

Relief of chronic pain in cats and dogs: multimodal drug therapy

B Duncan X Lascelles
BSc BVSc PhD MRCVS CertVA DSAS(ST) DECVS DACVS
North Carolina State University,
College of Veterinary Medicine,
4700 Hillsborough Street
Raleigh, NC 27606, USA

Duncan_Lascelles@ncsu.edu

Key Points:

- We must acknowledge that animals experience pain and that chronic pain is associated with significant disadvantages (disturbance of physiology, potentiation of other diseases such as cancer, worsening of the osteoarthritis, decreased activity, behavior changes (such as aggression, depression, anxiety), adverse alteration of the human-animal bond)
- A knowledge of the basic physiology of pain mechanisms and the basic pharmacology of analgesic drugs is essential for effective chronic pain prevention or alleviation
- Multiple classes of analgesic drugs *administered simultaneously* are more effective than a single class of analgesic
- Pain therapy should not just revolve around drugs; therapies such as surgery, physical therapy and rehabilitation (cold and heat therapy, massage, hydrotherapy, controlled exercise, swimming, passive physiotherapy) and acupuncture all have an important role to play in providing effective pain relief. Use of these non-drug therapies can limit the quantities of drugs used
- The best time to start analgesic therapy is as soon as possible in the case of trauma or chronic pain

You are only doing everything you can if you make the most use of multimodal therapy for chronic pain, e.g. NSAIDs concurrently with adjunctive drugs when required, together with concurrent non-drug therapies such as weight modulation, exercise, physical therapy, massage and acupuncture

In cats and dogs, the two main reasons for chronic pain are osteoarthritis and cancer. This chapter considers drug therapy for chronic pain. It must be remembered that non-drug therapies (weight modulation, physical therapy, massage, acupuncture) are extremely important in the alleviation of many forms of chronic pain.

Chronic pain and the need for a multimodal drug approach:

Osteoarthritic disease (OA) is the commonest form of chronic pain recognized in dogs, involving about 20% of the canine population at any time¹. This translates to about 10-12 million dogs in the United States. Clinical experience² and a review of experimental studies³⁻⁵ clearly reveals that NSAIDs do not provide complete pain relief in canine OA.³⁻⁵ In human medicine, there is a move towards greater use of a multimodal approach for chronic pain such as OA to improve pain relief,⁶⁻⁹ and a multimodal approach has been suggested for the alleviation of chronic pain in veterinary species.² The reason for suggesting a *multimodal drug approach* for the treatment of chronic pain results from what is now known about the changes induced in the central nervous system as a result of chronic pain, that is, the constant input of noxious signals from the periphery.

As more has become known about pain transmission over the last few years, it has become obvious that pain transmission involves a multiplicity of pathways and a multiplicity of mechanisms and transmitter systems.¹⁰⁻¹² It is therefore unlikely that a single class of analgesic, whatever the dose, is going to provide complete analgesia. This is confirmed by clinical experience. Much more effective is the combination of two or more classes of analgesics e.g. concurrent use of opioids, NSAIDs and local anesthetics for the effective control of peri-operative pain.¹³ A similar multimodal approach is also recommended for the management of chronic pain such as that associated with cancer or osteoarthritis.² The effect from these drugs is often supra-additive, and smaller doses of the individual drugs can be used, thus decreasing the likelihood of side effects from any one drug.

However, there is at present no scientific evidence to substantiate the assertion that multimodal drug therapy is of benefit in veterinary patients suffering from osteoarthritis. *Any suggestions and recommendations are based on information extrapolated from the human literature.* The investigation of the effectiveness and toxicity of multimodal therapy is an area of active research in veterinary medicine, and recommendations may well change as data is generated.

In human medicine, there is a significant amount of interest in cancer pain, interest in both the neurobiology of the pain, and interest in novel methods to alleviate cancer pain. However we know little about the relationship between pain and cancer in animals. In 1978, Yoxall¹⁴ stated that, “It is surprising, for instance, how much a dog’s quality of life, observed by the owner, may be improved by the administration of a simple analgesic if the dog is suffering from a tumour, which although painless on palpation, may be causing considerable chronic pain.” Despite this statement and the fact that obvious pain associated with specific tumours such as osteosarcoma has been emphasized for a long time as a diagnostic criterion, *there is a complete absence of controlled studies specifically investigating the potential occurrence of cancer pain in companion animals and a complete absence of studies specifically investigating the alleviation of pain in animals suffering from cancer.* There is almost nothing written about cancer pain in animals. In one of the recent and most comprehensive books on pain management,¹⁵ only 13 of 177 pages are devoted specifically to chronic pain in animals. In one of the most recent and comprehensive books on small animal clinical oncology,¹⁶ only 13 of 683 pages are devoted to pain control in cancer patients. There are no estimates for the numbers of animals with cancer pain that are receiving analgesic therapy, nor for how effective that therapy is. Given that recent surveys into the use of analgesics in the perioperative setting¹⁷⁻²⁰ found that significant numbers of animals were not receiving analgesic drugs, it is likely that the use of analgesics for cancer pain is even less. However, glucocorticoids provide some analgesia, and their use may be more widespread¹⁹. That said, the treatment of cancer pain in animals is likely to be sub-optimal.

Given the lack of animal clinical studies on chronic pain in general, the information in this chapter cannot be based on peer-reviewed investigations, and is therefore a combination of the author’s experience and the experience of others who are heavily involved in the treatment of cancer patients. It is also based on considered extrapolations from human medicine.

Integrated drug and non-drug multimodal approach to chronic pain management:

Relatively undefined in the veterinary literature is the benefit of non-drug therapies in the management of pain associated with conditions such as osteoarthritis and cancer. Clinically, the analgesic effect of therapies such as acupuncture and electroacupuncture, acupressure and transcutaneous electrical nerve stimulation are undefined, as is the analgesic effect of physical therapy (cold and heat therapy, massage therapy, passive physiotherapy, active controlled exercise including swimming, hydrotherapy). *However, despite the lack of experimental evidence for their efficacy, clinical experience recommends the use of such modalities, in conjunction with drug therapy as appropriate.*

In 2002, the American Pain Society published the first evidence-based, multidisciplinary arthritis pain management guideline, “APS Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis”.²¹ This document:

1. emphasizes the detrimental effects of untreated chronic pain
2. emphasizes the need for comprehensive pain assessment
3. outlines the evidence based medicine recommendations for multimodal drug therapy
4. outlines the evidence based medicine recommendations for concurrent multimodal non-drug therapy.

The use of multiple classes of drug and the integration of drug and non-drug therapies can be referred to as *integrated multi-modal pain therapy*.

Similarly, for cancer pain, the World Health Organisation has outlined a general approach to the management of cancer pain²² and it is based on the use of the following ‘groups’ of analgesics in a multimodal fashion:

- a. non-opioid analgesics (e.g non-steroidal anti-inflammatory drugs, acetaminophen)
- b. weak opioid drugs (e.g. codeine)
- c. strong opioid drugs (e.g. morphine)
- d. adjuvant drugs (e.g. corticosteroids, tri-cyclic antidepressants, anticonvulsants, NMDA antagonists)

Some types of chronic cancer pain will respond to non-opioid therapy alone. Pain of a greater intensity can be relieved with the combination of a non-opioid and a ‘weak’ opioid. More severe pain requires the addition of a higher dose of opioid, and the use of a ‘strong’ opioid that is titrated to the pain present. At any of these three levels, adjunctive analgesics can be used to augment analgesia. This approach is a sound one where the pain is initially at a relatively low level, and gradually becomes more severe.

Drug therapy for chronic pain

A basic approach to chronic pain management could be summarised as (adapted from²³):

- A. Assess the pain. Ask for the owners perceptions of the pain present, or the compromise of the quality of life
- B. Believe the owner. The owner sees the pet everyday in its own environment, and knows when alterations in behaviour occur. They can rarely suggest diagnoses, but they do know when something is wrong, and when their pet is in pain, just as a mother knows when something is wrong with her child

- C. Choose appropriate therapy depending on the stage of the disease (i.e. anything other than mild pain should be treated with more than one class of analgesic, or an analgesic drug combined with non-drug adjunctive therapy) and concurrent problems and drug therapy (i.e. consider pharmacological interactions)
- D. Deliver the therapy in a logical coordinated manner and explain carefully possible side effects to the owner
- E. Empower the clients to actively participate in their pet's quality of life – i.e. ask for feedback, and updates on how the therapy is working

The drugs that can be used for chronic pain management are outlined in figures 1 (cat) and 2 (dog). The following notes are not a comprehensive appraisal of each class of drug, rather pointers on their use in chronic pain patients.

Non-steroidal anti-inflammatory drugs (NSAIDs)

New impetus to the field of analgesia and inflammation research was provided by the finding that the cyclo-oxygenase enzyme (COX) exists in (at least) two different forms. It was found that COX activity was stimulated by bacterial endotoxin^{24 25} and that this increase in activity was due to the *de novo* synthesis of new COX protein. Shortly after this, the inducible COX protein was characterised as a distinct isoform of cyclo-oxygenase (COX-2) and shown to be coded by a different gene from that producing the constitutive enzyme, renamed COX-1^{26 27 28}. Thus there are now known to be two types of cyclooxygenase enzyme, one producing 'essential prostaglandins' (e.g. prostaglandins that are involved in maintaining mucosal integrity of the stomach) on a minute to minute basis, and another which becomes activated as a result of tissue trauma and results in the production of 'inflammatory or pain mediating prostaglandins'. However, it is not as simple as COX-1 being 'good' and COX-2 'bad', as COX-2 has been shown to be constitutively expressed in certain tissues such as the canine kidney²⁹. So, the theory would suggest very selective or specific COX-2 inhibitors (such as deracoxib, approved for use in dogs in the US) might be associated with fewer gastro-intestinal side effects. Although clinical experience with use of COX-2 selective drugs in humans suggests that fewer side effects occur with these agents (such as celecoxib, rofecoxib) than with non-selective NSAIDs (such as ibuprofen, aspirin), widespread clinical experience is required before a similar statement can be made with respect to COX-2 selective drug use in dogs. The theory would also suggest that the COX-2 selective drugs are not any safer at the kidney than the non-selective drugs. Again, widespread clinical experience in dogs is required to substantiate this, although the COX-2 selective drugs used in humans have been found to be associated with a similar incidence of renal toxicity as traditional NSAIDs.³⁰ Recently, COX-3 has been identified, but it appears it is one of the sites of action of paracetamol, and not (yet!) relevant to other NSAIDs.³¹

Apart from the concern over side effects produced by NSAIDs, discussion of cyclooxygenase enzymes has further relevance to cancer pain therapy. Of particular interest in cancer pain management is the recent laboratory finding that NSAIDs that inhibit COX-2 may not only produce pain alleviation in cancer pain states, but may also demonstrate anti-tumour effects³². Recent work has shown that a number of tumours express COX-2, especially epithelial tumours, and this has produced interest in the clinical use of NSAIDs for epithelial tumors in dogs.³³⁻³⁹ No studies in cats have been completed.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of drug therapy for chronic pain, especially osteoarthritis. The choice of NSAIDS available can be bewildering, but a few key points are:

- On a population basis all NSAIDs are equally efficacious in relieving pain associated with osteoarthritis, but for a given patient one drug is often more effective than another drug. This is probably even more true for cancer pain, where the mechanisms of cancer pain may be very different from one patient to another
- Gastrointestinal side effects associated with NSAID use appear to be more common with drugs that preferentially block COX-1 over COX-2
- There is no difference between COX-1 selective drugs and COX-2 selective drugs in renal toxicity. Both COX-1 and COX-2 are constitutively expressed in the kidney
- Liver toxicity with NSAIDS is an idiosyncratic event that can happen with any NSAID.

Thus, the veterinarian should start treatment using a NSAID with which he or she is comfortable, and possibly consider the aspect of COX-2 inhibition. Of the NSAIDs available in the UK, carprofen, meloxicam and piroxicam have been found to be preferential COX-2 inhibitors, with carprofen showing the most 'preference'. Deracoxib is a very selective COX-2 inhibitor, currently only approved for use in the dog in the US.

If the drug is effective, then it should be continued. If not, then therapy should be switched to another NSAID. The patient should be monitored for toxicity. This consists of two aspects:

1. informing the owner of potential toxicity, and what signs to watch for (lethargy, depression, vomiting, meleana, increased water ingestion)

2. regular blood work (and urinalysis) to evaluate renal function (urea, creatinine, urine specific gravity) and liver function (alkaline phosphatase and alanine aminotransferase, and, if these are raised, bile acids). A baseline should be obtained when therapy is initiated and parameters monitored on a regular basis thereafter. There are no guidelines on this, but the author repeats the evaluation after 2 – 4 weeks, and then at 2 – 4 month intervals as dictated by the individual patient and client. This re-evaluation is done more frequently as multiple drugs are used, as there is no information on clinical toxicity associated with combinations of analgesics administered chronically. Caution should be used when administering any NSAID to dogs with renal disease, and paracetamol may be a good alternative in these cases.

Use of non-steroidal anti-inflammatory drugs for chronic pain in the cat.

NSAIDs are considered potentially more toxic in the cat than in the dog or humans. Interestingly, there seems to be significant variation among individual cats in the metabolism of NSAIDs^{40,41} and also inconsistent variation in the rate of metabolism of different NSAIDs compared to other species. For example, flunixin appears to be metabolised relatively quickly in the cat compared to the dog.⁴² All of the kinetic studies performed in cats have been carried out on single doses, and as yet, no studies have examined the metabolism of chronically administered NSAIDs. However, given the fact that most of the NSAIDs have a relatively long half life in the cat, chronic dosing at the dosing level and frequency described for the dog is likely more dangerous than use in the dog.

In the dog and humans, NSAIDs form the basis of treatment of chronic pain. There are no licensed NSAIDs for chronic administration (greater than 5 days) in the cat, although a number can probably be used safely (see figure 1). However, none have been fully evaluated for safety in the cat. The key to safe chronic NSAID administration in the cat is the use of the smallest effective dose, and avoiding use, or using very decreased doses, in cats with renal disease. Carprofen seems to have a significantly prolonged half-life in cats (20 hours) compared to the dog (9 hours)^{40,41}. Given the relatively long half-life of carprofen in the cat, the margin of safety is likely to be reduced if dosing is carried out as in the dog. So, although injectable carprofen is approved for use in the cat as a single perioperative dose in the UK and other parts of the world (and appears effective in doses as low as 1mg/kg), there is not yet enough data on the repeated use of carprofen in cats to be able to make recommendations regarding its use chronically in cats. Meloxicam is formulated as a ‘honey’ tasting syrup, so not only is it palatable, but each drop is 0.1mg, making accurate dosing easy. This is the only NSAID that has been investigated clinically for efficacy in chronic pain (OAD),⁴³ although it is likely that all of the NSAIDs are effective in this situation. A number of the other NSAIDs have been compounded into palatable tasting flavours to suit “finicky” cats and administered in decreasing doses, although neither efficacy or stability in the compounded form have been investigated, nor has the toxicity associated with such dosing regimens been investigated. Unpublished work from Colorado State University has shown that the amount of active drug significantly decreased over the period of 1 week when piroxicam was compounded in an aqueous solution for use in cats. Drugs that are compounded into palatable mixtures for administration to cats need to be evaluated for stability.

Cats are more sensitive to NSAIDs than dogs, and therefore monitoring should probably be more frequent than is carried out in dogs. There are no guidelines for monitoring cats receiving chronic NSAID administration. The author considers it very important to monitor these patients closely, and suggests a biochemistry panel, PCV and TP and urinalysis measurements prior to starting the NSAID, and then re-evaluation at 1 week, 4 weeks and every 4 to 6 weeks thereafter, in conjunction with continual reassessment of the patient so that the dose can be tapered down to the smallest effective amount as soon as possible. Urinalysis should also be performed on a regular basis, although decreasing specific gravity is not an early indicator of renal disease as in the dog, rather a late phenomenon. Decreasing the dose to the lowest effective dose is probably a very important factor in limiting clinical toxicity of the NSAIDs in the cat. These suggestions are based on very limited information the author has gathered on the toxicity of NSAIDs in cats. Owners should be informed about the possibility of toxicity, and given the signs to look for.

If pain relief with NSAID therapy is inadequate, oral opioid medications, such as morphine or tramadol can be administered. Transdermal fentanyl can also be used but is expensive. Fentanyl, morphine, or tramadol can be used for dogs that cannot be given NSAIDs. Other agents that are used to treat chronic pain include amantadine (an NMDA antagonist); anticonvulsants, such as gabapentin; and tricyclic antidepressants, such as amitriptyline. These can all be combined with NSAIDs.

Opioids

Many veterinarians may be unfamiliar with the use of opioids outside of the perioperative period, but opioids can be a very effective part of the management of cancer pain as part of a multimodal approach (i.e. including NSAIDs, or adjunctive analgesics). Side effects of opioids can include diarrhoea, vomiting, occasionally sedation, and constipation with long term use. It is very often the constipation, and occasionally the sedation seen, which owners seem to object to most, especially with the administration of oral morphine. The drugs that appear to have been used clinically most often for the alleviation of chronic cancer pain are oral morphine, transdermal fentanyl, oral butorphanol, sub-lingual buprenorphine (cats only) and oral codeine. None of these drugs have been fully evaluated for clinical toxicity when administered long term, nor for efficacy against chronic cancer pain. Tables 1 and 2 give doses that are used by the author. It is important to realise that dosing must be done on an individual basis, and adjustment of the dose to produce analgesia without undesirable side effects requires excellent client-veterinarian interaction and communication.

Opioids for chronic pain in cats

There is currently no information on the long-term use of opioids for chronic pain in the cat. Interestingly, there seems to be significant individual variation in the level of analgesia obtained with certain opioids in the cat, especially morphine and butorphanol, in the acute setting. Interestingly, buprenorphine appears to produce predictable analgesic when given sublingually in the cat.

⁴⁴Compared to humans, the sublingual route appears more effective in cats and may be a result of differences in ionization in the alkaline environment (pH = 8-9) of the cat's mouth compared to that of humans (pH = 6.5 – 7). Sublingual administration of buprenorphine is well accepted by all cats, with no resentment or salivation, and so there is no need to compound the injectable solution. The small volume (0.066 mls per kg) makes administration simple. Based on clinical feedback from owners, this is a very acceptable technique for them to perform at home, and the authors have found it useful to use sublingual buprenorphine in the management of certain types of chronic pain in the cat. However, some owners do not like the behavioural changes it can induce in cats (euphoria) and also the dilated pupils. In addition, inappetance can occur after several days of treatment. Sometimes slightly lower doses can overcome these problems. In addition, prescribing of a less tightly controlled drug (buprenorphine) is more desirable than the more tightly controlled opioids, especially for “at home” use. When administered concurrently with other drugs, infrequent dosing, compared to what might be expected from the pharmacodynamics ⁴⁴, is all that is required.

NMDA antagonists

The NMDA receptor appears to be central to the induction and maintenance of central sensitization, ⁴⁵⁻⁴⁷ and the use of NMDA receptor antagonists would appear to offer benefit in the treatment of pain where central sensitization has become established (i.e. especially chronic pain) ⁴⁸. Ketamine, tiletamine, dextromethorphan and amantadine possess NMDA antagonist properties, among other actions. Unpublished work from North Carolina State University (M Papich, personal communication) suggests that dogs may not make the active metabolite after administration of dextromethorphan, probably negating its use in canine species for chronic pain. Recent publications suggest a benefit of using ketamine perioperatively in low doses ^{49,50}. Ketamine is not available in an oral preparation for long term administration. Amantadine has been used for the treatment of neuropathic pain in humans, ^{51,52}. It does not have the undesirable side effects associated with ketamine administration. The author has been using amantadine over the last few years as an adjunctive drug for the alleviation of chronic pain, particularly osteoarthritis, but also for cancer pain. It is used as an adjunct to a NSAID and it appears to augment pain relief with a low incidence of side effects (mainly agitation and diarrhoea over the first few days of administration). It usually takes about 5 to 7 days to have a positive effect. Suggested doses are given in figures 1 and 2. It should probably not be used in patients with congestive heart failure, nor in patients on selegiline, sertraline or tricyclic antidepressants.

Combination analgesics

Tramadol is classified as an opioidergic/monoaminergic drug ^{53,54}. It has been found to be effective in the alleviation of pain associated with osteoarthritis in humans, as part of a multimodal approach. ^{7,55-57} Tramadol is a synthetic derivative of codeine. Opioid receptors are well known to be involved in pain states, and the descending serotonergic system is known to be one of the body's

endogenous “analgesic” mechanisms. Tramadol, being a synthetic derivative of codeine, has action at the mu opioid receptor and also facilitates the descending serotonergic system. Tramadol is a drug that has been used in many parts of the world for perioperative pain in animals, and is occasionally used for chronic pain. The doses in the table are for the regular (not prolonged release) form of the drug. It has not been evaluated for toxicity in the dog or cat.

Paracetamol

Paracetamol (acetaminophen) is a non-acid NSAID; in fact many authorities do not consider it an NSAID but in a class of its own, as it probably acts on different mechanisms than the NSAIDs. Although its mechanism of action is poorly understood, recently it has been suggested that it acts on a new variant of the cyclooxygenase enzyme COX-3, which is present in central nervous system tissues^{31,58}. With any chronic pain, there are always central nervous system changes, so for what seems a “peripheral” problem, such as many cancers, centrally acting analgesics can be very effective. Paracetamol (acetaminophen) is very often the “rescue” analgesic in human trials of new NSAIDs. ***Although highly toxic in the cat, even in small quantities,*** it can be effectively used in dogs for pain control. No studies of toxicity have been done; but if toxicity is seen, it will probably affect the liver and so should be used cautiously in dogs with liver dysfunction. It can be used on its own or in a preparation combined with codeine and is initially dosed at about 10 to 15 mg/kg of paracetamol twice daily. The authors often use it as the first line of analgesic therapy in dogs with renal compromise where NSAIDs cannot be used, or in dogs that appear to be otherwise intolerant to NSAIDs (e.g. vomiting or gastro-intestinal ulceration).

Anti-convulsant drugs

Gabapentin is a structural analog of GABA (gamma-aminobutyric acid) and was introduced as an anti-epileptic drug. While its analgesic mechanism of action is unclear, it appears to interact with NMDA receptors and probably various ionic channels, although its exact mechanism of pain relief is unclear. It appears to be useful for neuropathic pain and central sensitisation in some patients. It is rapidly metabolised in the dog, and most often used for its anticonvulsive properties. It appears to have some analgesic properties at low doses, administered two to three times daily.

Tri-cyclic antidepressants

The tricyclic antidepressant amitriptyline does appear to be effective in the cat for pain alleviation in interstitial cystitis^{59,60} and many practitioners are reporting efficacy in other chronic pain conditions in the cat, including osteoarthritis. It has been used daily for periods up to 1 year for interstitial cystitis, and few side effects were reported. The author has also used amitriptyline in the cat for cancer pain with some encouraging results. It should probably not be used concurrently with amantadine until more is known about drug interactions.

Steroids

Steroids have a mild analgesic action, and can also produce a state of euphoria, and are often used for these reasons to palliate cancer and cancer pain in cats and dogs. They should not be used concurrently with NSAIDs.

Bisphosphonates

Bone pain induced by primary or metastatic bone tumours is thought to be due to, in large, osteoclast activity and drugs that block osteoclast activity can markedly reduce bone pain^{61,62}. Bisphosphonates are a class of drug that inhibit osteoclast activity, and can produce analgesia via this action. There is very little information on their use in dogs for palliation of bone pain, but they are starting to be used.⁶³

Nutraceuticals

These are often used in osteoarthritis, and there is evidence that they provide a mild anti-inflammatory effect and analgesic effect. The author has found them to be of benefit in the alleviation of chronic cancer pain, but only when used as part of a multimodal approach. The analgesic effect appears to be more predictable in cats than dogs.

References

1. Moore GE, Burkman KD, Carter MN, et al. Causes of death or reasons for euthanasia in military working dogs: 927 cases (1993-1996). *J Am Vet Med Assoc* 2001;219:209-214.
2. Lascelles BD, Main DC. Surgical trauma and chronically painful conditions--within our comfort level but beyond theirs? *J Am Vet Med Assoc* 2002;221:215-222.
3. Budsberg SC, Johnston SA, Schwarz PD, et al. Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. *J Am Vet Med Assoc* 1999;214:206-210.
4. Vasseur PB, Johnson AL, Budsberg SC, et al. Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal anti-inflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc* 1995;206:807-811.
5. Holtsinger RH, Parker RB, Beale BS, et al. The therapeutic efficacy of carprofen (Rimadyl-V) in 209 clinical cases of canine degenerative joint disease. *Veterinary and Comparative Orthopedics and Traumatology* 1992;5:140-144.

6. Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. *Am Fam Physician* 2000;61:1795-1804.
7. Schnitzer TJ. Non-NSAID pharmacologic treatment options for the management of chronic pain. *Am J Med* 1998;105:45S-52S.
8. Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther* 2001;23:1429-1445.
9. Freedman GM. Chronic pain. Clinical management of common causes of geriatric pain. *Geriatrics* 2002;57:36-41; quiz 42.
10. Muir WW, 3rd, Woolf CJ. Mechanisms of pain and their therapeutic implications. *J Am Vet Med Assoc* 2001;219:1346-1356.
11. Mannion RJ, Woolf CJ. Pain mechanisms and management: a central perspective. *Clin J Pain* 2000;16:S144-156.
12. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000;288:1765-1769.
13. Slingsby LS, Waterman-Pearson AE. Analgesic effects in dogs of carprofen and pethidine together compared with the effects of either drug alone. *Vet Rec* 2001;148:441-444.
14. Yoxall AT. Pain in animals - its recognition and control. *Journal of small Animal Practice* 1978;19:423-438.
15. Flecknell PA, Waterman-Pearson AE. *Pain Management in Animals*. London: W.B. Saunders; 2000;184.
16. Withrow SJ, MacEwen EG. *Small Animal Clinical Oncology*, 3rd ed. Philadelphia: W.B. Saunders; 2001;718.
17. Lascelles BDX, Capner CA, Waterman-Pearson AE. A survey of current British Veterinary attitudes to peri-operative analgesia for cats and small mammals. *Veterinary Record* 1999;145:601-604.
18. Capner CA, Lascelles BD, Waterman-Pearson AE. Current British veterinary attitudes to perioperative analgesia for dogs. *Vet Rec* 1999;145:95-99.
19. Watson AD, Nicholson A, Church DB, et al. Use of anti-inflammatory and analgesic drugs in dogs and cats. *Aust Vet J* 1996;74:203-210.
20. Dohoo SE, Dohoo IR. Postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Can Vet J* 1996;37:546-551.
21. Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis American Pain Society; 2002.
22. Committee WHOE. *Cancer Pain Relief: 2nd Edition*. In. Geneva: World Health Organisation; 1996.
23. Gaynor JS. *Cancer Pain Management*. In: Gaynor JS, Muir WW, eds. *Handbook of Veterinary Pain Management*. St. Louis: Mosby; 2002:447.
24. Fu JY, Masferrer JL, Seibert K, et al. The induction and suppression of prostaglandin H₂ synthase (cyclooxygenase) in human monocytes. *J Biol Chem* 1990;265:16737-16740.
25. Masferrer JL, Zweifel BS, Seibert K, et al. Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice. *J Clin Invest* 1990;86:1375-1379.
26. Xie WL, Chipman JG, Robertson DL, et al. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci U S A* 1991;88:2692-2696.

27. O'Banion MK, Sadowski HB, Winn V, et al. A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein. *J Biol Chem* 1991;266:23261-23267.
28. Fletcher BS, Kujubu DA, Perrin DM, et al. Structure of the mitogen-inducible TIS10 gene and demonstration that the TIS10-encoded protein is a functional prostaglandin G/H synthase. *J Biol Chem* 1992;267:4338-4344.
29. Ostrom RS, Gregorian C, Drenan RM, et al. Key role for constitutive cyclooxygenase-2 of MDCK cells in basal signaling and response to released ATP. *Am J Physiol Cell Physiol* 2001;281:C524-531.
30. Rossat J, Maillard M, Nussberger J, et al. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther* 1999;66:76-84.
31. Chandrasekharan NV, Dai H, Roos KL, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci U S A* 2002;99:13926-13931.
32. Sabino MA, Ghilardi JR, Jongen JL, et al. Simultaneous reduction in cancer pain, bone destruction, and tumor growth by selective inhibition of cyclooxygenase-2. *Cancer Res* 2002;62:7343-7349.
33. Mutsaers AJ, Glickman NW, DeNicola DB, et al. Evaluation of treatment with doxorubicin and piroxicam or doxorubicin alone for multicentric lymphoma in dogs. *J Am Vet Med Assoc* 2002;220:1813-1817.
34. Mohammed SI, Bennett PF, Craig BA, et al. Effects of the cyclooxygenase inhibitor, piroxicam, on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. *Cancer Res* 2002;62:356-358.
35. Schmidt BR, Glickman NW, DeNicola DB, et al. Evaluation of piroxicam for the treatment of oral squamous cell carcinoma in dogs. *J Am Vet Med Assoc* 2001;218:1783-1786.
36. Knottenbelt CM, Simpson JW, Tasker S, et al. Preliminary clinical observations on the use of piroxicam in the management of rectal tubulopapillary polyps. *J Small Anim Pract* 2000;41:393-397.
37. Knapp DW, Glickman NW, Widmer WR, et al. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. *Cancer Chemother Pharmacol* 2000;46:221-226.
38. Knapp DW, Chan TC, Kuczek T, et al. Evaluation of in vitro cytotoxicity of nonsteroidal anti-inflammatory drugs against canine tumor cells. *Am J Vet Res* 1995;56:801-805.
39. Barsanti JA. Piroxicam for bladder cancer. *J Vet Intern Med* 1995;9:113-114.
40. Taylor PM, Delatour P, Landoni FM, et al. Pharmacodynamics and enantioselective pharmacokinetics of carprofen in the cat. *Res Vet Sci* 1996;60:144-151.
41. Parton K, Balmer TV, Boyle J, et al. The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats. *J Vet Pharmacol Ther* 2000;23:73-79.
42. Lees P, Taylor PM. Pharmacodynamics and pharmacokinetics of flunixin in the cat. *British Veterinary Journal* 1991;147:298-305.

43. Lascelles BDX. Clinical efficacy of meloxicam ('Metacam') in cats with locomotor disorders. *Journal of Small Animal Practice* 2001;42:587-593.
44. Lascelles BD, Robertson SA, Taylor PM, et al. Comparison of the pharmacokinetics and thermal antinociceptive pharmacodynamics of 20mcg/kg buprenorphine administered sublingually or intravenously in cats. *Veterinary Anaesthesia and Analgesia* 2003;30:109 (Abstr).
45. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implication for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293-299.
46. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. *Curr Rheumatol Rep* 2002;4:313-321.
47. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001;413:203-210.
48. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage* 2000;20:358-373.
49. Slingsby LS, Waterman-Pearson AE. The post-operative analgesic effects of ketamine after canine ovariohysterectomy--a comparison between pre- or post-operative administration. *Res Vet Sci* 2000;69:147-152.
50. Wagner AE, Walton JA, Hellyer PW, et al. Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *J Am Vet Med Assoc* 2002;221:72-75.
51. Pud D, Eisenberg E, Spitzer A, et al. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998;75:349-354.
52. Eisenberg E, Pud D. Can patients with chronic neuropathic pain be cured by acute administration of the NMDA receptor antagonist amantadine? *Pain* 1998;74:337-339.
53. Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. *Drugs* 1997;18-24.
54. Oliva P, Aurilio C, Massimo F, et al. The antinociceptive effect of tramadol in the formalin test is mediated by the serotonergic component. *Eur J Pharmacol* 2002;445:179-185.
55. Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. *Drugs* 1996;52 Suppl 3:39-47.
56. Reig E. Tramadol in musculoskeletal pain--a survey. *Clin Rheumatol* 2002;21 Suppl 1:S9-11; discussion S11-12.
57. Adler L, McDonald C, O'Brien C, et al. A comparison of once-daily tramadol with normal release tramadol in the treatment of pain in osteoarthritis. *J Rheumatol* 2002;29:2196-2199.
58. Schwab JM, Schluesener HJ, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol? *Lancet* 2003;361:981-982.
59. Buffington CAT. Visceral pain in humans: lessons from animals. *Current Pain and Headache Reports* 2001;5:44-51.

60. Buffington CAT, Chew DJ, Woodworth BE. Feline interstitial cystitis. *Journal of the American Veterinary Medical Association* 1999;215:682-687.
61. Luger NM, Honore P, Sabino MA, et al. Osteoprotegerin diminishes advanced bone cancer pain. *Cancer Res* 2001;61:4038-4047.
62. Honore P, Luger NM, Sabino MA, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. *Nat Med* 2000;6:521-528.
63. Hintermeister JG, Kitchell BE. The use of pamidromate in the treatment of canine cancer: A pilot study. In: 20th Annual Conference of the Veterinary Cancer Society, Asilomar, California 2000;46.

Figure 1. Analgesics for Chronic Pain in Cats*

The following table is a summary of the author's recommendations for use of analgesics in cats for the alleviation of cancer pain. Sources for recommended doses are given. This table should be considered a guide, and recommendations may change as new information is produced, and more learned about the side effects of these drugs in cats

Drug	Cat Dose (mg/kg)	<i>Notes</i>	<i>Published Source of Information/ Reference on Analgesic Efficacy in Cats</i>
Paracetamol (acetaminophen)	Contraindicated	<i>Contraindicated—small doses rapidly cause death in cats.</i>	—
Amantadine	3.0 mg/kg PO q 24 hr	This drug has not been evaluated for toxicity but is well tolerated in dogs and humans, with occasional side effects of agitation and GI irritation. May be a useful addition to NSAIDs in the treatment of chronic cancer pain conditions. The 100 mg capsules need to be recompiled for cats.	†
Amitriptyline	0.5-2.0 mg/kg PO q 24 hr	This drug appears to be well tolerated for up to 12 months of daily administration. Occasionally drowsiness is seen (<10%). May be a useful addition to NSAIDs for treatment of chronic pain conditions.	Buffington CAT, Chew DJ, Woodworth BE. Feline interstitial cystitis. <i>J Am Vet Med Assoc.</i> 1999;215:682-687. Buffington T, Pacak K. Increased plasma norepinephrine concentrations in cats with interstitial cystitis. <i>Urology.</i> 2001;57:102.

Aspirin	10 mg/kg PO q 48 hr	Can cause significant gastrointestinal ulceration	—
Buprenorphine	0.02 mg/kg sublingual q 6-7 hr	Recent information from the University of Florida, using a research model, suggests that buprenorphine provides good analgesia when administered sublingually (20 mcg/kg; injectable formulation) and provides good analgesia predictably for 6 hours (IV buprenorphine provides analgesia for the same period when administered at the same dose). The sublingual route is not resented by cats and may be a good way to provide postoperative analgesia at home. Feedback from owners indicates that after 2-3 days dosing at this dose, anorexia develops. Smaller doses (5-10 mcg/kg) may be more appropriate for “long-term” administration, especially in combination with other drugs.	‡
Butorphanol	0.2-1.0 mg/kg PO q 6 hr	One study suggests using oral butorphanol after surgery may be beneficial. Generally considered to be a poor analgesic in cats except for visceral pain, however the author has found it to be useful as part of a multimodal approach to cancer pain therapy	Carroll GL, Howe LB, Slater MR, et al. Evaluation of analgesia provided by postoperative administration of butorphanol to cats undergoing onychectomy. <i>J Am Vet Med Assoc.</i> 1998;213:246-250.
Carprofen	Not enough data to enable recommendations for long term administration	—	—
Etodolac	Not recommended	—	—
Flunixin meglumine	1 mg/kg PO single dose		
Glucosamine / Chondroitin	Approx 15mg/kg chondroitin	This combination appears to produce mild	

sulphate combinations	sulphate PO q 12 to 24 hrs	anti-inflammatory and analgesic effects in cats more predictably than in dogs. Can be used in conjunction with NSAIDs, opioids and amantadine.	
Ketoprofen [§]	1 mg/kg PO q 24 hr; maximum 5 days	Probably well tolerated as pulse therapy for chronic pain, with a few days “rest” between treatments. Has also been used by some at 1mg/kg every 3 days long term.	†
Meloxicam	0.2 mg/kg PO on day 1, followed by 0.1mg/kg PO daily for 3 days, then 0.05 mg/kg daily for 3 days, then 0.025 mg/kg daily, and go to every other day if possible	This drug is particularly well received by cats due to its formulation as a honey syrup. Also, the drop formulation makes it very easy to gradually and accurately decrease the dose.	Lascelles BDX. Clinical efficacy of meloxicam ("Metacam") in cats with locomotor disorders. <i>J Small Anim Pract.</i> 2001;42:587-593.
Morphine (oral liquid)	0.2-0.5 mg/kg PO t.i.d.-q.i.d.	Best compounded into a palatable flavored syrup; however, cats usually strongly resent this medication. Morphine may not be as effective in cats as it is in dogs.	‡
Morphine (oral sustained release)	Tablets too large for dosing cats	—	—
Piroxicam	1 mg/cat PO daily for a maximum of 7 days. If longer term medication is considered, suggest every other day dosing, but see note at right.	This can be compounded into a palatable liquid; however, recent information suggests that the active drug decreases significantly over a 10-day period after compounding in an aqueous solution. In the authors' experience, significant drops in PCV (presumably due to GI hemorrhage) occur in up to 30% of cats after 2-3 weeks of every day drug therapy. Suggest alternate day therapy in the cat long term	†
Prednisolone	0.25 – 0.5 mg/kg PO q 24 hr	Can be particularly effective in cancers associated with significant inflammation (such as squamous cell carcinoma of the oral cavity in cats). NOT to be combined with	†

		concurrent NSAID administration	
Tolfenamic acid [§]	4 mg/kg PO q 24 hr for 3 days maximum	—	—
Tramadol	4 mg/kg twice daily	This drug has not been evaluated for toxicity in cats and has not yet been used extensively by the author for the treatment of cancer pain in cats. However, early results are encouraging.	†
Transdermal fentanyl patch	2-5 µg/kg/hr	A 25µg/hr patch can be applied to an “average” cat (7.7-11lb; 3.5-5.0 kg). In smaller cats, other methods of providing analgesia should be sought as it is not recommended to cut patches in half and covering half of the patch gives unpredictable results. The decay in plasma levels following patch removal is slow.	Franks JN, Boothe HW, Taylor L, et al. Evaluation of transdermal fentanyl patches for analgesia in cats undergoing onychectomy. <i>J Am Vet Med Assoc.</i> 2000;217:1013-1020. Glerum LE, Egger CM, Allen SW, et al. Analgesic effect of the transdermal fentanyl patch during and after feline ovariohysterectomy. <i>Vet Surg.</i> 2001;30:351-358.
Vedaprofen	Not recommended	—	—

* Adapted from Lascelles BDX. Drug therapy for acute and chronic pain in the cat. *Int J Pharm Compounding.* 2002;6:338-343.

† From authors' and colleagues' experience.

‡ From recent work by Sheilah Robertson [University of Florida] and Duncan Lascelles [while at University of Florida and University of Cambridge] and Pilly Taylor [University of Cambridge]. Manuscripts in preparation.

§ Drug indicated is licensed and approved for use at the stated dose in one of the following countries: United States, United Kingdom, Australia, New Zealand.

Figure 1. Analgesics for Chronic Pain in Cats*

The following table is a summary of the author's recommendations for use of analgesics in cats for the alleviation of cancer pain. Sources for recommended doses are given. This table should be considered a guide, and recommendations may change as new information is produced, and more learned about the side effects of these drugs in cats

Drug	Cat Dose (mg/kg)	<i>Notes</i>	<i>Published Source of Information/ Reference on Analgesic Efficacy in Cats</i>
Paracetamol (acetaminophen)	Contraindicated	<i>Contraindicated—small doses rapidly cause death in cats.</i>	—
Amantadine	3.0 mg/kg PO q 24 hr	This drug has not been evaluated for toxicity but is well tolerated in dogs and humans, with occasional side effects of agitation and GI irritation. May be a useful addition to NSAIDs in the treatment of chronic cancer pain conditions. The 100 mg capsules need to be recompounded for cats.	†
Amitriptyline	0.5-2.0 mg/kg PO q 24 hr	This drug appears to be well tolerated for up to 12 months of daily administration. Occasionally drowsiness is seen (<10%). May be a useful addition to NSAIDs for treatment of chronic pain conditions.	Buffington CAT, Chew DJ, Woodworth BE. Feline interstitial cystitis. <i>J Am Vet Med Assoc.</i> 1999;215:682-687. Buffington T, Pacak K. Increased plasma norepinephrine concentrations in cats with interstitial cystitis. <i>Urology.</i> 2001;57:102.

Aspirin	10 mg/kg PO q 48 hr	Can cause significant gastrointestinal ulceration	—
Buprenorphine	0.02 mg/kg sublingual q 6-7 hr	Recent information from the University of Florida, using a research model, suggests that buprenorphine provides good analgesia when administered sublingually (20 mcg/kg; injectable formulation) and provides good analgesia predictably for 6 hours (IV buprenorphine provides analgesia for the same period when administered at the same dose). The sublingual route is not resented by cats and may be a good way to provide postoperative analgesia at home. Feedback from owners indicates that after 2-3 days dosing at this dose, anorexia develops. Smaller doses (5-10 mcg/kg) may be more appropriate for “long-term” administration, especially in combination with other drugs.	‡
Butorphanol	0.2-1.0 mg/kg PO q 6 hr	One study suggests using oral butorphanol after surgery may be beneficial. Generally considered to be a poor analgesic in cats except for visceral pain, however the author has found it to be useful as part of a multimodal approach to cancer pain therapy	Carroll GL, Howe LB, Slater MR, et al. Evaluation of analgesia provided by postoperative administration of butorphanol to cats undergoing onychectomy. <i>J Am Vet Med Assoc.</i> 1998;213:246-250.
Carprofen	Not enough data to enable recommendations for long term administration	—	—
Etodolac	Not recommended	—	—
Flunixin meglumine	1 mg/kg PO single dose		
Glucosamine / Chondroitin sulphate combinations	Approx 15mg/kg chondroitin sulphate PO q 12 to 24 hrs	This combination appears to produce mild anti-inflammatory and analgesic effects in	

		cats more predictably than in dogs. Can be used in conjunction with NSAIDs, opioids and amantadine.	
Ketoprofen [§]	1 mg/kg PO q 24 hr; maximum 5 days	Probably well tolerated as pulse therapy for chronic pain, with a few days “rest” between treatments. Has also been used by some at 1mg/kg every 3 days long term.	†
Meloxicam	0.2 mg/kg PO on day 1, followed by 0.1mg/kg PO daily for 3 days, then 0.05 mg/kg daily for 3 days, then 0.025 mg/kg daily, and go to every other day if possible	This drug is particularly well received by cats due to its formulation as a honey syrup. Also, the drop formulation makes it very easy to gradually and accurately decrease the dose.	Lascelles BDX. Clinical efficacy of meloxicam ("Metacam") in cats with locomotor disorders. <i>J Small Anim Pract.</i> 2001;42:587-593.
Morphine (oral liquid)	0.2-0.5 mg/kg PO t.i.d.-q.i.d.	Best compounded into a palatable flavored syrup; however, cats usually strongly resent this medication. Morphine may not be as effective in cats as it is in dogs.	‡
Morphine (oral sustained release)	Tablets too large for dosing cats	—	—
Piroxicam	1 mg/cat PO daily for a maximum of 7 days. If longer term medication is considered, suggest every other day dosing, but see note at right.	This can be compounded into a palatable liquid; however, recent information suggests that the active drug decreases significantly over a 10-day period after compounding in an aqueous solution. In the authors' experience, significant drops in PCV (presumably due to GI hemorrhage) occur in up to 30% of cats after 2-3 weeks of every day drug therapy. Suggest alternate day therapy in the cat long term	†
Prednisolone	0.25 – 0.5 mg/kg PO q 24 hr	Can be particularly effective in cancers associated with significant inflammation (such as squamous cell carcinoma of the oral cavity in cats). NOT to be combined with concurrent NSAID administration	†

Tolfenamic acid [§]	4 mg/kg PO q 24 hr for 3 days maximum	—	—
Tramadol	4 mg/kg twice daily	This drug has not been evaluated for toxicity in cats and has not yet been used extensively by the author for the treatment of cancer pain in cats. However, early results are encouraging.	†
Transdermal fentanyl patch	2-5 µg/kg/hr	A 25µg/hr patch can be applied to an “average” cat (7.7-11lb; 3.5-5.0 kg). In smaller cats, other methods of providing analgesia should be sought as it is not recommended to cut patches in half and covering half of the patch gives unpredictable results. The decay in plasma levels following patch removal is slow.	Franks JN, Boothe HW, Taylor L, et al. Evaluation of transdermal fentanyl patches for analgesia in cats undergoing onychectomy. <i>J Am Vet Med Assoc.</i> 2000;217:1013-1020. Glerum LE, Egger CM, Allen SW, et al. Analgesic effect of the transdermal fentanyl patch during and after feline ovariohysterectomy. <i>Vet Surg.</i> 2001;30:351-358.
Vedaprofen	Not recommended	—	—

* Adapted from Lascelles BDX. Drug therapy for acute and chronic pain in the cat. *Int J Pharm Compounding.* 2002;6:338-343.

† From authors' and colleagues' experience.

‡ From recent work by Sheilah Robertson [University of Florida] and Duncan Lascelles [while at University of Florida and University of Cambridge] and Pilly Taylor [University of Cambridge]. Manuscripts in preparation.

§ Drug indicated is licensed and approved for use at the stated dose in one of the following countries: United States, United Kingdom, Australia, New Zealand.