore, inappetent or anorexic cats are far more likely to become dehydrated, which would increase the risks of renal adverse events if therapy were to be continued.

Cardiovascular disease

Inhibition of COX activity by NSAIDs can have a number of potential adverse cardiovascular effects in humans. These are uncommon or rare, but include occasional exacerbation of congestive heart failure (CHF) and/or hypertension due to water and salt retention mediated by COX-1 and COX-2 suppression in the kidneys; reduced platelet aggregation and bleeding as a result of inhibition of COX-1 mediated platelet thromboxane production; and thromboembolic disease due to inhibition of COX-2 mediated endothelial prostacyclin production.[77,96–98] While ex vivo inhibition of platelet thromboxane has been demonstrated for a number of NSAIDs in cats, studies have not been able to demonstrate a clinically beneficial effect in preventing thromboembolic disease, or in promoting unwanted bleeding.[56,99] Currently, there are no data on the potential effects of NSAID therapy on blood pressure or CHF in cats, or on whether COX-2 selective agents may have a prothrombotic effect in certain individuals, such as those with a propensity to develop thromboembolism.

Panel recommendations

Cardiovascular disease

- The risks of NSAID therapy in feline cardiovascular disease are unknown.
- The panel recommend that, based on human studies, hypertensive cats receiving NSAID therapy should have their blood pressure monitored regularly. Patients with congestive heart failure should also be monitored carefully, and the NSAID use should be titrated to the lowest effective dose.
- Given the relatively high prevalence of thromboembolic disease in cats, whether long-term use of highly selective COX-2 inhibitors might increase this risk, as has been recognised in humans, deserves further investigation.

Liver disease

In humans, NSAID-induced hepatotoxicity is an uncommon or rare event. It is regarded as an idiosyncratic reaction mediated by hypersensitivity or a metabolic aberration, possibly as a result of genetic polymorphism, although with salicylates it has a predictable dose-dependent occurrence.[77,100,101] The risk of this may be higher in patients receiving other potentially hepatotoxic drugs and varies between different NSAIDs, with toxicity usually developing within the first 6–12 weeks of therapy.[100–102] Idiosyncratic hepatotoxicity has also been reported in dogs receiving NSAIDs.[103]

Severe hepatotoxicity following clinical use of NSAIDs has not been reported in cats, although this may simply reflect the lower prevalence of NSAID prescribing in this species.[56] Although NSAIDs are metabolised by the liver, pre-existing liver disease does not appear to predispose to NSAID-induced hepatotoxicity.[38] As drug metabolising pathways are often well preserved in liver disease, withholding NSAID therapy in such patients may not necessarily be required without evidence of significant liver dysfunction,[38] although reducing doses in severe/advanced liver disease is recommended in humans.[104] In humans, pre-existing advanced liver disease may be a risk factor for NSAID-associated renal and GI adverse events.[63,81]

Panel recommendations

Liver disease

- Due to the rare potential for NSAIDs to cause hepatotoxicity in other species, routine biochemical monitoring, including liver enzymes, of cats receiving long-term NSAID therapy is recommended.
- Dose-reduction (titration) should be considered in cats with pre-existing liver disease. In the presence of severe liver dysfunction (eg, as evidenced by moderate to severely elevated bile acids), and/or hypoalbuminaemia (of any cause), NSAIDs should be used with extreme caution, if at all.

NSAIDs and concomitant drug therapy

Glucocorticoids

Concomitant use of glucocorticoids and NSAIDs carries a well-characterised increased risk for adverse GI events in humans and dogs,[38,56] with an estimated 2- to 15-fold greater risk for peptic ulcer disease in humans.[59,63]

Angiotensin converting enzyme inhibitors and diuretics

The use of ACEIs (and/or angiotensin receptor antagonists) and/or diuretics along with an NSAID carries a well-recognised risk for development of acute NSAID-associated renal adverse events in humans,[63,75,81,105] and there is evidence of a higher risk when all three drugs are used together.[105] Both ACEIs and NSAIDs may individually result in altered renal haemodynamics and reduced GFR, thus together the risk may be compounded, and the use of diuretics may lead to volume depletion and a greater renal dependence on prostaglandins to maintain GFR.[105]

Anticoagulants

Although COX-1 inhibiting NSAIDs may suppress platelet thromboxane production and reduce platelet aggregation, clinically significant bleeding as a result of this is rare in humans and, to date, has not been reported in cats.[56,61,63] However, NSAIDs may appreciably potentiate the effect of warfarin, and other highly protein-bound drugs, through competitive protein binding[63] and the use of these drugs together should be avoided.

Panel recommendations

Concurrent drug therapy

- The panel recommend that concurrent use of NSAIDs and glucocorticoids should be avoided whenever possible. For short-acting glucocorticoids, a 'washout' period of around 5 days may be appropriate before starting an NSAID,[61] but longer times should be given when long-acting steroids have been used.
- Because NSAIDs are highly protein-bound and have the potential to displace other protein-bound drugs, concurrent use of protein-bound drugs with a low margin of safety, such as warfarin, digoxin, anticonvulsants such as phenobarbitone, and chemotherapeutic agents, should be pursued with great care, if at all.
- Based on data from other species, it is likely that the concomitant use of ACEIs and/or diuretics with NSAIDs will increase the risk of renal adverse effects. Appropriate care is needed if using such combinations, with increased monitoring and the use of the lowest effective NSAID dose. The use of analgesics such as opioids should be explored as alternatives to NSAIDs, or to help minimise the dose of NSAIDs required.

Monitoring cats receiving long-term NSAID therapy

Adverse drug events (ADEs) related to NSAID use most commonly affect the GI system, liver, kidneys and platelet function, but lessons learned from the long-term use of these agents in dogs suggest that this class of drug is often used inappropriately and without screening and monitoring.[106]

While the need for, and benefit of, NSAID therapy in many situations is clear, screening and monitoring is important for the clinician, owner and patient, to help minimise the likelihood of ADEs occurring. Until further data become available, especially from pharmacovigilance studies, suggested protocols for screening and monitoring cats on long-term NSAID therapy have to be based on a knowledge of the use of these drugs in both animals and humans, and it is important that protocols are adapted to the individual needs of the patient.

Testing and screening before treatment

Thorough patient evaluation before commencing therapy is crucial, with a view to identifying concurrent conditions or therapies that may impact on NSAID administration, and allowing informed client consent to be obtained.

TABLE 2 Suggested monitoring of cats on long-term NSAID therapy

Parameter		Always required	Suggested minimum	Ideal if possible
Review history with owner		✓	✓	✓
Full clinical examination (including blood pressure measurement wherever possible)		✓	✓	✓
Haematology	Haematocrit		✓	
	Complete blood count			✓
Serum chemistry	Total protein, albumin			✓
	Urea		✓	✓
	Creatinine		✓	✓
	ALT, ALP		✓	✓
	AST, GGT, bile acids			✓
	Na, K			✓
Urinalysis	Specific gravity		✓	✓
	'Dipstick' biochemisty		✓	✓
	Protein:creatinine ratio			✓
	Sediment analysis			✓

Panel recommendations

Screening before therapy

- A thorough history and physical examination is mandatory in all cats prior to commencement of NSAID therapy, paying particular attention to conditions and therapies that may impact on NSAID therapy. Wherever possible this should include blood pressure measurement (Fig 9).
- Ideally, the physical examination should be accompanied by laboratory testing. Laboratory evaluation should focus on the renal and hepatic systems, along with plasma proteins and haematocrit (see Table 2). The latter parameters may be surrogate markers of GI bleeding and/or mucosal damage. This aids in identifying potential problems and establishes a baseline for later comparison.
- Abnormalities identified in the clinical examination and on laboratory testing do not necessarily preclude the use of NSAIDs, but the risks and benefits of embarking on therapy must be discussed with the owner, and concurrent diseases may affect subsequent monitoring recommendations.

Screening during treatment

In dogs, most NSAID-related ADEs occur between 14 and 30 days (range 3–90) after the start of treatment.[107] However, it is recognised that the time for an ADE to develop is extremely variable, probably being dependent on the individual drug, the dose and the individual patient. In humans, hepatotoxicity is usually reported within the first 6 months of therapy, with more than 60% of cases reported in the first 3 months,[102] whereas acute renal failure is usually reported early, often within the first few days or weeks of commencing drug administration.[78]

Based on appropriate use of NSAIDs in other species, the prevalence of ADEs is low in healthy patients. However, the frequency of certain ADEs increases in some patient groups, and these can therefore be classified

FIG 9 Blood pressure measurement should ideally be performed as a screening measure before NSAID therapy in cats

Adverse drug effects are typically reversible with prompt recognition and intervention.

as having a 'higher' or 'lower' risk. This approach enables treatment and monitoring plans to be adjusted according to perceived risks.[57,59,60,62,63,81] Critically, ADEs are typically reversible with prompt recognition and intervention. Categorising patients as having a higher or lower risk of ADEs has clear benefits and should be equally applicable to cats, although at present this has to be based largely on knowledge of ADEs in other species, due to the lack of feline-specific data.

Panel recommendations

Classification of patients

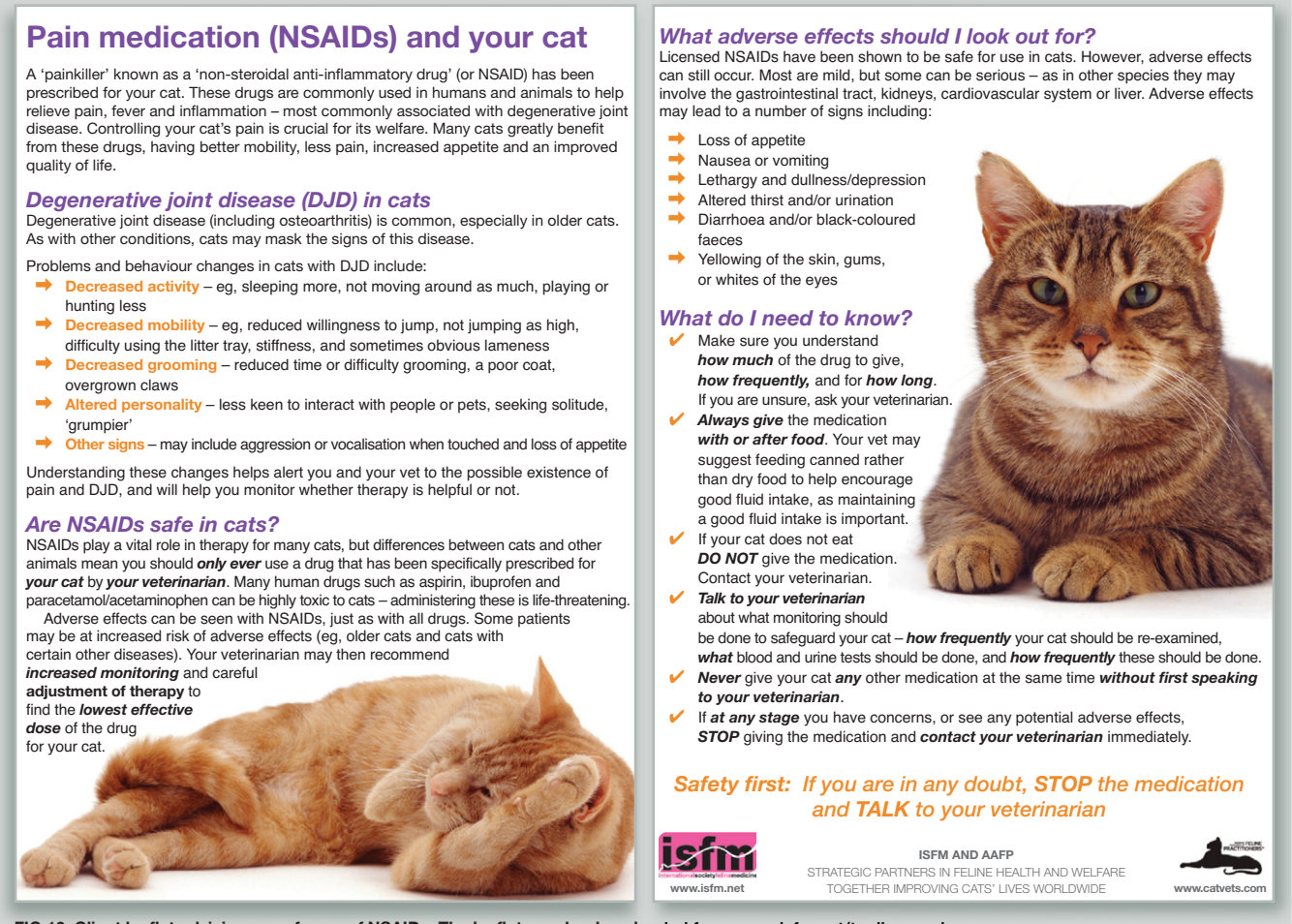
Clinical recognition of patients that may have an increased risk of an ADE relating to NSAID therapy is important – not necessarily to avoid therapy, but to encourage more cautious dosing and increased relevant monitoring. Based primarily on experience in human medicine, the panel cautiously suggest that more vigilant monitoring may be required in the following situations:

- An increased risk of renal ADEs may be anticipated in cats with functional volume depletion (renal hypoperfusion, including that associated with hypotension during anaesthesia); older cats (eg, >8–10 years of age); cats with concurrent cardiovascular, renal or hepatic disease; and cats receiving concurrent therapy with ACEIs, diuretics and β-blockers. As in humans, there may be a greater risk of NSAID-induced hyperkalaemia in patients receiving potassium supplements.
- An increased risk of GI ADEs may be anticipated in cats that are older; have had a previous history of NSAID-induced GI signs; have renal disease; are receiving glucocorticoid or anticoagulant therapy; have a history of GI disease; or have concurrent liver or other serious disease.
- An increased risk of hepatic ADEs may be anticipated in cats that are older; have renal disease; or are receiving multiple drug therapies.
- An increased risk of cardiovascular ADEs may be anticipated in cats that are older; have hypertension; or have pre-existing renal or cardiac disease. Particular care should be taken with unstable disease such as congestive heart failure or thromboembolic disease.
- The panel recommend that, where NSAIDs are used in patients with perceived higher risks of developing ADEs, greater care is taken, efforts are made to use the lowest effective dose, and increased monitoring is undertaken (see Table 2).

Panel recommendations

Monitoring during therapy

- Monitoring should take place routinely while cats are on NSAID therapy (Table 2), but the panel recognise that the extent of monitoring will be affected by many factors, including the presumed risk for the individual patient, financial constraints and owner compliance. Furthermore, multiple visits to the veterinary clinic can be stressful for some cats. Any recommendations have to be adjusted to individual situations.
- Involvement of owners in monitoring therapy is crucial. Owners need to be made aware of signs that should prompt cessation of therapy and/or the need for veterinary advice. Ideally a client leaflet, such as the one that accompanies these guidelines (Fig 10), or one supplied by the drug manufacturer, should be used to reinforce such information.
- To reduce the potential for ADEs, the panel suggest that NSAID therapy is always given with or after food. If the cat does not eat then therapy should be withheld.
- An initial reassessment of all cats is recommended after the first 5–7 days of therapy, and sooner if there is concern. Although rare, acute renal failure can be life threatening and can be seen within the first few days of therapy. In some cases a telephone conversation with the owner may suffice.
- A routine re-evaluation of all cats (Table 2) is recommended after the first 2–4 weeks of NSAID therapy. Thereafter, the frequency of re-evaluation should be based on perceived risks and patient characteristics.
- For 'lower risk' patients, the panel recommend that a re-evaluation (Table 2) should generally take place at least every 6 months.
- For 'higher risk' patients, the panel recommend that re-evaluation (Table 2) should generally take place every 2–6 months, depending on the perceived risks.
- The potential risk of ADEs is a dynamic process, and at each visit the veterinarian should reassess the patient status based on the history, physical examination ± laboratory data and determine the most appropriate ongoing monitoring.



Pain medication (NSAIDs) and your cat

A 'painkiller' known as a 'non-steroidal anti-inflammatory drug' (or NSAID) has been prescribed for your cat. These drugs are commonly used in humans and animals to help relieve pain, fever and inflammation – most commonly associated with degenerative joint disease. Controlling your cat's pain is crucial for its welfare. Many cats greatly benefit from these drugs, having better mobility, less pain, increased appetite and an improved quality of life.

Degenerative joint disease (DJD) in cats

Degenerative joint disease (including osteoarthritis) is common, especially in older cats. As with other conditions, cats may mask the signs of this disease.

Problems and behaviour changes in cats with DJD include:

- **Decreased activity** – eg, sleeping more, not moving around as much, playing or hunting less
- **Decreased mobility** – eg, reduced willingness to jump, not jumping as high, difficulty using the litter tray, stiffness, and sometimes obvious lameness
- **Decreased grooming** – reduced time or difficulty grooming, a poor coat, overgrown claws
- **Altered personality** – less keen to interact with people or pets, seeking solitude, 'grumpier'
- **Other signs** – may include aggression or vocalisation when touched and loss of appetite

Understanding these changes helps alert you and your vet to the possible existence of pain and DJD, and will help you monitor whether therapy is helpful or not.

Are NSAIDs safe in cats?

NSAIDs play a vital role in therapy for many cats, but differences between cats and other animals mean you should ***only ever*** use a drug that has been specifically prescribed for ***your cat*** by ***your veterinarian***. Many human drugs such as aspirin, ibuprofen and paracetamol/acetaminophen can be highly toxic to cats – administering these is life-threatening.

Adverse effects can be seen with NSAIDs, just as with all drugs. Some patients may be at increased risk of adverse effects (eg, older cats and cats with certain other diseases). Your veterinarian may then recommend ***increased monitoring*** and careful **adjustment of therapy** to find the ***lowest effective dose*** of the drug for your cat.

What adverse effects should I look out for?

Licensed NSAIDs have been shown to be safe for use in cats. However, adverse effects can still occur. Most are mild, but some can be serious – as in other species they may involve the gastrointestinal tract, kidneys, cardiovascular system or liver. Adverse effects may lead to a number of signs including:

- Loss of appetite
- Nausea or vomiting
- Lethargy and dullness/depression
- Altered thirst and/or urination
- Diarrhoea and/or black-coloured faeces
- Yellowing of the skin, gums, or whites of the eyes

What do I need to know?

- ✔ Make sure you understand ***how much*** of the drug to give, ***how frequently,*** and for ***how long***. If you are unsure, ask your veterinarian.
- ✔ ***Always give*** the medication ***with or after food***. Your vet may suggest feeding canned rather than dry food to help encourage good fluid intake, as maintaining a good fluid intake is important.
- ✔ If your cat does not eat ***DO NOT*** give the medication. Contact your veterinarian.
- ✔ ***Talk to your veterinarian*** about what monitoring should be done to safeguard your cat – ***how frequently*** your cat should be re-examined, ***what*** blood and urine tests should be done, and ***how frequently*** these should be done.
- ✔ ***Never*** give your cat ***any*** other medication at the same time ***without first speaking to your veterinarian***.
- ✔ If ***at any stage*** you have concerns, or see any potential adverse effects, ***STOP*** giving the medication and ***contact your veterinarian*** immediately.

Safety first: *If you are in any doubt,* ***STOP*** *the medication and* ***TALK*** *to your veterinarian*

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FIG 10 Client leaflet advising on safe use of NSAIDs. The leaflet may be downloaded from www.isfm.net/toolbox and www.catvets.com/professionals/guidelines/publications

Adverse events and adverse event reporting (pharmacovigilance)

If ADEs are encountered or undesirable effects are seen, these should be managed as appropriate. If adverse GI events are observed, NSAID therapy should be withheld, and appropriate supportive therapy introduced, until any mucosal lesions have healed. If therapy is re-instituted, it should be done so at the lowest effective dose with consideration given to the concomitant use of omeprazole (0.7–1.0 mg/kg PO q24h) or misoprostol (5.0 µg/kg PO q8h),[99,108] and/or a different NSAID where licensing permits.

Hepatotoxicity or acute renal failure are usually reversible in other species on drug withdrawal and appropriate supportive therapy, providing they are detected early enough – this emphasises the importance of patient monitoring and of ensuring clients are involved in this process. In humans, it is recommended that a three-fold increase in ALT should lead to cessation of NSAID therapy. Milder increases may prompt more attentive monitoring, with further investigations being warranted if the ALT fails to return to baseline concentrations.[57] Re-institution of alternative NSAID therapy after hepatotoxicity or acute renal failure should be done very cautiously. Increases in blood pressure have been documented in other species with NSAID therapy, and this should be monitored in cats – antihypertensive therapy or more intense antihypertensive therapy should be used as appropriate.

All ADEs should be reported to the relevant pharmaceutical company and regulatory board to help the patient and enable accurate collation of information so that we can learn more about when and why they occur.

Acknowledgements

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SUMMARY POINTS

- It is only recently that NSAIDs have become licensed for long-term use in cats in some countries.
- The panel believe that these drugs have a major role to play in the management of chronic pain in cats, but at present only limited feline-specific data are available.
- To date, published studies of the medium- to long-term use of the COX-1 sparing drug meloxicam in older cats and cats with chronic kidney disease provide encouraging data that these drugs can be used safely and should be used to relieve pain when needed.
- While further data are needed, and would undoubtedly lead to refinement of the guidelines presented here, the panel hope that these recommendations will encourage rational and safe long-term use of NSAIDs in cats, thereby improving patients' quality of life in the face of painful disease conditions.

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