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PRACTICE GUIDELINES

2024 ISFM and AAFP consensus guidelines on the long-term use of NSAIDs in cats

Practical relevance: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used and are effective for the management of pain in cats. These Guidelines will support veterinarians in decision-making around prescribing NSAIDs in situations of chronic pain, to minimise adverse effects and optimise pain management. Information is provided on mechanism of action, indications for use, screening prior to prescription, use in the presence of comorbidities, monitoring of efficacy, and avoidance and management of adverse effects.

Clinical challenges: The cat's unique metabolism should be considered when prescribing any medications, including NSAIDs. Chronic pain may be challenging to detect in this species and comorbidities, particularly chronic kidney disease, are common in senior cats. Management of chronic pain may be complicated by prescription of other drugs with the potential for interactions with NSAIDs.

Evidence base: These Guidelines have been created by a panel of experts brought together by the International Society of Feline Medicine (ISFM) and American Association of Feline Practitioners (AAFP). Information is based on the available literature, expert opinion and the panel members' experience.

Keywords: Carprofen; meloxicam; robenacoxib; analgesia; chronic kidney disease; osteoarthritis; degenerative joint disease; pain management; chronic pain

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesics in veterinary medicine, with robust evidence available for safety and efficacy in feline pain management.[1,2] In 2010, consensus guidelines from the International Society of Feline Medicine (ISFM) and American Association of Feline Practitioners (AAFP) on the long-term use of NSAIDs in cats were published,[3] providing practical and clinically applicable information for veterinary professionals. Since then, more research and new NSAIDs approved for use in cats have become available; hence, this group of drugs continues to play a key part in the management of both acute and chronic (maladaptive) pain (see box).

The '2022 ISFM Consensus Guidelines on the Management of Acute Pain in Cats'[1] discuss the use of NSAIDs in acute pain scenarios, often as part of multimodal pain management regimens. The present Guidelines provide practitioners with consensus information and advice on the appropriate use of NSAIDs in the management of chronic pain. Additional aims are to support caregivers to optimise their cat's quality of life, to minimise the potential for adverse effects and to provide a number of educational resources (see 'Resources for caregivers').

Chronic (maladaptive) pain

Chronic pain is considered maladaptive, pathological or long-term pain because it persists beyond the expected course of an acute disease process, serves no biological purpose, is not associated with healing and has no clear end point. Chronic pain can be associated with long-term diseases (eg, degenerative joint disease [DJD], periodontal disease), but can also exist without a primary identifiable cause (ie, be a disease in its own right).[2]

RESOURCES FOR CAREGIVERS

The ISFM and AAFP have produced resources for caregivers to complement the information and advice offered in these Guidelines.

- ISFM guides for caregivers:
  - 'Treating chronic (long-lasting) pain with NSAIDs'
  - 'Changes to the home environment for cats with muscle/joint pain or mobility problems'
  - 'Encouraging your cat to drink'
- AAFP client brochure:
  - 'Treating chronic pain with NSAIDs'

Available as supplementary material. Also at:

icatcare.org/advice-cat-carer-guides

catfriendly.com/NSAIDs

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The widespread role of prostaglandins in chronic pain partly explains the predictable response of most chronic pain conditions to NSAID therapies.

Mechanism of action of NSAIDs

Anti-inflammatory drugs act on different pathways of the arachidonic acid cascade to produce anti-inflammatory, analgesic and antipyretic effects (Figure 1). They inhibit cyclooxygenase (COX) enzymes in cell membranes, which in turn limits the synthesis of prostaglandins (PGs).[3,4] The most relevant COX isoforms are COX-1 and COX-2, and each is responsible for the production of PGs with diverse physiological effects. PGs produced from COX-1 activity play a role in gastroprotection (secretion of gastric mucus and production of bicarbonate), maintenance of renal perfusion under hypotensive/hypovolaemic states and vascular homeostasis (thromboxane and prostacyclin production). PGs produced from COX-2 are predominantly induced after tissue injury and trigger inflammation via numerous inflammatory mediators (ie, endotoxins, cytokines, growth factors), which sensitise peripheral nerves (eg, joint tissues in DJD, or tissues surrounding a tumour [eg, transitional cell carcinoma, squamous cell carcinoma, mammary carcinoma]).[5] Although this inflammatory process is often related to peripheral sensitisation, it can potentially evolve to central sensitisation.

Therefore, inhibition of COX-1 activity results in adverse effects whereas inhibition of COX-2 activity results in therapeutic (analgesic, anti-inflammatory and antipyretic) effects. However, COX-1 can also be associated with inflammation and COX-2 can be involved in homeostatic functions.

Different NSAIDs are associated with different degrees of inhibition of COX isoforms; drugs with greater COX-2 inhibitory effects relative to COX-1 (ie, COX-2 preferential, COX-2 selective or COX-1 sparing) are, in theory, expected to produce fewer adverse effects. However, any NSAID can induce significant adverse effects when dosage regimens are not followed or contraindications for use exist.

NSAIDs in cats

Meloxicam and robenacoxib are the most widely studied NSAIDs in cats, with strong evidence of safety and efficacy for the management of DJD-related pain (Box 1),[6–10] including in cats with stable, early chronic kidney disease (CKD) (see later).[13] They are licensed for long-term use in several countries. The unique feline metabolism must be considered when prescribing any medication for this species. Cats have deficient glucuronidation capabilities and are, therefore, at greater risk of toxicity when being administered drugs relying on this pathway for clearance (hence why paracetamol

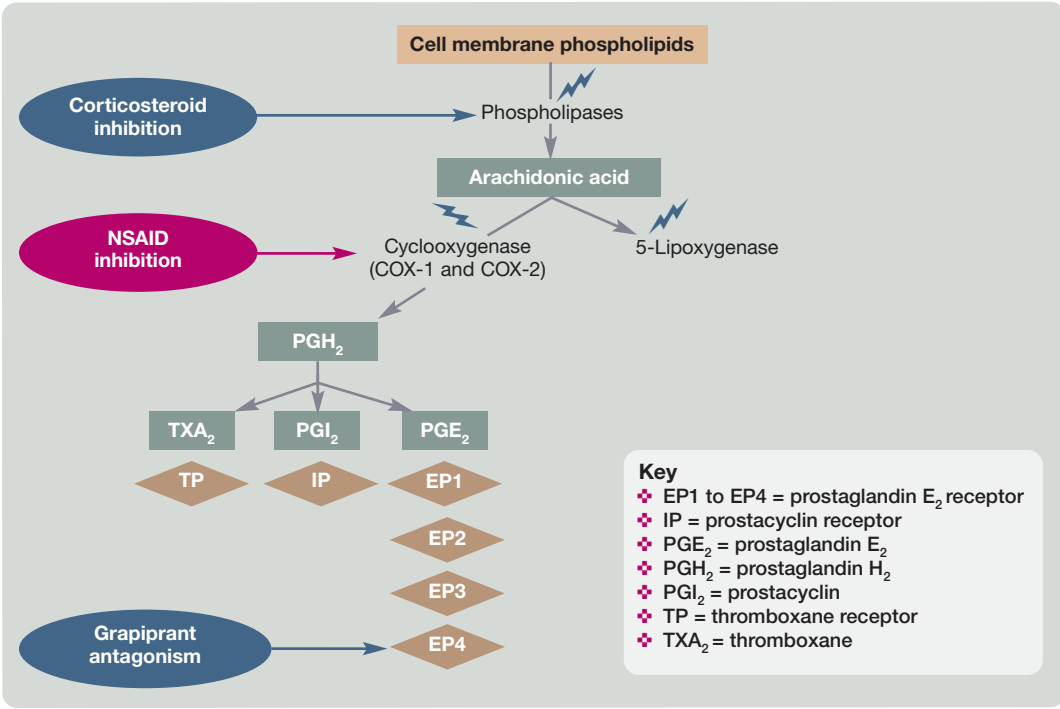


Figure 1 **Simplified version of the arachidonic acid cascade with focus on cyclooxygenase (COX)-dependent prostaglandin (PG) production. Corticosteroids act by inhibiting the action of phospholipase enzymes early in the cascade. NSAIDs act by inhibiting COX-1 and COX-2 enzymes, with consequent inhibition of PG biosynthesis. Grapiprant is an antagonist of the EP4 receptor.** *Figure adapted with permission from Monteiro and Steagall (2019)*[4]

Box 1

Degenerative joint disease and osteoarthritis in cats

The term 'degenerative joint disease' (DJD) encompasses degeneration of all types of joints (synovial, appendicular, intervertebral, fibrocartilaginous), whereas osteoarthritis (OA) refers to a chronic, low-grade inflammatory, overall degenerative process of synovial joints that is not driven by infection or immune-mediated disease. Cats with musculoskeletal pain may have a combination of osteoarthritic pain and pain from non-synovial joints.[7,11,12] For these reasons, the term 'DJD' is preferred when referring to cats being treated for musculoskeletal/joint pain.

[acetaminophen] is contraindicated in this species).[14] Meloxicam has been shown to be primarily metabolised by oxidative pathways with faecal elimination in cats.[15] Robenacoxib is also primarily excreted via faeces, but its metabolic pathway in cats remains unknown.[16]

The safety and/or efficacy of other NSAIDs, such as carprofen, ketoprofen, tolfenamic acid and vedaprofen, has been investigated in cats, but these studies have generally involved use of these drugs for the treatment of acute post-surgical and/or acute musculoskeletal pain,[17–19] or for short periods in healthy or osteoarthritic cats.[20,21] For NSAIDs such as cimicoxib and deracoxib, only limited pharmacokinetic data in healthy cats exist.[22,23] Whether any of these NSAIDs are safe or effective for the management of long-term pain in cats remains unknown. For this reason, they should not be administered to cats for this purpose.

Other anti-inflammatory drugs

Other anti-inflammatory drugs include grapiprant, corticosteroids, metamizole (dipyrone) and paracetamol. However, for various reasons, these drugs are not indicated for long-term administration and management of pain in cats.

Grapiprant is a non-COX-inhibiting NSAID. It is a PG receptor antagonist that targets the EP4 receptor (Figure 1). The drug is licensed in some countries for the control of pain and inflammation in dogs with OA, but only limited safety data exist in cats; moreover, there is unknown safety and efficacy for long-term pain.[24] As such, the panel members do not recommend its use for chronic pain management in cats. Corticosteroids have potent anti-inflammatory properties that are commonly associated with important adverse effects. They are not considered primarily as analgesic drugs and are not used for long-term pain management. Metamizole produces analgesic and antipyretic effects via the inhibition of a subform of COX-1 present in the central nervous system;[25] its adverse effects (such as agranulocytosis seen in other species)[26] and role in long-term pain management in cats are not known. Paracetamol is strictly contraindicated in cats due to the significant risk of inducing methaemoglobulinaemia.[14]

Meloxicam and robenacoxib are the most widely studied NSAIDs in cats.

Long-term use of NSAIDs is indicated particularly when inflammation is a contributing factor to chronic pain.

Box 2

Common causes of chronic pain

- Chemotherapy-induced neuropathy and radiation-induced skin burns
- CKD (eg, pyelonephritis, urolithiasis)
- DJD/OA (Figure 2)
- Dental and oral disease (eg, gingivitis, periodontitis, stomatitis; Figure 3)
- Dermatological conditions (eg, otitis, severe pruritus, burns, chronic wounds)
- Neuropathic pain (feline orofacial pain syndrome, feline hyperaesthesia syndrome, diabetes-induced neuropathy; Figure 4)
- Gastrointestinal conditions (eg, megacolon, constipation, inflammatory bowel disease)
- Neoplasia (eg, feline injection-site sarcoma, oral squamous cell carcinoma)
- Ocular conditions (eg, corneal ulcers, uveitis, glaucoma; Figure 5)
- Persistent postsurgical pain (eg, limb or tail amputation, thoracotomy, mastectomy, chronic pain syndrome after onychectomy; Figure 6)
- Previous trauma
- Urogenital conditions (eg, FIC)

CKD = chronic kidney disease; DJD = degenerative joint disease; FIC = feline idiopathic cystitis; OA = osteoarthritis

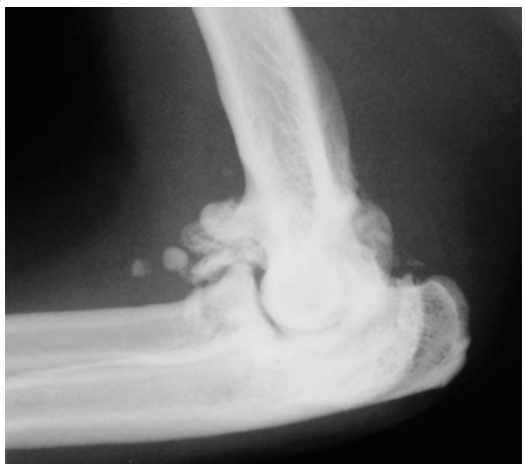


Figure 2 Lateral radiograph of an elbow showing severe osteoarthritic changes. *Image courtesy of Sam Taylor*

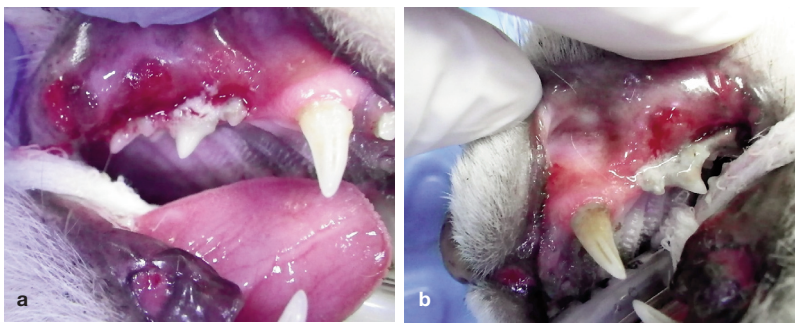
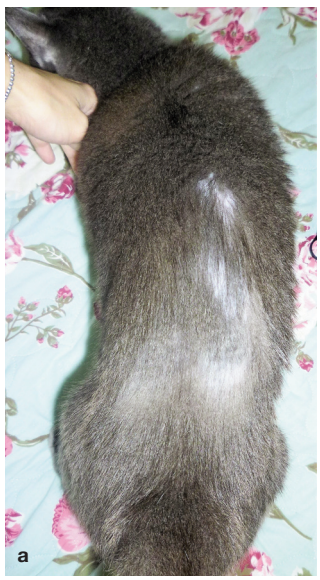


Figure 3 (a,b) Advanced periodontal disease in an 11-year-old female cat. Severe gingivitis – a source of inflammatory pain – is evident and the cat would be observed pawing at the mouth while eating. Following dental treatment under general anaesthesia, including tooth extractions, the caregivers reported that the clinical signs had subsided, and their cat was once again displaying friendly behaviours. *Images courtesy of Beatriz Monteiro*



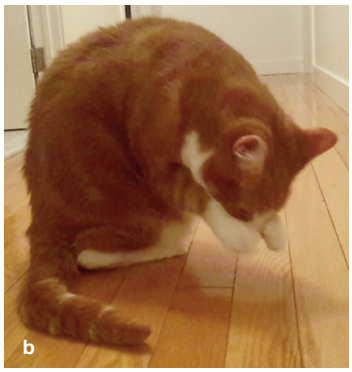


Figure 4 Sources of neuropathic pain. (a) Suspected feline hyperaesthesia syndrome. This cat would suddenly start plucking hair around the thoracolumbar area and would react to touching of this same area, showing signs of allodynia (ie, pain after a non-painful stimulus such as touch). (b) A cat with feline orofacial pain syndrome. This cat would frantically rub its face with the front paws and would vocalise for no identified reason, even after dental treatment. *Images courtesy of Beatriz Monteiro*

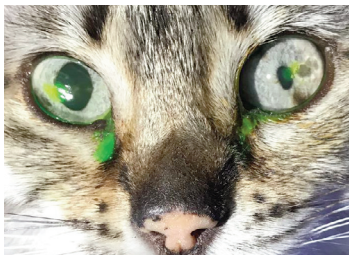


Figure 5 Ophthalmic conditions such as a corneal ulcer, as pictured in this cat, can cause chronic pain. *Image courtesy of Clarisse D'Aout*

Figure 6 Persistent postsurgical pain following onychectomy. This cat would frequently keep the left paw lifted while sitting, to avoid bearing weight on it, and even several years after surgery would resent being touched on the paw. *Image courtesy of André Desrochers*

Many of the behavioural changes associated with chronic pain will be best observed (and most readily displayed) in the home setting.

Indications for long-term use of NSAIDs in cats

Long-term use of NSAIDs may be indicated for the treatment of several chronic pain conditions in cats (Box 2), particularly when inflammation is a contributing factor.[3] In cats, many chronic pain states involve mixed, albeit varying, contributions from inflammatory, neuropathic and functional (dysfunctional) pain, with resultant changes in somatosensory system processing. As discussed, NSAIDs act to inhibit the production of PGs, which play a role in pain and sensitivity in both the peripheral and central nervous system. The widespread role of PGs in chronic pain partly explains the predictable response of most chronic pain conditions to NSAID therapies.

The most common chronic pain states in cats relate to DJD, and these are also the best studied as regards the use of NSAIDs. However, there are other chronic diseases involving significant inflammation and pain for which NSAIDs may form an important part of the treatment protocol for achieving patient comfort, although the literature is scarce.[2] Some examples include feline lower urinary tract disease (FLUTD), of which 55–65% of cases involve feline idiopathic cystitis (FIC),[27] gingivostomatitis, uveitis, skin disease and some types of cancer (Box 2).

Chronic pain should be managed using a multimodal approach, ideally involving pharmacological and non-pharmacological therapies.

FLUTD/FIC

In cats with FIC, NSAID therapy is often part of a multimodal analgesia protocol and used in combination with environmental modifications, reduction of stress and dietary management.[28,29] NSAIDs may be important in pain relief (given that the disease is associated with significant inflammation), but treatment for the underlying cause may require environmental and dietary changes, for example.[30]

While the use of NSAIDs in the management of non-obstructive FIC is not well studied, NSAIDs have been evaluated in cats with urethral obstruction. A retrospective case series involving 192 male cats with urinary obstruction revealed no association between the recurrence of obstruction and the administration of meloxicam.[31] A subsequent prospective, randomised, placebo-controlled clinical trial in cats with obstructive FIC found that short-term administration of oral meloxicam (0.1 mg/kg on day 1 and 0.05 mg/kg on the following 4 days) did not reduce the prevalence of urinary obstruction relapse when compared with placebo.[32] The treatment duration in the latter study may have been too short; and other factors may have influenced reobstruction. Another prospective, randomised clinical trial evaluating cats with obstructive FIC treated with low-dosage meloxicam (0.025 mg/cat PO q24h) in combination with alprazolam and phenoxybenzamine for 14 days, did not find any reduction in long-term recurrence rates or signs of FIC (up to 6 months after discharge) when compared with cats not receiving meloxicam, although the study was underpowered.[33]

In cats with idiopathic cystitis, NSAID therapy is often part of a multimodal protocol incorporating environmental modifications, reduction of stress and dietary management.

The studies described did not specifically focus on pain management, rather mostly on the impact of NSAID therapy on the disease itself. Therefore, cats may have benefited from pain relief as a result of treatment with NSAIDs, even if outcomes in terms of recurrence rates were not affected. Another consideration, given that most of these studies were underpowered, is the possibility of a type II error having occurred (ie, a false-negative finding).

Administration of NSAIDs to cats with FLUTD may be appropriate as part of a multimodal regimen involving analgesia and environmental modification, depending on the individual case and any contraindications. The risk of acute kidney injury (AKI) in cats with various causes of FLUTD and ongoing decreased water intake, and particularly cats with urethral obstruction, azotaemia, hyperkalaemia and dehydration, must not be overlooked.

Dental/oral disease

Feline chronic gingivostomatitis (FCGS), another very painful condition affecting many cats, is characterised by significant persistent (potentially lifelong) oral inflammation. The inflammatory component involves the mucogingival junction, and buccal and caudal oral mucosa, producing erosive and bleeding lesions. Clinical signs of severe oral pain include reduced grooming, halitosis, repelling behaviour (hissing, swiping), weight loss and lethargy, among others.[34,35] Treatment should focus on management of the periodontal disease (eg, dental extractions), while addressing other factors (eg, pathogens).

NSAID therapy with long-term administration may be part of a multimodal analgesic approach for postoperative pain management and given alongside other medical treatments.[36] Postoperative pain is severe after multiple dental extractions in cats with FCGS, with one prospective clinical trial reporting changes in behaviours and feeding in cats for up to 3 days after surgery, even when receiving opioids, local anaesthetic blocks and

NSAIDs.[37] Some of these cats may require hospitalisation and long-term administration of opioids, as well as NSAIDs.

Prospective, randomised studies on the use of NSAIDs for the palliative treatment of FCGS are scarce in the literature. One such investigation, a 12-week, randomised, double-blinded clinical study of 13 cats with caudal stomatitis, reported that clinical signs were improved in 77% of cats receiving a combination of bovine lactoferrin oral spray and piroxicam (0.3 mg/kg PO q48h).[38]

Neoplasia

NSAIDs may also be beneficial for the treatment of some cancers, as well as for palliative care. Certain neoplasms (eg, transitional cell carcinoma of the urinary bladder, mammary carcinoma, oral squamous cell carcinoma; Figure 7) may have a COX expression pattern, with therapeutic and prognostic implications.[39–42] Specifically, COX-2 expression by neoplasms is linked to angiogenesis, decreased apoptosis, inflammation, cell proliferation and matrix metalloproteinase production.[43]

Figure 7 **A female cat with oral squamous cell carcinoma affecting the rostral mandible. Clinical signs included decreased appetite, halitosis, ptyalism and dysphagia for approximately 1 month. Changes in behaviour, including irritation and difficulty in jumping up, were also reported by the caregiver.** *Image courtesy of Beatriz Monteiro*

Long-term therapy with oral piroxicam was retrospectively reviewed in 73 cats with a variety of neoplasms; doses of 0.13–0.41 mg/kg q24h were given over a treatment period ranging from 1–38 months. Treatment was not associated with changes in haematological and biochemical profile, but 29% of cats presented with increased vomiting and other mild and transient adverse effects.[44] In another retrospective study, meloxicam (ie, a COX-2 preferential NSAID in cats) was used as the primary treatment in 11 senior cats with transitional cell carcinoma of the urinary bladder.[45] Dosage regimens included a mean initial dose of 0.09 mg/kg (range 0.01–0.3) PO q24h for the first 3–7 days and a mean maintenance dose of 0.04 mg/kg (range 0.01–0.1) PO q24h thereafter, and clinical improvement (ie, decreases in haematuria and/or dysuria) was reported. Most neoplasms had a higher prevalence of COX-1 than COX-2 expression; those cats with transitional cell carcinoma with COX-2 expression had lower mean survival times than those with negative COX-2 expression.[45] A 2022 phase 1 (dose escalation) clinical trial demonstrated that low-dose oral meloxicam in combination with standard-dose toceranib (starting dose of 0.01 mg/kg meloxicam on opposite days to toceranib, increasing up to a maximum of 0.02 mg/kg q24h) was well tolerated in 21 cats with cancer not involving the kidneys, and there were no significant adverse effects necessitating treatment interruption.[46]

Assessment of chronic pain

Behavioural signs

Behavioural signs continue to be the best indicator of chronic pain states in cats.[47] Unlike acute pain scales, instruments for chronic pain assessment mostly rely on caregiver observation of behavioural changes. These vary by condition, but changes often relate to the cat's routine activities, mobility, social interactions, mood or temperament.[48] Most of the instruments that have been validated are for assessment of chronic pain associated with DJD; additional instruments evaluating the effects of chronic pain have been developed to assess health-related quality of life.

A core element in the assessment of pain associated with chronic disease conditions is the use of clinical metrology instruments (caregiver questionnaires) to capture behavioural changes, which are best identified in the home environment. This approach is combined with review of home video clips and photographs, and veterinarian examinations.

Table 1 summarises the various tools available for chronic pain assessment.

Physical examination findings

Veterinary assessments include comprehensive physical examinations (see guidance on cat friendly interactions in the '2022 AAFP/ISFM Cat Friendly Veterinary Interaction Guidelines: Approach and Handling Techniques'[57]) and additional examinations, as indicated (orthopaedic, neurological, dental/oral, ophthalmic). Sedation should be considered when needed to thoroughly examine painful areas (including the oral cavity), but it must be remembered that sedatives/anxiolytics can often change behavioural indicators of pain.[58] Further investigations, such as imaging, may be indicated based on physical examination findings.

As many of the behavioural changes associated with chronic pain will be best observed (and most readily displayed) in the home setting, short video clips (20–30 s) of specific behaviours captured by caregivers, such as walking, going up and down stairs, and jumping up and down, are an excellent extension of the examination/consultation room assessment (see Table 1).

Behavioural signs are the best indicator of the presence of chronic pain in cats. They are also critical in monitoring a cat's response to NSAID treatment.

Table 1 Tools for chronic pain assessment in cats

Tool	Condition	User	Ease of use	Purpose	Validation
Physical examination	All	Veterinarian	Moderate, requires training	Screening, diagnosing, monitoring	Not formally validated for assessment of pain
In-clinic observation	All	Veterinarian and veterinary nurse/ technician	Moderate, requires training	Monitoring	Not formally validated for assessment of pain
Home video clips and photographs	All	Caregiver collects information, veterinarian evaluates	Moderate, requires instructions	Screening, monitoring	Not formally validated for assessment of pain
Activity monitor	All	Clinical research	Challenging to set up and operate	Monitoring	Validated for DJD[49]
Feline Musculoskeletal Pain Screening Checklist (Feline MiPSC)[a]	OA/DJD	Caregiver	Simple	Screening	Validated[50]
Feline Musculoskeletal Pain Index (FMPI)[b]	OA/DJD	Caregiver	Simple	Monitoring	Validated[51,52]
Montreal Instrument for Cat Arthritis Testing (Caretaker) (MI-CAT[C])[c]	OA/DJD	Caregiver	Simple	Monitoring	Moderately validated[53,54]
Client Specific Outcome Measures – feline (CSOMf)[d]	All	Caregiver	Moderate	Monitoring	Moderately validated[52,55]
Health-related quality of life (HRQL)[e]	All	Caregiver	Simple	Monitoring	Moderately validated (not specific to pain)[56]

The aim of this table is to summarise relevant conditions for each approach to chronic pain assessment, as well as who the primary user is, how easy the assessment is to use and what the purpose is. The final column provides information on whether the assessment tool has been validated for its purpose with respect to pain – that is, whether (for the conditions indicated) the tool has been demonstrated to be a valid measure of the impact of pain. DJD = degenerative joint disease; OA = osteoarthritis
[a]Figure 5 in Enomoto et al (2020)[50] – pubmed.ncbi.nlm.nih.gov/32122226
[b]painfreecats.org/the-fmpi
[c]ars.els-cdn.com/content/image/1-s2.0-S0168159117303271-mmc2.pdf
[d]cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments
[e]newmetrica.com/vetmetrica-hrql

Overview of indicators of chronic pain

Table 2 provides an overview of indicators of chronic pain, incorporating both behavioural signs and physical examination findings. In cases where chronic pain is suspected, but signs are equivocal, trial analgesic therapy can be useful (Box 3).

Trial analgesic therapy can be useful when chronic pain is suspected, but hard to detect.

Box 3

Use of trial analgesic therapy to assist the diagnosis of chronic pain

Signs of chronic pain in cats can be subtle. Trial analgesic therapy can be useful when chronic pain is suspected, but hard to detect. Once appropriate diagnostics have been performed, analgesics may be prescribed. A decrease in or resolution of clinical signs (application of objective measures, as indicated in Table 1, may be helpful), and/or an improvement in appetite, social interaction, and so on, may confirm the presence of chronic pain.

The use of standardised measures (Table 1) is recommended to monitor the response to trial analgesic therapy, but it should be noted that the absence of an improvement following trial therapy may not completely rule out chronic pain. Chronic pain is difficult to treat and there is relatively little evidence for the efficacy of analgesics for chronic pain in cats (beyond the use of NSAIDs and anti-nerve growth factor monoclonal antibodies [anti-NGF mAbs] for osteoarthritic pain). Thus, a lack of response should be interpreted cautiously.

Practical long-term NSAID therapy

Patient assessment

Before prescribing long-term NSAID therapy, cats should be assessed for suitability and to identify any contraindications or factors to be considered in dosage and monitoring. Box 4 presents a suggested screening protocol.

Table 2 Overview of behavioural signs and physical examination findings that can be associated with chronic pain conditions in cats

Pain condition	Behavioural signs	Physical examination findings	Comments
Dental and oral pain	Dropping food, chewing on one side of the mouth or chewing more slowly. Resistance to handling of the mouth. Subtle signs may include only decreased appetite or a change in food preferences. Head held down. Reluctance to having the head and oral area petted or palpated	Resistance to oral examination. Ptyalism and halitosis. Gingivitis or stomatitis may be seen. Enlarged mandibular lymph nodes. Grooming may have decreased, resulting in an unkempt haircoat. Weight loss	Ensure retraction of lower lip to allow examination of all teeth. Sedation may be needed for full oral examination. Some lesions are only identified on radiography (Figure 8). Some cats show few signs other than weight loss from a chronic reduction in food intake
DJD	Changes in mobility and performance of daily activities. Lower overall activity. Changes (reduction) in social interaction and tolerance of petting/handling. Changes in elimination habits	Muscle loss (Figure 9). Pain and decreased range of motion on flexion/extension of joints. Unkempt haircoat may be seen	Caregiver video clips of the cat jumping up and down, going up and down stairs, walking and playing are useful in diagnosis
Neoplasia	A wide range of behavioural changes is possible, dependent on the site of the cancer	Dependent on the site of the cancer	Bone pain may present with similar clinical signs as DJD. Oral examination under sedation may be needed to identify oral neoplasia
FLUTD (eg, urolithiasis, FIC)	Pollakiuria, dysuria, straining, haematuria and vocalisation during elimination (Figure 10). Urination outside the litter tray/box	Small painful bladder (FIC) or large firm bladder (ie, obstruction). Pain on abdominal palpation	House-soiling can persist past resolution of clinical signs if learned avoidance of the litter tray/box has occurred
Neuropathy/neuropathic pain	Excessive attention paid to a particular area, including overgrooming of that area. Cats with feline hyperaesthesia syndrome may show rippling/twitching of skin spontaneously or when touched, may appear to be trying to bite their hind end or chase their tail, and may vocalise (growl, hiss or yowl) and/or run away	Significant reaction (often with vocalisation and skin rippling) to palpation of an area. Evidence of self-trauma	Caregiver video clips of specific behaviours may be useful. Condition may be exacerbated by stress
Persistent postsurgical pain	Excessive licking of the site of previous surgery	Sensitivity to palpation of the site of previous surgery. Evidence of self-trauma	Although there may be a record of surgery or trauma, a lifelong history with information on procedures (eg, onychectomy as a kitten) or injuries may be unavailable
Ear/skin infection	Scratching and overgrooming. With ear infection, a low head carriage, head tilt or other unusual head position may be seen	Erythema, debris and areas of alopecia from overgrooming (Figure 11). Signs and lesion distribution will be disease-dependent	Full otic examination may require sedation, particularly if painful
Abdominal pain (eg, pancreatitis, urolithiasis (Figure 12], cholecystitis)	Abnormal behaviour, including reduced interaction with caregivers, and increased hiding/sleeping. Inappetence and other signs of illness (eg, vomiting)	Resentment of abdominal palpation, lip licking and weight loss/reduced body condition. Other indicators will be dependent on pathology (eg, jaundice)	Pain on abdominal palpation may be hard to detect. Further tests are needed for diagnosis

DJD = degenerative joint disease; FIC = feline idiopathic cystitis; FLUTD = feline lower urinary tract disease

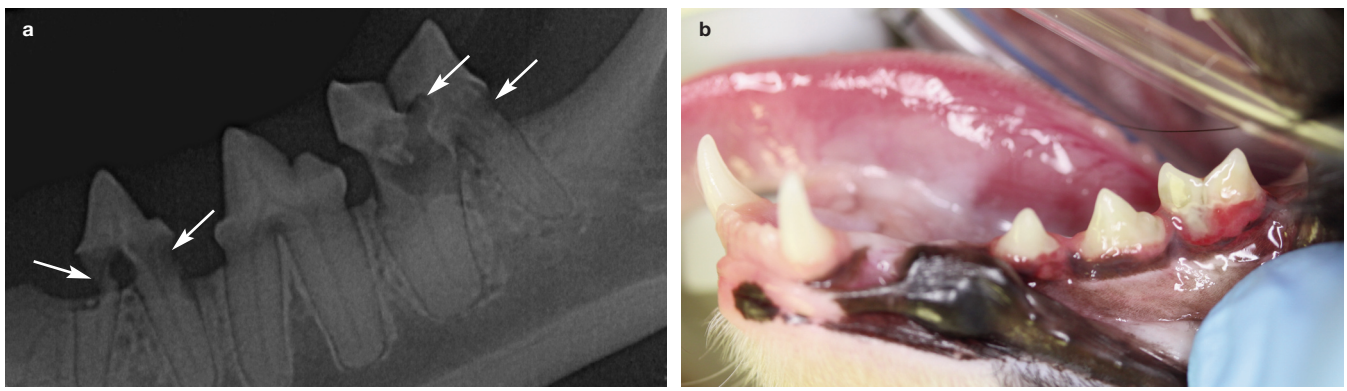


Figure 8 **(a) Radiograph of resorptive lesions (arrows) likely to be causing chronic pain. (b) Appearance on clinical examination; the lesion on tooth 307 is not visible.** *Images courtesy of Rachel Perry*

Figure 9 **A 20-year-old cat with moderate to severe DJD in multiple joints. Note the generalised loss of muscle mass.** *Image courtesy of Beatriz Monteiro*

Figure 10 **Pollakiuria and haematuria in a cat with FIC.** *Image courtesy of Sam Taylor*

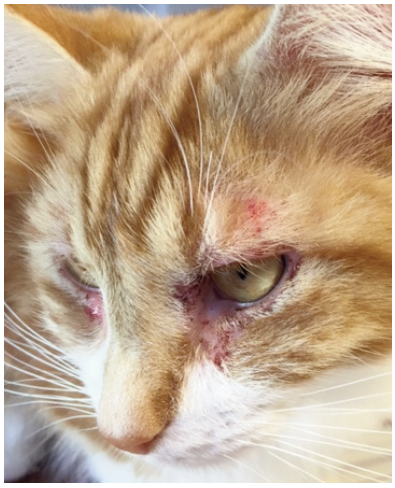
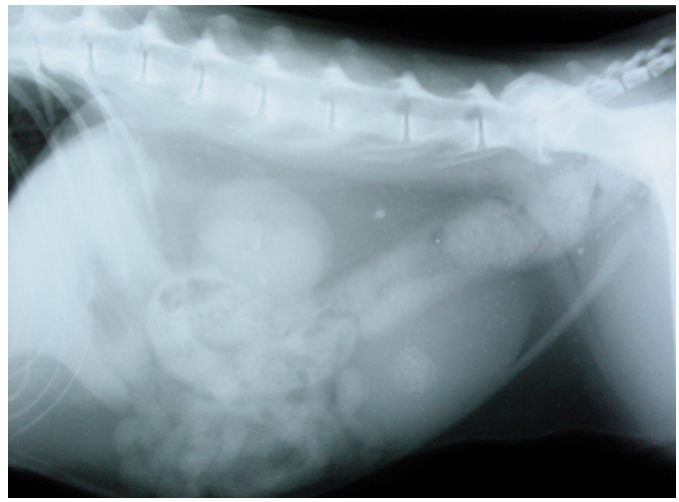


Figure 11 **Erythema, excoriation and alopecia in a young cat with food-responsive dermatitis.** *Image courtesy of Sam Taylor*

Figure 12 **Radiograph of a cat with urolithiasis presenting with pain on abdominal palpation. Note also the presence of lumbar spondylosis, which may be an additional cause of pain.** *Image courtesy of Marina Aylagas*



Screening allows discussion with clients about risk assessment and facilitates transparent informed consent. If long-term NSAIDs are pursued, screening creates an opportunity to minimise the risk of adverse drug effects (eg, by discontinuing glucocorticoids, maintaining adequate hydration, controlling blood pressure, monitoring laboratory trends, etc).

Medicating cats

Cats are notoriously difficult to medicate with oral drugs. While this may be the subject of many a cartoon and animation on the internet, these sadly reflect the reality of the negative experience that can result for cats and their caregivers. Difficulty with drug administration impacts treatment compliance, the bond between cats and caregivers, and the well-being of both.[59,60]

Box 4

Screening prior to NSAID therapy

A comprehensive history, thorough physical examination and some basic laboratory tests are critical in determining if a cat is a good candidate for long-term NSAID therapy.

- **History** should disclose chronic illness, such as CKD, chronic enteropathy or diabetes mellitus, which could make a cat prone to dehydration. History-taking should also include concurrent medications, especially those that affect the kidneys (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors) or those that could affect the gastrointestinal tract (eg, glucocorticoids), as these could increase the risk of adverse effects of NSAIDs
- **Physical examination** should be systematic and include the following: assessment of hydration status and mucous membrane colour; body weight, body condition score and muscle condition score; heart and lung auscultation; and abdominal palpation, including evaluation of kidney size and shape. Additionally, systolic blood pressure assessment (Figure 13) and fundic examination are recommended prior to administering long-term NSAIDs
- **Laboratory testing,** including a haematocrit as a minimum, or ideally a complete blood count, is helpful to evaluate for anaemia. A serum chemistry profile helps to determine pretreatment renal function and liver status. Assessment of urine specific gravity is essential; ideally, dipstick testing and a sediment examination is performed, and, if proteinuria is present, a urine protein:creatinine (UPC) ratio is determined

Figure 13 **Assessment of blood pressure is important prior to prescribing long-term NSAIDs. Note that blood pressure assessment in this cat is being performed in the base of the carrier, using headphones to minimise noise and stress.** *Image courtesy of Sam Taylor*

For cats, protective (negative) emotions associated with forceful administration of medications may cause stress and exacerbate the underlying condition; in patients with chronic pain, which are likely to be receiving multiple medications ('pill burden'), the issue is complicated further. For caregivers, the negative emotional, physical, financial and time impact of chronic conditions in the home care situation[61] – the 'caregiver burden' – requires recognition by, and support from, the veterinary team. Involving veterinary nurses/technicians in providing that support, including giving demonstrations on how to administer medication (Box 5), and following up with caregivers with open conversations on the challenges and successes they have encountered, can be highly beneficial.[59]

The 'caregiver burden' (the negative emotional, physical, financial and time impact of chronic conditions in the home care situation) requires recognition by, and support from, the veterinary team.

Box 5

Supporting caregivers in medicating cats with NSAIDs

Supporting caregivers needing to medicate cats can have positive effects on the cat–caregiver bond and success of therapy. Practical considerations include:

- Demonstrating aspects of medicating, including drawing up the correct volume of medication into the syringe, and giving tablets or liquid directly to the cat
- Use of pill putty-type treats, liquid treats (Figure 14) and other ways of hiding medications, in order to aid compliance
- Rewarding the cat, following successful medication, with a positive experience such as a treat or a positive social interaction (eg, brushing or playing with a favourite toy)

Figure 14 **Use of liquid treats to hide medications can aid compliance with treatment regimens.** *Image courtesy of Sam Taylor*

Choosing the NSAID

For reasons discussed above, meloxicam and robenacoxib are the NSAIDs of choice for long-term pain management in cats. In practice, the choice of one vs the other is based on preference, availability, palatability and formulation. Proprietary meloxicam (eg, Metacam, Boehringer Ingelheim; Meloxidyl, Ceva) and robenacoxib (Onsior, Elanco) for cats are available, with different label recommendations in different countries. Generic formulations of meloxicam are also available, which are identical to the branded drug in terms of active ingredient, safety, strength, route of administration, purity, quality and intended use.[62] Compounded NSAID products (including transdermal) are available in some countries, but veterinarians should be aware of the lack of guarantee of potency, bioavailability, efficacy, purity, quality control and safety of such products.[63]

Choosing an orally administered drug for long-term treatment requires careful thought as regards palatability and ease of administration. In one study, oral meloxicam was reported to be palatable when given with food on a long-term basis to cats with OA.[10] A separate clinical trial found both meloxicam and ketoprofen to be effective analgesics in cats with acute or chronic locomotor disorders when either was administered for 5 days; however, meloxicam was assessed to be significantly more palatable than ketoprofen.[64]

Choosing the dosage regimen

Dosing should follow label recommendations. Yet, for myriad reasons, this is not often the practice and clinicians may select alternative regimens to suit the individual cat. Dosing recommendations may vary on a case-by-case basis, with the aim of reaching an ideal balance between treatment compliance, maximum efficacy and minimum risk of adverse effects. Honest and empathetic communication with caregivers is key, as not only are they involved in administering medications, they are also directly involved with the clinical monitoring of the cat (vis-à-vis efficacy and safety). As such, they are part of the healthcare team.[65] Indeed, treatment outcomes and caregiver satisfaction are likely to improve when caregivers are empowered (see box).

Caregiver empowerment

In the context of the present discussion, empowerment is the outcome of a partnership between veterinarian and caregiver in which the latter is provided with knowledge, resources and tools, and is given authority to make informed decisions related to the cat's treatment.[65]

Unfortunately, when long-term medication is initiated, caregivers are not always given information on how to medicate their cat.[60] Accompanying guides on treating chronic pain with NSAIDs (see 'Resources for caregivers') are intended to help address this problem.

Frequency of administration of NSAIDs is usually daily (q24h), although some veterinarians may recommend administration every other day (q48h) or even less frequently. It is important to note that inadequate frequency of administration (q48h or q72h) may lead to suboptimal treatment if pain is not appropriately monitored. Differences in clinical response are partly explained by the pharmacokinetic and pharmacodynamic profile of different drugs, but primarily are due to individual patient variability, and the severity and stage of disease.[66,67] This underlines the importance of frequent monitoring of efficacy and safety, and of implementing dose titration as required.

Other dosing considerations, including timing of administration and use of the 'lowest effective dosage', are discussed below.

- **Timing of administration** may impact analgesic efficacy. Circadian body rhythms influence physiological functions and pathogenesis of diseases such as OA, with consequent impacts on treatment outcomes.[68] Thus, synchronising treatment administration with the biological rhythm of disease activity can help to optimise outcomes.[69] For example, the peak effect of the medication should coincide with the time that the cat experiences most pain, whether that is during periods of daytime activity or at night when pain might disturb sleep.
- **Use of the lowest effective dosage** is recommended by the panel members and other panels of experts,[2] although limited efficacy data are available on this topic. As NSAID-related adverse effects are dose-dependent, there is a strong rationale for using this approach, and it has been reported in several studies with cats, including those with stable CKD and those with cancer.[10,46,70–72] With regard to efficacy, only a few studies have demonstrated analgesic effects of a lower-than-approved dose of meloxicam;[8,73] equivalent data are not yet available for robenacoxib.
- **Accuracy of dose adjustments** for orally administered drugs may present a challenge and will depend on the formulation of the drug. Liquid formulations may be more easily adjusted to a target dose than tablets.
- **Pairing NSAID administration with food,** given immediately after drug administration or at the same time, has numerous advantages. It ensures the medication will not become trapped in the oesophagus. Pairing medication administration with a positive stimulus is also an example of 'classical conditioning', which contributes to reduced stress. Occasionally, adding medications to food can cause or exacerbate food aversion, so caregivers should be cautioned against mixing NSAIDs with the cat's regular food, unless readily accepted, to avoid food aversion developing or worsening. Because gastrointestinal issues, including inappetence, are the most common adverse effect of NSAIDs, it may be wise to offer a small amount of food prior to mixing the drug with food, to ensure the cat's appetite is normal. If the cat refuses food, the NSAID should be withheld and veterinary advice sought.

Switching medications

Reasons for switching one NSAID for another might include cost, availability, formulation, lack of clinical efficacy or development of adverse effects. A washout period (when the patient receives no NSAIDs) is recommended to reduce the risk of adverse effects. Although recommendations remain anecdotal, longer washout periods should be applied when the reason for switching NSAIDs is related to adverse effects, to allow for resolution of the adverse effects and any related pathology. Box 6 provides tips on this, as well as other practical aspects of NSAID therapy. Potentially, non-NSAID analgesics might be used during the washout period.

Box 6

Practical NSAID therapy

- Perform diagnostic tests and use validated pain scales for chronic pain, where possible (Table 1)
- Start with the full dose of the NSAID on day 1 (Table 3)
- For overweight or obese cats, calculate the NSAID dosage based on lean body weight rather than current weight
- For underweight cats and/or those with reduced body condition, consider investigating for underlying illness and enhancing nutrition before treating with NSAIDs
- Weigh cats and perform body condition scoring regularly (including at home) to allow dosage adjustments, as required
- Maintain the cat on the recommended long-term dose for the specific NSAID product for a few weeks
- Gradually decrease the dosage while monitoring the treatment response (ideally with the same validated pain scale[s] as initially used) to achieve the lowest effective dosage
- Consider decreasing the frequency of administration, while monitoring efficacy
- If switching NSAIDs for reasons other than adverse effects, implement ideally a 7-day washout period, with monitoring for worsening signs of pain (which, in some cases, will necessitate a shorter period)
- If switching NSAIDs because of adverse effects, a minimum of 7 days of washout is recommended; the washout period should be long enough to allow the adverse effects and any pathology to resolve

Table 3 Recommended dosages of commonly used NSAIDs for long-term pain management in cats

NSAID	Dosage recommendations*	Comments	References
Meloxicam	❖ 0.1 mg/kg PO once	First dose to be administered when starting long-term treatment	Benito et al (2013)[74]
	❖ 0.01–0.05 mg/kg PO q24h	Normally start at 0.05 mg/kg, following first dose (see above) Lowest effective dosage may be used long-term	Guillot et al (2013)[8] Gunew et al (2008)[10] Gruen et al (2015)[73] Benito et al (2013)[74]
Robenacoxib	❖ 1 mg/kg (range 1–2.4) PO q24h	Formulation available in 6 mg tablets; number of tablets depends on body weight Lowest effective dosage may be used long-term	King et al (2016)[6] Adrian et al (2021)[7] King et al (2021)[72]

*Veterinarians are advised to consult medication data sheets for more information. NSAID = non-steroidal anti-inflammatory drug; PO = orally

Anaesthesia and surgery when cats are receiving long-term NSAIDs

Prior to anaesthesia and surgery, knowledge of medications the cat is currently receiving is vital to avoid inadvertent overdosage and adverse effects – underlining the need for excellent history-taking (Box 4). Cats on long-term NSAID therapy undergoing surgery or diagnostic procedures under anaesthesia should receive the same NSAID perioperatively, unless it is contraindicated, and this may be in injectable form and followed up with oral administration, depending on label recommendations.[75]

The greatest concern with respect to NSAID use during anaesthesia and surgery pertains to the risk of renal adverse effects, including AKI. Preanaesthetic assessment (clinical examination, body weight and condition, hydration status), assessment of blood pressure and, if indicated, preanaesthetic blood tests, should be performed. Continuous monitoring of blood pressure during anaesthesia, ensuring a minimum mean arterial pressure of 70 mmHg (or >90 mmHg if using Doppler), is recommended. Fluid therapy should be provided, with fluid rates and types chosen on a case-by-case basis. Some cats will benefit from intravenous fluids prior to the procedure to ensure hydration. NSAIDs should not be administered to hypovolaemic or hypotensive patients. If hypotension resolves, it may be preferable to give NSAIDs at the end of, or after, the procedure. The 'AAFP Feline Anesthesia Guidelines' provide further information on perianaesthetic management.[76]

Cats requiring long-term NSAIDs postsurgery

Some surgical procedures may induce substantial postoperative pain, sustained nociceptive activity, and extensive tissue damage and inflammation, requiring off-label long-term NSAID therapy. Key considerations with respect to long-term NSAID therapy after surgery are outlined in Box 7.

Cats on long-term NSAID therapy undergoing surgery or diagnostic procedures under anaesthesia should receive the same NSAID perioperatively, unless it is contraindicated.

Box 7

Long-term NSAID therapy after surgery

For cases where long-term NSAID therapy is required after a surgical procedure, the panel members' recommendations are as follows:

- The pros and cons of long-term NSAID therapy after surgery should be evaluated on a case-by-case basis with clinical judgement
- Risks and potential adverse effects should be discussed with the caregiver
- The rationale for using these drugs should not only take into consideration the classic NSAID-induced adverse effects, but also possible drug interactions (eg, with concomitant administration of corticosteroids or angiotensin receptor blockers such as telmisartan), as well as comorbidities (see 'NSAIDs and comorbidities')
- Timing of NSAID administration can be critical for postoperative pain relief and may be determined based on risks related to surgery and anaesthesia, such as intraoperative bleeding, hypovolaemia, dehydration, and any potential for AKI with intraoperative hypotension and insufficient fluid therapy
- Use of parenteral fluids during surgery is strongly advocated to reduce the risk of renal toxicity associated with perioperative and/or long-term postoperative NSAID therapy
- In line with many drug label recommendations, use of the lowest effective dosage for the shortest duration, consistent with individual response (ie, pain assessment, severity of pain, follow-up data and prognosis), is advocated
- Veterinarians should familiarise themselves with label indications, dosage information and routes of administration

Monitoring the clinical response to NSAIDs

Just as behavioural signs are the best indicator of the presence of chronic pain in cats, they are also critical in monitoring a cat's response to NSAID treatment. This is particularly true for conditions with a neuropathic component, as NSAIDs may be inadequate to address this type of pain.[77] Thus, it is important to have benchmarks to ensure that a real response is seen vs a caregiver placebo effect (ie, improved outcome ratings in the absence of improvement in objective measures).[78] Regular reassessment is needed to evaluate whether pain has been controlled, and to refine the pain management plan, as required.

Serial measurements using pain monitoring tools – such as the FMPI, CSOMf or MI-CAT(C) clinical metrology instruments for musculoskeletal conditions described in Table 1 – are helpful for standardisation of monitoring, particularly when multiple clinicians and staff members will be talking with the caregivers. These instruments generate a score that can be tracked over time. In addition, video updates of the same behaviours that were used in diagnosis can be invaluable for monitoring progress and response to therapy. For cats with DJD, while individual changes in behaviour will occur, those that have objectively been shown to be improved by NSAID treatment include jumping, stair use, gait/speed, agility and play,[51,79] as well as mood/happiness.[7]

More generally, as many cats treated with long-term NSAIDs are senior (>10 years old), they should ideally be benefitting from regular 'wellness' checks to aid early identification of comorbidities (see below) or loss of body condition, and to address any caregiver concerns. Involvement of the whole veterinary team, including veterinary nurses/technicians, can be beneficial for promotion and undertaking of this type of monitoring.

Frequency of blood test monitoring for cats on NSAIDs

A question that often arises is 'how often should blood tests be repeated when cats are receiving NSAIDs?' Unfortunately, there are no clinical data to define or guide clinicians on how frequently to perform monitoring blood tests. Clinical pathology testing should be tailored according to the individual cat and caregiver considerations. However, 6-monthly reassessment of stable patients with a minimum laboratory database to identify potential adverse effects is recommended.

Objective measures can be used to monitor cats' response to NSAID therapy.

NSAIDS and comorbidities

Commonly, cats requiring long-term analgesic support have pre-existing medical conditions, and the presence of such comorbidities can be a cause for concern when prescribing NSAIDs. For example, up to 69% of cats of all ages with DJD have concomitant CKD.[6,70,80–82] History-taking and appropriate screening prior to institution of NSAID therapy (Box 4) are important, as is consideration of the potential for interactions with concurrent medications (see 'NSAIDs and other drugs').

The remainder of this section considers the most common comorbidities, with a particular focus on CKD.

Chronic kidney disease

Cyclooxygenase enzymes (both COX-1 and COX-2) are constitutively expressed in the kidneys of cats,[83] and the PGs they produce promote normal renal physiology, perfusion, autoregulation, sodium–water balance and renin production. In patients with CKD, the concern is that NSAID administration could cause constriction of afferent arterioles, thus affecting renal blood flow and glomerular filtration rate (GFR), with accompanying elevations in creatinine and symmetric dimethylarginine (SDMA), and progression of renal disease. Several studies have been performed to investigate the use of NSAIDs, specifically meloxicam and robenacoxib, in cats with CKD, allowing updated guidance to inform patient selection, drug, dosing and monitoring recommendations.[6,10,13,70,71] For a summary of this research, and general recommendations stemming from it, see the box 'Long-term use of NSAIDs in cats with CKD: what is the research telling us?'.

Other comorbidities

CKD, as well as being a common comorbidity in cats with DJD and chronic pain, is also the most common condition associated with hypertension, with azotaemia reported in up to 74% of hypertensive cats.[87] Treatment of hypertension is a priority to prevent target organ damage,[88] but the combination of NSAIDs and antihypertensive drugs can potentially result in complications. Alternatively, non-NSAID treatments for management of chronic pain may be appropriate for hypertensive cats (see 'NSAIDs and other drugs'). Other comorbidities such as hyperthyroidism may complicate, but should not preclude, the management of chronic pain, which may include NSAID therapies.

In practice, each case should be evaluated individually when it comes to the use of NSAIDs.

Long-term use of NSAIDs in cats with CKD: what is the research telling us?

Meloxicam studies

In a prospective open-label study, the administration of oral meloxicam (0.01–0.03 mg/kg q24h) for 6 months was deemed safe in cats with OA but without CKD, based on the lack of reported clinical signs and no difference in serum creatinine concentrations between the treatment group and the case-matched non-arthritis group.[10] Subsequently, two clinical studies on the long-term (6 months) use of meloxicam in cats with CKD were published,[70,80] and the results were reviewed by the World Small Animal Veterinary Association (WSAVA) Global Pain Council.[13] In the opinion of the panel members, although these reports offered optimism for the use of NSAIDs in cats with CKD (the study authors concluding that NSAIDs were 'safe' in cats with 'stable' CKD[70,80]), critical review is warranted. Both studies with meloxicam were retrospective and allocation of cats to treatment groups was not blinded, but rather clinician dictated, opening up the studies to numerous biases. Moreover, the dosages used were variable, ranging from 0.01–0.05 mg/kg PO q24h, and conclusions were based on serum creatinine and blood urea nitrogen (BUN) levels and urine concentrating ability, which may not be highly sensitive markers of renal function.

Longevity in cats, with and without pre-existing CKD, treated with meloxicam long-term (0.02 mg/kg PO q24h for >6 months) was also examined in one of the two clinical studies.[70] Cats with CKD treated with meloxicam lived a median of 18.6 years, and 1608 days after CKD diagnosis,[70] which is favourable compared with earlier published survival times of cats with CKD (637–1151 days).[84,85] Theories for this lifespan difference encompass improved mobility during NSAID therapy, including increased ability to walk to the water bowl and maintain hydration, increased ability to play and interact with family, and overall improved quality of life. Prolonged lifespan might also be due to decreased inflammation within the kidney, slowing progression of renal disease.[71]

In a more recent study on the use of meloxicam in cats with CKD, 21 cats with International Renal Interest Society (IRIS) stage 2 or 3 disease were randomly divided into either a placebo (n = 6) or treatment (n = 15) group.[71] The treatment group cats were administered meloxicam, at 0.02 mg/kg q24h, for 6 months. Monitoring was more extensive than in the studies discussed above – incorporating blood pressure, blood chemistry, SDMA, GFR (iohexol clearance), urinalysis, UPC, urinary transforming growth factor-beta 1 (TGF-β1):creatinine ratio, urinary clusterin, urinary cystatin B and serum inosine measurements – and was performed at baseline, and at 1, 3 and 6 months. At 6 months, the mean UPC was greater in the meloxicam group, with no difference between the groups for any other measured variable, indicating no change in renal excretory function. Cats in this study did not have a painful musculoskeletal disease; therefore, the efficacy of the tested dosage (0.02 mg/kg q24h), which is below the labelled dosage and dosages known to be efficacious in client-owned cats with OA, is unknown.

Robenacoxib studies

Robenacoxib has been evaluated for clinical safety in cats with OA, with and without CKD.[6,14] In the first study, a total of 194 cats with OA were enrolled, including 40 cats with CKD, and randomly allocated to receive either robenacoxib (target dosage 1 mg/kg, range 1.0–2.4, PO q24h) or placebo for 28 days.[6] No differences in adverse effects were observed between the treatment and placebo groups, nor were there differences between the groups in terms of BUN or creatinine alterations from baseline values. Moreover, robenacoxib was well tolerated, even in cats with IRIS stage 2 or 3 CKD.[6]

In a follow-up study, the authors pooled the results from four separate clinical trials in order to report adverse effects in 449 cats with chronic musculoskeletal disease, including 126 cats with pre-existing CKD, receiving either robenacoxib (target dosage 1 mg/kg, range 1.0–2.4, PO q24h) or placebo for 4–12 weeks.[72] The study found no increased risk of having one or more adverse effects in cats receiving robenacoxib vs placebo, even those with pre-existing IRIS stage 1, 2 or 3 CKD. Creatinine concentrations increased in the robenacoxib group during treatment (by +4.36 µmol/l; 95% confidence interval [CI], 0.21–8.50) but did not change significantly in the placebo group. However, the clinical relevance of this creatinine increase is undetermined, as related adverse effects were similar between groups, with two of the robenacoxib-treated cats developing renal insufficiency and one placebo-treated cat developing renal failure. Pelligand et al[86] documented that healthy cats (n = 7) receiving robenacoxib (1–2 mg/kg PO q12–24h for 48 h) in combination with furosemide (2 mg/kg PO q12h) also had increased serum creatinine concentrations from baseline compared with placebo (13.9 µmol/l increase for q24h dosing, 22.4 µmol/l increase for q12h dosing), but maintained a stable GFR as measured by endogenous urinary creatinine clearance. While short-term use of robenacoxib has appeared to be safe in cats with CKD, a prospective study looking at GFR, and perhaps UPC, would be helpful to further elucidate the long-term renal effects and safety of robenacoxib in cats with CKD.

What to conclude?

There is limited evidence supporting or refuting the long-term use of NSAIDs in cats with chronic pain and concomitant CKD. What is clear is that if NSAID therapy is to be considered, adequate patient selection is paramount. NSAIDs can be used in many cats with 'stable' CKD (see box), but should be avoided if CKD is unstable (progressive) or the cat is dehydrated, hypovolaemic or hypotensive. This requires monitoring of laboratory parameters (including UPC) to help identify a stable patient and potential candidate for NSAID therapy. Routine rechecks allow tapering to the lowest effective dosage for the individual cat and early recognition of adverse effects.

'Stable' CKD

Stable CKD is defined as a patient with minimal changes in body weight and creatinine concentrations over a period of at least 2 months, and which is normotensive and non-proteinuric, or has controlled concurrent conditions including hypertension (see 'NSAIDs and other drugs'), hyperphosphataemia and proteinuria, and no evidence of urinary tract infection.

Clinicians and caregivers should plan a treatment regimen that focuses on improving feline welfare and quality of life; in other words, one that provides pain relief while minimising the risk of adverse effects. If uncertainties exist regarding the suitability of a cat for NSAID administration, other analgesics should be considered (eg, anti-NGF mAbs if the underlying condition is DJD). Further general recommendations are presented in Box 8.

Box 8

Use of NSAIDs in cats with CKD: panel members' recommendations

- Optimal patient selection is crucial, and cats should be screened prior to starting NSAID therapy (Box 4)
- The ideal cat has stable, IRIS stage 1, 2 or 3 CKD (see earlier definition of 'stable' CKD)
- The cat should be well hydrated and eating/drinking well, with normal blood pressure and controlled concurrent disease, prior to starting long-term NSAID therapy
- The risks vs benefits of NSAID use should be discussed with the caregiver
- An NSAID should be selected that has been studied in cats with CKD (eg, meloxicam or robenacoxib)
- An appropriate oral dose should be chosen based on evidence in cats, and tapered to the lowest effective dosage over time (eg, a starting dosage for meloxicam may be 0.02 mg/kg q24h)
- Caregivers should encourage cats to maintain ideal hydration throughout therapy by providing ample access to fresh water and considering wet food options. Further suggestions for ways of increasing water intake in cats are provided in an accompanying guide (see 'Resources for caregivers')
- Caregivers should be educated on how to monitor for adverse effects of NSAIDs, dehydration and signs of progression of renal disease (see 'Resources for caregivers')
- IRIS guidelines, available at iris-kidney.com, on management of CKD should be followed for treatment and monitoring recommendations
- Cats should be monitored for adverse effects and ongoing need for NSAIDs, as well as the potential for alternative therapies. This can be conducted in conjunction with CKD recheck assessments, and at least every 6 months is a reasonable timeframe for cats receiving meloxicam;[71] more frequent monitoring of creatinine concentrations might be advisable in cats receiving robenacoxib[6]
- Between assessments at the veterinary clinic, caregivers can be encouraged to monitor body weight, and body and muscle condition score at home, as well as to report any changes in behaviour, appetite or other concerns promptly

NSAID administration: adverse effects and contraindications

An adverse drug event (ADE) is defined as an undesired effect (eg, adverse effect) or lack of effect for claimed indications of a drug.[89] An ADE is a common reason NSAID treatment is stopped or the patient is switched to an alternative NSAID or different class of drug. ADEs may occur after correct use of an NSAID (ie, idiosyncratic drug reactions), but many are related to incorrect drug use. Importantly, there are various recognised contraindications to the use of NSAIDs in cats (Box 9). ADEs may occur when cats are given human NSAID products, such as ibuprofen, resulting in severe toxicity.[90]

Human NSAID products given to cats are likely to cause severe toxicity.

Potential adverse effects of NSAIDs relate to the consequences of PG inhibition and include gastrointestinal irritation, renal and hepatic damage, and prolonged bleeding time (see 'Mechanism of action of NSAIDs'). The timing of ADEs is not predictable.

Prevalence of ADEs

The prevalence of NSAID-related ADEs in cats is unknown. The number of cats receiving long-term NSAID therapy is difficult to track and not all ADEs are reported (see box). Even in dogs, where long-term NSAID therapy is more common and more drugs are authorised for use, it is difficult to critically evaluate evidence related to ADEs.[91]

Box 9

Contraindications to the use of NSAIDs

Absolute contraindications

- Hypovolaemia
- Dehydration
- Hypotension
- Advanced kidney disease – IRIS stage 4
- Progressive/unstable kidney disease
- Concurrent treatment with drugs that affect renal function (eg, aminoglycosides)
- Liver dysfunction/failure (eg, hepatic lipidosis)
- Concurrent corticosteroid treatment
- Anorexia, vomiting, melaena and/or diarrhoea
- Acute gastrointestinal disease, gastrointestinal disease with compromised mucosa

Caution required

- Advanced age (eg, 'super'-senior cats [>15 years])
- Stable CKD – IRIS stage 1, 2 or 3 (see 'NSAIDs and comorbidities')
- Anaemia or thrombocytopenia
- Other gastrointestinal disease without mucosal compromise
- Bleeding disorders
- Concurrent treatment with other drugs (Table 4): eg, ACE inhibitors/angiotensin receptor blockers, diuretics, anticoagulants and highly protein-bound drugs such as warfarin, digoxin and anticonvulsants (eg, phenobarbital)

Reporting of ADEs

To increase the knowledge base surrounding ADEs, it is important they are reported so that they can be investigated. Reports should be made to the relevant pharmaceutical company and regulatory body, based on geographical location (eg, in the USA, the Food and Drug Administration's Center for Veterinary Medicine; in the UK, the Veterinary Medicines Directorate; in Europe, the European Medicines Agency). Pharmaceutical companies are obliged to investigate ADEs as part of their pharmacovigilance responsibilities and may supply support to assist in the treatment of affected patients. Regulatory bodies can create databases that facilitate the identification of causes of ADEs.

Any NSAID can induce significant adverse effects when dosage regimens are not followed or contraindications for use exist.

The gastrointestinal tract

Gastrointestinal effects are the most commonly reported ADEs in cats receiving NSAID therapy and range from mild (vomiting) to catastrophic (gastrointestinal perforation). Vomiting has been reported in up to 14% of cats receiving long-term NSAID therapy but may not trigger withdrawal of treatment.[44] PGs play a role in mucosal protection and repair, and maintenance of gastrointestinal blood flow, and it is by inhibiting production of PGs that NSAIDs may cause gastrointestinal damage, resulting in anorexia, diarrhoea and vomiting.

Bleeding into the gastrointestinal tract from mucosal erosions may result in haematemesis or haematochezia/melaena, which caregivers should be informed to report immediately to their veterinary team. In other species, ulceration and perforation are usually associated with long-term inappropriate administration of two NSAIDs or an NSAID in combination with a corticosteroid, use of higher than labelled doses or lack of close patient monitoring.[92] Repeated dosing of carprofen, which is labelled for a single dose, was the likely cause of a duodenal perforation in one cat.[93]

The kidney

The key to understanding the risks of kidney injury associated with NSAID therapy lies in the role of PGs in euvolaemic and hypovolaemic states. Data from feline-specific studies are available. One reported that short-term use of meloxicam (0.2 mg/kg PO once on day 1, followed by 0.1 mg/kg q24h on days 2 to 5) had no effect on GFR when cats were euvolaemic.[94] In a further study, meloxicam was administered for up to 7 days (0.2 mg/kg SC once on day 1, followed by 0.1 mg/kg SC q24h on days 2 to 7) to healthy cats with a reduced renal mass (experimentally induced); no changes in GFR, creatinine concentrations or UPC were recorded.[95] Dehydration and hypovolaemia increase the risk of adverse effects and advice should be given to all caregivers on improving their cat's water intake (see 'Resources for caregivers').[96]

A review of ADEs in the UK found that renal insufficiency occurred significantly more often in dogs and cats when injectable vs oral NSAIDs were administered; NSAIDs included in the study were carprofen, ketoprofen, meloxicam and robenacoxib.[96] A potentially confounding factor is that injectable formulations are used most commonly when patients are under anaesthesia, and thus might be prone to hypotension or hypovolaemia, but it highlights that additional caution is required in this scenario (see 'Anaesthesia and surgery when cats are receiving long-term NSAIDs').

Clinical signs of NSAID-associated renal adverse effects are generally difficult to assess in the clinical setting unless renal disease is significant and changes are severe. Signs are nonspecific and may include decreased appetite, vomiting, thirst and depression. Creatinine concentrations and BUN are not sensitive indicators of early kidney disease and it is recommended that SDMA, urine specific gravity and UPC are also monitored. See 'NSAIDs and comorbidities' for more detailed discussion on the use of NSAIDs in cats with CKD.

The liver

Drug-induced liver injury (DILI) occurs at variable times after drug exposure, and can range from mild and transient elevations in liver enzymes to liver failure and death.[97] In humans, there is no gold standard for diagnosis of DILI, which usually relies on circumstantial evidence (ie, exposure to drugs, and illness or changes in liver enzymes and/or liver function). Three types of DILI are described: hepatocellular, cholestatic and mixed.[98] Hepatic transaminases (alanine transaminase [ALT] and aspartate aminotransferase [AST]) may be elevated in various conditions in cats (liver disease, hyperthyroidism, neoplasia) which can confuse detection of hepatotoxicity related to NSAID treatment. Increases in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are not induced by NSAID therapy in cats.

While liver enzymes are not good indicators of liver function, their elevation after initiation of NSAID therapy could suggest DILI. Although there are no clear guidelines on when to stop administration of NSAIDs in cats based on liver enzyme values, it would be prudent to stop and/or to run liver function tests if aminotransferase enzymes are two or three

times higher than the upper normal limit after initiation of therapy. Liver function tests may include assessment of serum bile acids; additionally, decreased albumin and cholesterol and elevated bilirubin levels are suggestive of poor liver function. However, decisions are at the discretion of the clinician and dependent on the individual patient. If there are no alternative treatments to alleviate pain in a cat, the risks (including other ADEs) and benefits of continuing treatment must be considered.

Coagulation and bleeding

NSAIDs may have effects on coagulation, as the balance between the activity of COX-1 and COX-2 enzymes promotes haemostasis (ie, avoids thrombosis and uncontrolled bleeding). This balance could be disrupted after the administration of NSAIDs. In vitro and in vivo measurements of coagulation and bleeding include platelet aggregation, partial prothrombin time and buccal mucosal bleeding time, and should be considered where clinically relevant. That said, NSAIDs authorised for use in cats are unlikely to have any clinically significant effect on coagulation or bleeding. However, the interaction between NSAIDs and warfarin is reported to cause increased risk of bleeding in humans and this combination of drugs should be avoided in cats when possible.[99] The use of NSAIDs with other anticoagulants, such as clopidogrel and rivaroxaban, has not been studied in cats but is likely also to increase the risk of haemorrhage, as in humans.

Responding to ADEs

The risk of NSAID-induced adverse effects is minimised by judicious selection of patients, consideration of concurrent medications, frequent monitoring, accurate drug administration and caregiver education. In the event of ADEs, supportive therapy is initiated on a case-by-case basis, and the duration of treatment may be variable.

✣ **Gastrointestinal effects** If adverse gastrointestinal effects occur, supportive therapy should be instituted until mucosal lesions heal. Intestinal epithelium is replenished every 3–4 days.[100] Clinical signs should thus improve within a few days of stopping NSAID therapy and instituting supportive care in mild cases of gastrointestinal erosion; more serious intestinal erosions and ulcerations may take longer to heal, potentially requiring hospitalisation. Treatment includes ensuring good hydration with oral, subcutaneous or intravenous fluid administration, and use of gastrointestinal protectants. Proton pump inhibitors, histamine type-2 receptor antagonists, misoprostol and sucralfate decrease gastric acidity and support or promote mucosal protective mechanisms.[101] Guidance on the appropriate use of these agents can be found in an open access consensus statement from the American College of Veterinary Internal Medicine.[101]

✣ **Liver injury** Management of DILI includes cessation of NSAID administration and institution of supportive care. The latter may involve fluid therapy and treatment of any other clinical signs such as gastrointestinal erosions. Products to support liver function (eg, milk thistle, *S*-adenosyl-L-methionine [SAMe] and silybin–phosphatidylcholine complex [Denamarin, Nutramax Laboratories]) are widely used in cats but challenges of compliance with oral medication should always be considered.[59] SAMe may be hepatoprotective; this suggests potential benefits as synthesis is diminished in liver disease, which may lead to exacerbation of liver injury. However, clinical evidence for the use of these products in humans and cats is lacking.[102] Confirmation of DILI is made if liver enzymes return to baseline values shortly after cessation of treatment. The half-life of ALT and AST has been reported to be about 3.5 h and 80 mins, respectively, in cats.[103]

NSAIDs and other drugs

Cats that may benefit from NSAID therapy are frequently receiving other medications. Knowledge of potential drug interactions or the influence of combined medications on the risk of adverse effects is important. Potential drug interactions with NSAIDs and precautions to consider in cats receiving concurrent treatments are described in Table 4.

In humans, treatment of CKD with ACE inhibitors in combination with NSAIDs can lead to adverse effects,[104] especially decreased GFR and possible AKI. A study in healthy cats showed no difference in GFR (as determined by iohexol clearance) when concurrent treatment with benazepril and robenacoxib was given for 7 days;[82] however, a long-term study in cats with CKD would be beneficial to better understand this potential risk. In humans receiving diuretic therapy, the effect of volume depletion amplifies the potential for NSAID-

The risk of NSAID-induced adverse effects is minimised by judicious selection of patients, consideration of concurrent medications, frequent monitoring, accurate drug administration and caregiver education.

Table 4 Drug categories of potential concern when cats receiving medications are prescribed NSAIDs

Drug category	Concerns when prescribed with NSAIDs*	Available feline research	Precautions to consider*
ACE inhibitors	Decreased GFR, and increased creatinine concentration and AKI (in humans). NSAIDs might interfere with action of ACE inhibitors, making them less effective	In healthy cats, no effect on GFR was seen when benazepril and robenacoxib were administered together for 7 days.[82] No data are available for cats with CKD	Avoid NSAIDs or use lowest effective dosage if ACE inhibitors are necessary. Monitor creatinine concentration, blood pressure and UPC closely
Amlodipine	Can cause hypotension, which could increase the risk of NSAID-induced renal injury. NSAIDs can make amlodipine less effective at controlling hypertension (in humans)	No data in cats	Avoid combination if possible. Monitor creatinine concentration and blood pressure, if used concurrently
Angiotensin receptor blockers	Can cause hypotension, which could increase the risk of NSAID-induced renal injury. NSAIDs can make angiotensin receptor blockers less effective at controlling hypertension (in humans)	No data in cats	Avoid combination if possible. Monitor creatinine concentration and blood pressure, if used concurrently
Diuretics	Can lead to dehydration, which can increase the risk of NSAID-induced renal injury. NSAIDs can decrease the efficacy of some diuretics	No data in cats	Avoid NSAIDs or use the lowest effective dosage if diuretics are necessary. Monitor creatinine concentration closely
Fluoxetine	Can increase the risk of GI adverse effects of NSAIDs (in humans)	No data in cats	Avoid combination if possible
Glucocorticoids	Can increase the risk of NSAID-induced GI lesions (in humans)	No data in cats	Avoid combining glucocorticoids and NSAIDs in cats. Aim for a 5- to 7-day washout period for short-acting steroids; allow for a longer washout for long-acting steroids. Consider GI protectants if washout is not possible
Other NSAIDs	Combining NSAIDs can increase the risk of NSAID-induced GI lesions, hepatic injury and AKI (in humans)	No data in cats	Avoid combining NSAIDs. For example, do not give a cat injectable meloxicam and then discharge with oral carprofen for use at home

*These concerns are based on research in other species; precautions have been extrapolated to cats until further research is available
ACE = angiotensin-converting enzyme; AKI = acute kidney injury; GFR = glomerular filtration rate; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug; UPC = urine protein:creatinine ratio

induced renal injury,[105] and this adverse effect is also a concern in cats. Thus, administration of ACE inhibitors and/or diuretics with NSAIDs should be avoided in cats when possible, with close monitoring if these medications are needed concurrently. Preferably, alternative analgesic drugs should be provided to manage chronic pain in this circumstance.

In humans, NSAIDs can increase tubular sodium and water retention; this can lead to hypertension and make therapy with ACE inhibitors, amlodipine and angiotensin receptor blockers less effective, as well as triggering decompensated heart disease.[106] If NSAIDs are used concurrently with blood pressure medications, monitoring of blood pressure is important to maintain the patient in a normotensive state. Hypertension can result in target organ damage, such as retinal detachment and blindness, while hypotension can result in renal hypoperfusion and AKI. Since it can be challenging to predict the peaks and troughs of a feline patient's blood pressure throughout the day or week based on a series of measurements performed during a single appointment, it is advised to avoid combining NSAIDs with antihypertensive drugs when possible and to seek alternative analgesics.

NSAID therapy in itself carries a risk of gastrointestinal adverse effects, but this risk can be increased when NSAIDs are administered with glucocorticoids. Dogs with gastrointestinal ulceration at post-mortem examination were found to be 3.4 times more likely to have received glucocorticoids than dogs without ulcers;[107] while this effect is not well documented in cats, caution is warranted. Similarly, administration of multiple NSAIDs concurrently can increase the risk of gastrointestinal bleeding, hepatic injury and AKI in humans,[108] and is also best avoided in cats.

Meloxicam can be used in combination with toceranib in cats with cancer to provide support for pain and inflammation, but routine screening and monitoring should be performed, especially in cats with underlying CKD or urothelial cancer.[46]

Alternatives to NSAIDs

Chronic pain should be managed using a multimodal approach, ideally involving pharmacological and non-pharmacological therapies (eg, environmental modifications and complementary treatments such as acupuncture, laser therapy and physical therapy). When NSAIDs are not an option, or when a feline patient needs additional analgesic support, alternative medications and strategies are available.

✣ **Anti-NGF mAbs** Frunevetmab (Solensia, Zoetis) is an anti-NGF mAb provided as a monthly subcutaneous injection and used to manage the pain of OA in cats. In one study, caregivers reported significantly better global improvement in frunevetmab-treated cats vs placebo,[11] and a further randomised, placebo-controlled, double-blinded superiority study showed significant improvement in frunevetmab-treated cats over placebo on various outcome measures.[109] Adverse effects can include dermatitis, alopecia and pruritus.[12,110] Similar to NSAIDs, anti-NGF mAbs are recommended as first-line treatments for DJD/OA in cats and dogs according to pain management guidelines from the WSAVA and American Animal Hospital Assocation.[2,111] Long-term studies (beyond 6 months) and studies investigating the safety of frunevetmab with concurrent NSAIDs and other medications, and in the face of comorbidities, are still needed in cats. There are, for example, currently limited published data on the safety and efficacy profile of this anti-NGF mAb in cats with DJD/OA and concomitant CKD, although the mentioned studies included some cats with IRIS stage 1 and 2 CKD.[11,12,109]

✣ **Gabapentin** In practice, gabapentin might be used alone or in combination with NSAIDs to provide analgesia for cats with DJD. In a small (n = 20) blinded, randomised, placebo-controlled study,[112] gabapentin (10 mg/kg PO q12h) decreased activity in geriatric cats with OA (sedation was the most common adverse effect reported), while improving impaired activities, when compared with placebo; the researchers used activity monitors and client-specific outcome measures, respectively, to investigate these outcomes. As well as sedation, some cats showed ataxia, weakness and muscle tremors during gabapentin treatment.[112] Gabapentin may decrease arterial blood pressure in cats with and without CKD, which should be considered when using with NSAIDs.[113]

✣ **Pregabalin** Although studied as an anxiolytic in cats,[114] pregabalin may also have utility as an analgesic in cats, as it does in other species.[115]

Cats with chronic pain treated with NSAIDs and suffering an acute flare-up of existing disease may benefit from additional analgesics such as opioids.

✣ **Tramadol** The synthetic opioid tramadol has been shown to have good oral bioavailability in cats. Clinical trials have found that geriatric cats with OA had improved mobility and caregiver-assessed quality of life when administered 2 mg/kg tramadol PO q12h, as compared with placebo,[116] and that tramadol decreased outcomes related to central sensitisation in cats (measured by temporal summation).[117] In another investigation with a similar population,[118] 15 cats receiving meloxicam (oral transmucosal spray) alone or with tramadol for 25 days showed some improvement using different outcome measures, and treatment was generally safe. Self-limiting gastrointestinal adverse effects were more common in the cats receiving the meloxicam/tramadol combination (n = 5) than those receiving meloxicam alone (n = 1).[118] The half-life of tramadol is longer in cats than in dogs, allowing q12h dosing for cats.[119] Dose-dependent adverse effects can include gastrointestinal upset, euphoria and sedation,[116] and the tablets are bitter. The transdermal formulation of tramadol has been found to result in undetectable or low plasma concentrations of the drug and should be avoided.[120]

✣ **Amantadine** This medication is an antagonist of *N*-methyl-D-aspartate receptors, which play a role in central sensitisation and, hence, chronic pain. A blinded, placebo-controlled study showed that amantadine improved caregiver-identified impaired mobility and quality of life in cats with OA, although activity was decreased in the treatment group.[121]

✣ **Omega-3-enriched diets and omega-3 supplements** Although only three studies met the criteria for inclusion, a systematic review and meta-analysis of enriched therapeutic diets concluded that there was evidence to support the use of omega-3 supplements and enriched diets in cats with OA.[122,123] One study reported improved mobility, activity and positive changes in behaviour when the diet was supplemented with 1.53 g eicosapentaenoic acid (EPA) and 0.31 g docosahexaenoic acid (DHA) per 1000 kcal of metabolisable energy.[122] In cats, 60–70 mg/kg body weight of EPA and DHA combined is suggested, and it is recommended to start at one-quarter to one-half of the goal dosage to avoid gastrointestinal upset. 'Joint diets' may also be beneficial for cats with OA.[124]

Rescue analgesia

There may be occasions when a cat with chronic pain needs a 'rescue' analgesic; for example, when there is an acute flare-up of an existing disease (eg, FIC), or the cat undergoes surgery related or unrelated to their chronic condition (acute-on-chronic pain). Rapid-onset relief is best achieved with opioids, such as buprenorphine or methadone.

Cat friendly techniques to reduce chronic pain

Emotions and pain perception

Pain is both a sensory and an emotional experience.[125] The sensory experience refers to the perceptual qualities of the sensation – what it 'feels like' (eg, sharp/burning/tingling, anatomical location, severity). The emotional experience refers to how this sensation makes one feel – how aversive or unpleasant it is (eg, heightened fear–anxiety, frustration).

The pain experience that is ultimately perceived is the result of multiple modulatory mechanisms acting on the pain pathway; collectively, they increase or decrease the nociceptive message coming from the periphery and the spinal cord before it reaches the brain to be consciously perceived. These mechanisms that facilitate or inhibit pain relate to the neurobiology of the individual, including how the pain pathway is functioning. However, there are numerous other factors – such as the cat's physical and social environment, previous experiences, cognitive function and emotional state – that also influence pain perception (Figure 15).

The protective (negative) emotion of pain results in learning that guides behaviours and influences future decisions to avoid harm. Overall, protective emotions increase pain perception, whereas engaging (positive) emotions decrease pain perception.[126–128] Therefore, all measures taken to minimise protective emotions and promote engaging emotions, both in the home and veterinary clinic environment, can contribute to decreased pain perception in cats. Although protective emotions generally increase the pain experience, a phenomenon known as stress-induced analgesia can occur in situations of extreme stress, pain or fear, producing a reduction in pain as a survival benefit. For example, analgesia in an animal with a broken bone may allow escape from a life-threatening situation.[129] However, as soon as the animal is back to safety, the pain will return. In practice, this means that pain may be underestimated in highly stressed patients, and strategies that reduce fear–anxiety will decrease such confounding effects.

Environmental modifications in the home to decrease pain

To decrease protective emotions and lessen their impact on the chronic pain state, environmental modifications can be made in the home that focus on providing for cats' behavioural and emotional needs. As discussed in the '2022 ISFM/AAFP Cat Friendly Veterinary Environment Guidelines'[130] and the '2023 AAFP/IAAHPC Feline Hospice and Palliative Care Guidelines',[131] pillars of an ideal environment for cats include a safe place, multiple and separated resources, opportunities for play and predatory behaviour, positive, consistent and predictable social interactions with humans and other animals, and respect for the importance of a cat's sense of smell and other senses. These all reflect aspects of the natural history that has shaped the domestic cat's environmental needs.

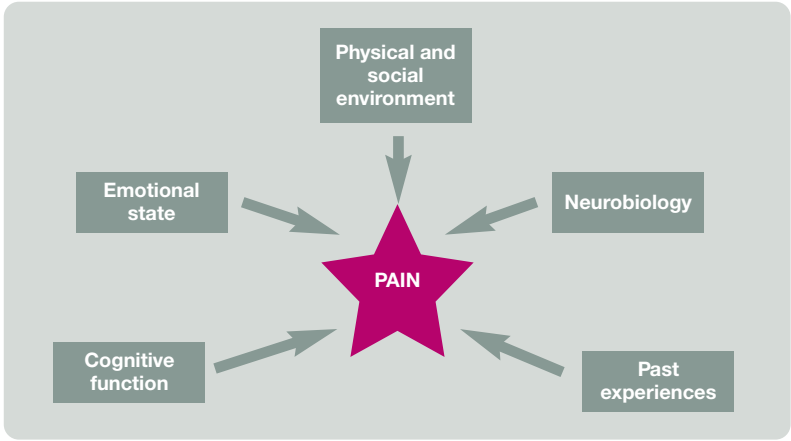


Figure 15 **Pain perception is influenced by numerous internal and external factors, which can increase or decrease it.** *Adapted from Monteiro et al (2023),[2] with permission from the WSAVA*

A phenomenon known as stress-induced analgesia means that pain may be underestimated in highly stressed patients.

As mid-ranking predators (mesopredators), cats can display prey-like behaviours, particularly when feeling threatened. They have also evolved sophisticated forms of communication using scent deposition and will use three-dimensional (3D) space to avoid conflict and retreat from actual or perceived threats. When cats have pain that interferes with their ability to access safe spaces, this increases protective emotions, which may, in turn, increase pain. Moreover, this can lead to behaviours that may affect both the human–cat bond and the relationships between the cat and other pets in the home. These are likely to involve changes in mood, and include increased hiding and decreased sociability.

Figure 16 **Ramps or steps up to favoured places can benefit cats with chronic pain.** *Image courtesy of Sam Taylor*

Cats with chronic pain will benefit from modifications that increase the accessibility of safe spaces, and preserve access to important resources including food, water, litter trays/boxes, scratching substrates and preferred resting areas. Research has shown that the provision of 3D spaces decreases tension between

Figure 17 Raised food and water bowls can benefit cats with DJD. *Image courtesy of Sam Taylor*

Figure 18 Nail and coat care are important considerations for cats with chronic pain. *Image courtesy of Sheilah Robertson*

group-housed cats,[132] and that jumping is one of the behaviours that is improved with analgesic treatment in cats with DJD.[79] Steps, ramps (Figure 16) or pieces of furniture can be introduced so that cats can more readily access spaces such as beds, couches or perches. Cats with impaired mobility also need safe and secure passage between areas in their home. This may involve providing rugs or other non-slip surfaces, and possibly gates or cat doors/flaps to prevent other pets from accessing certain safe spaces.

Litter trays/boxes should be provided in accessible areas and be large enough to allow the cat to move around comfortably, with at least one low side to make entry and exit easier for the cat. It may also be helpful to have food and water bowls raised off the ground (Figure 17). Addressing a cat's changing environmental or behavioural needs may additionally include providing scratching substrates in both horizontal and vertical orientations, and checking more frequently on nail care; for cats that cannot groom as effectively owing to pain, gentle grooming may be needed (Figure 18). Warm beds or safe (non-electrical, reflective, self-warming) heat pads are a further environmental enhancement that may benefit cats with pain from joint disease.

More detail on these and other adjustments that can be made to the home environment is provided in an accompanying guide for carers of cats with chronic muscle/joint pain or mobility problems (see 'Resources for caregivers').

Environmental modifications in the clinic

In recent times, there has been growing recognition of the central role of caregiver observations/videos and careful history-taking in the diagnosis of pain in cats.[111] Notwithstanding, in-clinic examination remains an important component for identifying and diagnosing painful conditions. To best assess pain in the clinic, it is critical that cats are relaxed so that accurate assessments can be made. As stress increases, perception of pain also increases, until a peak is reached beyond which stress may reduce demonstration of painful responses (see 'Emotions and pain perception'). The onus, therefore, is on the veterinary team to provide a cat friendly environment in the clinic, not only to facilitate chronic pain assessment but to enhance feline wellbeing more generally. The use of medications to reduce anxiety prior to clinic visits (eg, gabapentin,[133] pregabalin[114]) is unlikely to interfere with the detection of orthopaedic pain, although this has not been studied. Gabapentin has, however, been shown to affect gait and, therefore, findings on neurological examination.[58]

All measures taken to minimise protective (negative) emotions and promote engaging (positive) emotions, both in the home and veterinary clinic environment, can contribute to decreased pain perception in cats.

A comprehensive review of this subject is provided in the '2022 ISFM/AAFP Cat Friendly Veterinary Environment Guidelines'[130] and the '2022 AAFP/ISFM Cat Friendly Veterinary Interaction Guidelines: Approach and Handling Techniques'.[57] Briefly, environmental conditions in the veterinary clinic should promote engaging emotions and interactions by considering the physical and sensory experience that cats will have during the veterinary visit. This experience, which begins at home with acclimation to carriers and transport, encompasses the clinic and waiting area, the veterinary examination itself, discharge and finally transition back into the home. Taking the time to view the whole experience from the cat's perspective (including the surfaces, smells, sounds and sights that the cat will be exposed to), and to consider even small ways to decrease stressors, will help to make examinations as productive as possible.

SUMMARY POINTS

- Either alone, or in combination with other drugs, NSAIDs are used for the management of chronic pain in cats. Most frequently, this is pain from DJD, but a range of indications exist including dental pain, lower urinary tract pain, cancer-related pain and neuropathic pain.
- Behavioural signs are the best indicators of chronic pain in cats. The use of caregiver videos of the cat in the home environment and clinical metrology instruments allows both identification of pain and monitoring of the efficacy of NSAIDs.
- Appropriate screening should be performed before NSAIDs are prescribed, including physical examination, measurement of systolic blood pressure and a minimum laboratory database (haematocrit or, ideally, a complete blood count, plus serum biochemistry).
- Excellent communication with caregivers is essential. In particular, caregivers should be supported with administration of NSAIDs, monitoring for adverse effects and efficacy, and with environmental modifications aiming to reduce pain and stress.
- Cats with stable CKD may be treated with NSAIDs dependent on individual cat assessment and appropriate caregiver education.
- Adverse drug events should be reported to the relevant regulatory body and the potential for drug interactions considered before prescribing NSAIDs.

Note for readers
Ultimate responsibility for interpretation of the information in these Guidelines lies with the veterinary practitioner. The Guidelines may describe the use of products, formulations, methods or techniques that are not necessarily available or licensed for use in cats in a reader's own country.

Conclusions

Management of chronic pain in cats should be multimodal, involving both pharmacological interventions and environmental modifications. NSAIDs can benefit cats with chronic pain as an element of this multimodal approach, provided they are prescribed after appropriate screening and with the caregiver embraced as part of the team, being both informed and supported by veterinary professionals. Chronic pain assessment using validated tools is paramount for monitoring the efficacy of long-term NSAIDs for pain management. Additionally, intertwining environmental modifications and paying attention to engaging emotions, can result in positive outcomes for cats in chronic pain.

MANAGEMENT OF ACUTE PAIN IN CATS

For discussion on the use of NSAIDs for acute pain conditions in cats, see the '2022 ISFM Consensus Guidelines on the Management of Acute Pain in Cats'.

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Supplementary material

The following supplementary material files are available at go.jfms.com/3TyBXub:

- ISFM guide for caregivers – 'Treating chronic (long-lasting) pain with NSAIDs'.
- ISFM guide for caregivers – 'Changes to the home environment for cats with muscle/joint pain or mobility problems'.
- ISFM guide for caregivers –'Encouraging your cat to drink'.
- AAFP client brochure –'Treating chronic pain with NSAIDs'.

Conflict of interest

Members of the panel have received financial remuneration for providing educational material, speaking at conferences and/or consultancy work, including from pharmaceutical companies producing NSAIDs used in cats; however, none of these activities cause any direct conflict of interest in relation to these Guidelines. Specific relevant details are given below.

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