Control of Cancer Pain in Veterinary Patients

James S. Gaynor, DVM, MS

The treatment of cancer has become more commonplace in veterinary practice as knowledge, drugs, and therapeutic techniques evolve. Although some cancers still are not effectively treated, many owners attempt various measures at prolonging their pet’s life. Regardless of the prognosis, it is vitally important to attempt to alleviate the pet’s pain. It is estimated that cancer pain can be effectively managed in 90% of human beings with currently available drugs and techniques.\(^1\) There is no reason to believe that the same success could not be achieved in small animals.

There are four main steps in ensuring that pain management is optimized in veterinary patients. The first step is to ensure that veterinarians have the appropriate education and training about the importance of alleviating pain, assessment of pain, available drugs and potential complications, and interventional techniques. The next step is educating the client about realistic expectations surrounding pain control and conveying the idea that most patients’ pain can be managed. This involves letting the client know that owner involvement in evaluating the pet and providing feedback on therapy is crucial to success. The veterinarian and owner should all participate in developing effective strategies to alleviate pain. Client involvement also helps to decrease the potential feeling of helplessness. The third step is to assess the pet’s pain thoroughly at the start and throughout the course of therapy, and not just when it gets severe. The fourth step is having good support from the veterinary practice or institution for the use of opioids and other controlled substances.

Effective alleviation of pain requires some basic understanding of pain itself. Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”\(^2\)\(^–\)\(^4\) Although this definition was originally developed for use in human beings, it applies to animals as well. The emotional component is often overlooked and untreated. The physiology of pain has been described in great detail elsewhere.\(^5\) It is important to realize that there are different types of pain that a patient can experience, necessitating different
approaches to therapy (Box 1). Following are some basic definitions for terms used when discussing pain in general, and cancer pain in particular:

**IMPORANCE OF ALLEVIATING PAIN**

The alleviation of pain is important for physiologic and ethical reasons. Briefly, pain can induce a stress response in patients that is associated with elevations in corticotropin, cortisol, antidiuretic hormone (ADH), catecholamines, aldosterone, renin, angiotensin II, and glucose, along with decreases in insulin and testosterone. These changes can result in a general catabolic state with muscle protein catabolism and lipolysis, in addition to retention of water and sodium and excretion of potassium. A prolonged stress response can decrease the rate of healing. In addition, the stress response can have adverse effects on the cardiovascular and pulmonary systems, fluid homeostasis, and gastrointestinal tract function. It is important to minimize the stress response to have better overall health of the patient that has cancer.

Veterinarians have an ethical obligation to treat animal pain. Most undertreatment of animal pain, however, is likely a result of lack of adequate knowledge and not a lack of concern. Outward show of concern for the pet and family is important for demonstrating a bond-centered approach to cancer therapy and pain management. Most owners who are willing to undergo the emotional stress and financial commitment to cancer therapy have already shown that they have a strong attachment to their pet. It is important for the veterinarian to foster good communication surrounding primary therapy and pain treatment and, at the same time, demonstrate empathy for

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Basic definitions for terms used when discussing pain in general, and cancer pain in particular</th>
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<tbody>
<tr>
<td>Acute pain follows some bodily injury, disappears with healing, and tends to be self-limiting.</td>
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<tr>
<td>Breakthrough pain is a transient flare-up of pain in the chronic pain setting and can occur even when chronic pain is under control.</td>
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<tr>
<td>Chronic pain lasts several weeks to months and persists beyond the expected healing time when nonmalignant in origin.</td>
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<td>Cancer pain can be acute, chronic, or intermittent and is related to the disease itself or to the treatment.</td>
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<tr>
<td>Pre-emptive analgesia is the administration of an analgesic drug before stimulation to prevent sensitization of neurons, thus improving postoperative analgesia.</td>
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<tr>
<td>Local anesthesia is the temporary loss of sensation in a defined part of the body without loss of consciousness.</td>
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<tr>
<td>Neuropathic pain originates from injury or involvement of the peripheral or central nervous system and is described as burning or shooting, possibly associated with motor, sensory, or autonomic deficits.</td>
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<tr>
<td>Regional anesthesia is the loss of sensation in part of the body by interrupting the sensory nerves conducting impulses from that region of the body.</td>
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<tr>
<td>Somatic pain originates from damage to bones, joints, muscle, or skin and is described in human beings as localized, constant, sharp, aching, and throbbing.</td>
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<tr>
<td>Visceral pain arises from stretching, distention, or inflammation of the viscera and is described as deep, cramping, aching, or gnawing, without good localization</td>
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<tr>
<td>Wind-up is central sensitization attributable to an increase in the excitability of spinal neurons, contributing to the severity of postoperative pain.</td>
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the owner. This fosters the doctor-client-patient relationship and helps to build goodwill within and outside the practice.

**ASSESSMENT OF PAIN**

Assessment of pain in animals can be difficult and frustrating. Understanding types of pain and their causes can be helpful. Often, veterinarians need to rely on the experience in people to help define the pain in animals. Technicians and other staff members are usually the ones who experience the postoperative period more than the doctors. Pain assessment is typically delegated to these staff members. Recognition and assessment of pain is the first and probably the most difficult step in providing analgesia to dogs and cats. It is often easiest to assume that an animal is in pain if a person undergoing similar trauma or surgery would be in pain. A patient usually tolerates mild pain without a problem and does not exhibit any behavioral changes. Patients with mild pain often are not treated. Patients experiencing moderate pain usually exhibit changes in behavior, appetite, activity, positioning, or posture. These patients also tend to respond significantly to palpation of the painful area. Severe pain can be thought of as intolerable, and is often manifested as unprovoked crying, whimpering, or howling associated with violent thrashing. Sometimes, the patient may not exhibit these behaviors, because the associated movements enhance the excruciating pain. Nonspecific physiologic responses to pain include elevated heart rate and blood pressure, abnormal cardiac rhythm, panting, salivation, dilated pupils, and behavior that presents as vicious and uncontrollable. It is important to remember that there are differences in variables among individuals, breeds, and species.

Cancer pain typically begins as acute mild pain and then potentially progresses to a chronic pain state that may be mild to severe in nature. Practitioners should attempt to intervene early to prevent wind-up and problem chronic pain.

Classification as to origin of pain is also important, because some drugs have greater efficacy for different types of pain. Somatic pain originates from damage to bones, joints, muscle, or skin and is described in human beings as localized, constant, sharp, aching, and throbbing. Osteosarcoma is an example of somatic pain. Visceral pain arises from stretching, distention, or inflammation of the viscera and is described as deep, cramping, aching, or gnawing, without good localization. An enlarging visceral tumor can elicit visceral pain. Neuropathic pain originates from injury or involvement of the peripheral or central nervous system and is described as burning or shooting, possibly associated with motor, sensory, or autonomic deficits. Many soft tissue tumors have neuropathic components because of compression or invasion of nervous components.

Assessment of pain can be accomplished systematically with a pain scoring scale. The objective of a pain scoring system is to place a quantitative value on a specific variable, add up the variables, and compare the total with some predetermined assessment of pain. There are many different pain score scales, and no single scale is perfect. Some investigators have also used a visual analog scale (VAS). A VAS would need to be validated for several people at each practice to ensure consistent scoring. Every pain scale requires a subjective assessment of another individual’s experience, however, and, by its nature, is inherently flawed. Response to analgesic therapy is important to note and guide the practitioner to the analgesic requirement for the degree of pain the patient is experiencing. When doubt exists as to whether the patient is in pain, or how painful, a trial of analgesic therapy must be instituted.

Failure to assess pain initially and throughout the course of cancer treatment is a leading factor in undertreatment. Pain should be assessed early, with the goal of
characterizing the pain as to location, intensity, and probable cause. Client engagement in this process helps to determine aggravating and relieving factors. After a good assessment is performed, goals for pain control can be set with the client. In addition to examining patients frequently, clients should be consulted on a regular basis, at least by telephone, to ensure an accurate assessment of a pet’s pain.

DRUGS AND TECHNIQUES FOR ALLEVIATION OF PAIN

Throughout this issue, doses are mentioned in the text. It can be assumed that the doses are appropriate to dogs and cats unless otherwise noted.

Drug treatment is the cornerstone of cancer pain management. It is effective and affordable for most patients and owners. The general approach to pain management should follow the World Health Organization ladder, which is a three-step hierarchy (Fig. 1).\(^3\) Within the same category of drugs, there can be different side effects for individuals. Therefore, if possible, it may be best to substitute drugs within a category before switching therapies. It is always best to try to keep dosage scheduling as simple as possible. The more complicated the regimen, the more likely it is that non-compliance may occur. Mild to moderate pain should be treated with a nonopioid, such as a nonsteroidal anti-inflammatory drug (NSAID), ensuring that there are no systemic contraindications. As pain increases, some type of opioid should be added to the regimen. As pain becomes more severe, increase the dose of the opioid. It should be noted that tachyphylaxis is common with opioids when used chronically and increasing the dosage, potentially to higher than the “normal” range, does not necessarily mean increasing the likelihood of adverse affects. Drugs should be dosed on a regular basis and not just as needed as pain becomes moderate to severe.

Fig. 1. World Health Organization cancer pain control ladder. (Adapted from http://www.who.int/cancer/palliative/painladder/en/. Accessed June 26, 2008; with permission.)
Continuous analgesia facilitates maintaining patient comfort. Additional doses of analgesics can then be administered as pain is intermittently more severe. Adjuvant drugs can be administered to help with specific types of pain and anxiety.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

Nonopioid analgesics include such drugs as carprofen, etodolac, deracoxib, meloxicam, tepoxalin, firocoxib, aspirin, carprofen, ketoprofen, and acetaminophen (Table 1). All except acetaminophen are considered NSAIDs. Despite the low anti-inflammatory activity of acetaminophen, it possesses beneficial effects of analgesia; minimal risk for bleeding in thrombocytopenic patients; decreased gastrointestinal effects; and synergy with opioid analgesics, such as codeine. Acetaminophen may also be helpful for breakthrough pain control in dogs already receiving NSAIDs. Acetaminophen should

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog Dose</th>
<th>Cat Dose</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>10–15 mg/kg PO q 12 h for 5 days</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Acetaminophen (300 mg) + codeine (30 or 60 mg)</td>
<td>Dose on acetaminophen, 10–15 mg/kg</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Amantadine</td>
<td>3–5 mg/kg PO q 24 h</td>
<td>3–5 mg/kg PO q 24 h</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>0.5–2.0 mg/kg PO q 24 h</td>
<td>5–10 mg PO q 24 h</td>
</tr>
<tr>
<td>Carprofen</td>
<td>4.4 mg/kg SC single dose 4.4 mg/kg PO q 24 h</td>
<td>1–4 mg/kg SC single dose Not recommended for oral use</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>1–2 mg/kg PO q 24 h 3–4 mg/kg PO q 24 h, 7-day limit</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Firocoxib</td>
<td>10 mg/kg PO q 24 h</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2–40 mg/kg PO q 24 h</td>
<td>2–40 mg/kg PO q 24 h</td>
</tr>
<tr>
<td>Imipramine</td>
<td>0.5–1.0 mg/kg PO q 8 h</td>
<td>2.5–5.0 mg/kg PO q 12 h</td>
</tr>
<tr>
<td>Ketamine (as NMDA receptor antagonist rather than anesthetic)</td>
<td>0.5 mg/kg IV, followed by 10 μg/kg/min during surgery, followed by 2 μg/kg/min for next 24 h</td>
<td>0.5 mg/kg IV, followed by 10 μg/kg/min during surgery, followed by 2 μg/kg/min for next 24 h</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1–2 mg/kg IV, IM, SC initial dose 1 mg/kg PO q 24 h up to 5 days</td>
<td>0.5–2 mg/kg IV, IM, SC initial dose 0.5–1 mg/kg PO q 24 h up to 5 days</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.2 mg/kg IV, SC 0.2 mg/kg initial loading dose, then 0.1 mg/kg PO q 24 h</td>
<td>0.1 mg/kg SC 0.1 mg/kg PO on day 1, then 0.05 mg/kg PO q 24 h</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>1–2 mg/kg diluted over 2–4 h IV, SC</td>
<td>1–1.5 mg/kg diluted over 2–4 h</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.3 mg/kg PO q 24–48 h</td>
<td>0.3 mg/kg PO q 24–48 h</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2–4 mg/kg PO q 6–12 h</td>
<td>2–4 mg/kg PO q 6–12 h</td>
</tr>
</tbody>
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*Abbreviations: h, hours; IM, intramuscular; IV, intravenous; PO, per os; q, every; SC, subcutaneous.*
be avoided in cats because of their inadequate cytochrome P-450–dependent hydroxylation.\textsuperscript{18}

Mild to moderate pain, especially that arising from intrathoracic masses, intrabdominal masses, and bone tumors and metastases, can be relieved with NSAIDs. When pain increases, NSAIDs have an opioid-sparing effect such that better analgesia can be achieved with lower doses of opioids. NSAIDs have central analgesic and peripheral anti-inflammatory effects mediated by means of inhibition of cyclooxygenase (COX). The choice of NSAID ultimately depends on available species information, clinical response, and tolerance of side effects. Most NSAIDs have been formally investigated only in dogs, leaving anecdotal information for use in cats, although good information does exist for meloxicam in cats.\textsuperscript{19} The most common side effect of aspirin administration in dogs is gastric irritation and bleeding because of loss of gastric acid inhibition and cytoprotective mucous production normally promoted by prostaglandins. NSAIDs approved for use in dogs have a low incidence of side effects, most commonly, vomiting, diarrhea, and inappetence. Other less common side effects include renal failure and hepatic dysfunction that may lead to failure.\textsuperscript{20}

NSAIDs that are more selective for inhibition of COX-2 seem to have fewer gastrointestinal effects and potentially fewer renal effects.\textsuperscript{21,22} Therefore, more selective COX-2 inhibitors, such as carprofen, meloxicam, deracoxib, firocoxib, and the dual-inhibitor tepoxalin should be considered priority NSAIDs in patients that have cancer. A blood chemistry panel should be performed before initiating NSAID therapy. If there is evidence of liver or renal disease, dehydration, or hypotension, another approach to therapy should be considered. Therapy with older NSAIDs, such as aspirin and ketoprofen, may also inhibit platelet function, leading to bleeding and oozing. Therapy with NSAIDs should be stopped if this occurs. If clinical effectiveness is not achieved with one NSAID, it should be discontinued and another started 7 days later to avoid additive or synergistic COX inhibition effects. Aspirin should be avoided in dogs because of the increased possibility of gastrointestinal bleeding, even with buffered formulations.\textsuperscript{2,23} Administering misoprostol as a synthetic prostaglandin can help to provide gastrointestinal protection during shorter switchover periods. All patients that have cancer should be closely monitored for gastrointestinal bleeding if receiving NSAID therapy during chemotherapy that may induce thrombocytopenia.

OPIOIDS

Opioids are the major class of analgesics used in the management of moderate to severe cancer pain. They are most effective and predictable and have low risk associated with them.\textsuperscript{24} The most common parenteral opioids used in small animals are morphine, hydromorphone, oxymorphone, fentanyl, codeine, meperidine, buprenorphine, and butorphanol (\textsuperscript{Table 2}). Parenteral opioids should be used in the perioperative period and should be discontinued when a patient can be switched to oral medication. Common oral opioids include morphine, oxycodone, buprenorphine, and codeine with or without acetaminophen (see \textsuperscript{Table 2}).

As a patient’s pain increases, the required dose of opioid also increases. Veterinarians may be reluctant to administer high doses of opioids for fear of adverse side effects. It is important to remember that veterinarians have an ethical obligation to benefit the patient by alleviating pain. Opioids can be administered while managing side effects to help the patient maximally. Side effects of opioid administration include diarrhea, vomiting, and dysphoria or sedation initially, with constipation with long-term use but, less commonly, sedation and dysphoria. The initial gastrointestinal effects occur most frequently with the first injection in the perioperative period and usually
do not occur with subsequent dosing. Dosing to effect may reduce this occurrence. These effects usually do not occur with oral dosing. When sending a patient home with oral medications, it is important to discuss with the owner that dosing is individual. It is possible that a given dose is perfect, does not provide enough analgesia, induces sedation, or induces dysphoria or excitement. Adjusting of the dose requires excellent doctor-client interaction. Bradycardia is also possible after opioid administration but is most common if opioids are administered parenterally. If bradycardia occurs, an anticholinergic, such as atropine or glycopyrrolate, should be administered rather than discontinuing the opioid.

Opioids are classified as full \( \mu \)-receptor agonists, partial agonists, and \( \kappa \)-agonist–\( \mu \)-antagonists. Examples of the full \( \mu \)-receptor agonists include morphine, oxymorphone, fentanyl, codeine, and meperidine. In normal healthy animals, opioids may produce sedation, which is usually acceptable, or dysphoria, an exaggerated unrest, which usually is undesirable. These adverse effects are noted when pain does not exist or is overestimated, and a relative overdose of the opioid was thus administered. Full \( \mu \)-agonists induce the best analgesia in a dose-dependent manner and are not limited by a ceiling effect. As pain increases, larger doses may be administered, again stressing the importance of “dosing to effect.” Morphine or hydromorphone should be the most commonly used injectable opioid for the acute treatment of cancer-related pain. Morphine is available in multiple injectable and oral formulations, including short-duration tablets and liquids and sustained-release tablets. Oral morphine may be the most effective method for providing longer term analgesia to dogs and cats.

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog Dose</th>
<th>Cat Dose</th>
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<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.005–0.02 mg/kg SC, IM, IV q 4–8 h</td>
<td>0.005–0.02 mg/kg SC, IM, IV q 4–8 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01–0.02 buccally q 6–12 h</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.2–0.8 mg/kg SC, IM q 2–6 h</td>
<td>0.1–0.4 mg/kg SC, IM q 2–6 h</td>
</tr>
<tr>
<td></td>
<td>0.5–2 mg/kg PO q 6–8 h</td>
<td>0.1 mg/kg IV q 1–2 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5–2 mg/kg PO q 6–8 h</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.5–1 mg/kg PO q 4–6 h</td>
<td>0.5 mg/kg PO q 6 h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.01–0.04 mg/kg SC, IM</td>
<td>0.005–0.04 mg/kg SC, IM</td>
</tr>
<tr>
<td></td>
<td>0.002–0.005 mg/kg IV</td>
<td>0.002–0.005 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>2–20 ( \mu )g/kg/h IV</td>
<td>2–20 ( \mu )g/kg/h IV</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.05–0.2 mg/kg SC, IM</td>
<td>0.05–0.1 mg/kg SC, IM q 2–6 h</td>
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<tr>
<td></td>
<td>0.05–0.1 mg/kg IV q 2–6 h</td>
<td>0.03–0.05 mg/kg IV q 1 h</td>
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<td></td>
<td>0.05–0.1 mg/kg/h</td>
<td>0.01–0.05 mg/kg/h</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.25–1.0 mg/kg SQ, IM q 4–6 h</td>
<td>0.05–0.1 mg/kg IM, SC q 4–6 h</td>
</tr>
<tr>
<td></td>
<td>0.05–0.1 mg/kg IV q 1–2 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05–0.1 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 mg/kg epidurally q 12–24 h</td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate:</td>
<td>2–5 mg/kg q 12 h</td>
<td>Not recommended</td>
</tr>
<tr>
<td>sustained release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and oral liquid</td>
<td>1.0 mg/kg PO q 4–6 h</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.025–0.2 mg/kg IV, IM, SC</td>
<td>0.02–0.2 mg/kg IV, IM, SC</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.1–0.3 mg/kg PO q 8–12 h</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*Abbreviations: h, hours; IM, intramuscular; IV, intravenous; PO, per os; q, every; SC, subcutaneous.*
with moderate to severe pain. Patients receiving nonopioid analgesics at set dosing intervals should also be provided with some short-duration opioid for breakthrough pain. Oxymorphone is only available as an injectable analgesic. Oxymorphone and most other opioids may induce panting by changing the temperature set point in the brain.\textsuperscript{24} This usually is not an issue, except when attempting thoracic or abdominal radiography. This effect may be avoided by dosing to effect in many cases. Meperidine is short acting in animals, limiting its use as an analgesic in patients that have cancer. Codeine is available alone or with acetaminophen, allowing some flexibility in choice of oral medications. Fentanyl is an injectable drug that is potent and effective. All the previously mentioned parenteral opioids may be administered by an intermittent intravenous, intramuscular, or subcutaneous route. A problem with this type of intermittent dosing is that patients often become painful before their subsequent dose and then are extremely sedated after dosing. An alternate dosing regimen would use continuous infusion of an opioid. Fentanyl is an appropriate drug for continuous infusion because it is short acting. This enables the practitioner to alter the dose as necessary from minute to minute to achieve good analgesia and potentially minimal sedation if desired.

Oxycodone, an excellent oral analgesic in dogs, may be used for primary pain control or for the control of breakthrough pain. Oral oxycodone is currently being used more and more frequently for severe pain in dogs. It seems to induce less sedation and dysphoria than oral morphine and provides a greater degree of pain control than oral codeine. Buprenorphine is an example of a partial $\mu$-agonist. It does not produce the same degree of analgesia as morphine and has a ceiling effect. The advantage of buprenorphine is that it has a long duration of action, 6 to 12 hours. It also has a long time to onset, approximately 40 minutes, even when given intravenously. Buprenorphine is a unique drug in that larger doses may actually produce less analgesia because of a bell-shaped dose-response curve. Tapering the dose to the individual may be difficult. If an animal does not have adequate analgesia after receiving buprenorphine, dosing with a morphine-like drug may not produce any results because of buprenorphine’s strong affinity for $\mu$-opioid receptors. Buprenorphine is not easily reversible. Experimentally, it takes 1000 times the normal dose of naloxone to reverse it in a normal dog.\textsuperscript{25–27} Because of the inherent lack of maximal analgesia compared with morphine, buprenorphine should only be used for mild to moderate cancer pain in dogs. If any doubt exists as to severity of pain, one can start with a pure $\mu$-opioid and adjust the dose to the desired effect. If a low dose produces analgesia, one can assume that buprenorphine is adequate for future management.

There are good data to suggest that cats get excellent analgesia when buprenorphine is administered intravenously or buccally. The buccal route seems to induce equivalent analgesia.\textsuperscript{28,29} There is also some evidence that the buccal route may be effective in dogs.\textsuperscript{30} It remains to be seen if this is beneficial in dogs based on actual pain relief and cost.

Another group of opioids available are the $\kappa$-agonist-$\mu$-antagonists, of which butorphanol is an example. Butorphanol may reverse the effects of drugs like morphine, a pure $\mu$-agonist, but provides analgesia and sedation of its own. Butorphanol is also reversible with naloxone and nalmefene. The analgesia is not as good as that produced by morphine. Even in large parenteral doses, butorphanol produces analgesia of short duration in dogs\textsuperscript{31} and, as such, may not be useful for cancer pain.

An alternative to administering oral opioids to provide multiple-day analgesia is to apply a transdermal fentanyl patch. Fentanyl patches require 12 to 24 hours to take effect and last 2 to 4 days in dogs but require 12 hours to take effect in cats. Additional analgesia must be provided during the first 0.5 to 1 day after patch placement. If an
opioid is selected, pure \( \mu \)-agonists must be used. One problem with transdermal fentanyl is related to unreliable plasma levels in dogs,\(^{32-34} \) probably because of failure of patch application or inappropriate dosing. Fentanyl patches may not provide enough analgesia for severe pain,\(^{33} \) but they allow lower doses of additional drugs. Fentanyl patches are expensive and should not be the first approach to chronic therapy. Additionally, the usefulness of a fentanyl patch may be limited by sedation or dysphoria, necessitating removing the patch prematurely. Transdermal fentanyl is most appropriate in those patients that do not tolerate oral medication. Fentanyl patches should not be prescribed when young children are in the household, because potential removal with ingestion is a concern.

Epidural opioids, especially morphine, have been used as a method for perioperative analgesia. With placement of an epidural catheter, epidural opioids can be administered for days to weeks. This may be appropriate for long-term pain control in patients that have vertebral mass(es) or other forms of cancer that induce severe pain. The reader is referred to the discussion on epidural analgesia elsewhere in this issue.

Although not truly an opioid, tramadol, a serotonin reuptake inhibitor, can provide significant pain control in addition to an NSAID. Tramadol can bridge the gap between an NSAID alone and the addition of a potent oral opioid for extended periods. Although the pharmacokinetics of tramadol suggest high dose and frequent administration,\(^{35} \) most canine and feline patients develop significant comfort at 2 to 3 mg/kg administered orally two to three times daily.

The appropriate dose of an opioid is the dose that produces analgesia with the fewest side effects. The need for increased doses often reflects progression of disease. Long-term use produces opioid tolerance, increasing doses or frequency to achieve equivalent results. As previously mentioned, veterinarians should not be afraid of increasing doses in patients and should remember the need for analgesia. A distinct advantage of using opioids for pain control is that they are reversible with naloxone or nalmefene if unacceptable side effects occur. Prolonged use may produce constipation. Oral laxatives can help to alleviate this problem.

\( \alpha_2 \)-AGONISTS

Xylazine, medetomidine, and dexmedetomidine are three \( \alpha_2 \)-agonists approved for use in small animals in the United States. They are noncontrolled parenteral agents and provide excellent visceral analgesia but only for 20 minutes to 2 hours.\(^{36-39} \) Their effects can be virtually completely reversed with yohimbine or atipamezole, respectively. The \( \alpha_2 \)-agonists should not be the first or sole choice in providing analgesia around the time of surgery to patients that have cancer because they greatly reduce cardiac function and oxygenation.\(^{36,40,41} \) \( \alpha_2 \)-Agonists have synergistic effects with opioids. When used in microdoses (0.5–1 \( \mu \)g/kg administered intravenously, 1–3 \( \mu \)g/kg/h), this effect can be useful after surgery for inducing additional analgesia and alleviating dysphoria and anxiety.

\( N \)-METHYL-\( D \)-ASPARTATE RECEPTOR ANTAGONISTS

Ketamine has been used for many years as an induction agent to general anesthesia in normal and compromised patients. It has been well established that ketamine provides reasonable somatic but poor visceral analgesia.\(^{42} \) Ketamine has been identified as an \( N \)-methyl-\( D \)-aspartate (NMDA) receptor antagonist. NMDA receptors are believed to play a role in the processes leading up to central sensitization and wind-up. As an NMDA receptor antagonist, ketamine reduces postoperative pain and
cumulative opioid requirements for a variety of procedures in human beings. This is accomplished with doses that are much smaller than those for anesthesia. In fact, these doses of ketamine should not be considered as direct analgesic doses but as NMDA antagonist doses inducing an indirect analgesic effect, essentially allowing other analgesics to work more effectively. As such, it is uncommon for patients to develop behavioral or cardiovascular effects. In fact, microdose ketamine may actually decrease the incidence of opioid-induced dysphoria after surgery. Intraoperative microdose ketamine has been demonstrated to be effective for pain control long after discontinuing administration. Dogs recovering after this type of therapy for forelimb amputation are more comfortable in the perioperative period and after the dog has been sent home. When used in this manner, ketamine should be administered as a bolus (0.5 mg/kg administered intravenously), followed by an infusion (10 μg/kg/min) before and during surgical stimulation. A lower infusion rate (2 μg/kg/min = 0.12 mg/kg/h) may be beneficial for the first 24 hours after surgery, with an even lower rate (1 μg/kg/min = 0.6 mg/kg/h) for the next 24 hours. In the absence of an infusion pump, ketamine can be mixed in a bag of crystalloid solutions for administration during anesthesia. Using anesthesia fluid administration rates of 10 mL/kg/h, ketamine at a dose of 60 mg (0.6 mL) should be added to a 1-L bag of crystalloid fluids to deliver ketamine at a rate of 0.6 mg/kg/h. Higher doses of ketamine (1–2 mg/kg/h) may provide significant direct analgesia effects. It is unclear if an NMDA antagonist effect occurs at these higher doses.

Amantadine, an oral anti-influenza A medication that also has NMDA antagonist effects, can be administered at 3 mg/kg orally once daily to prevent wind-up. It should be part of the early intervention in patients that have osteosarcoma. Although the specific pharmacokinetics have not been determined for amantadine, good information is available for rimantadine, a similar medication.

TRANQUILIZERS

A concern that frequently arises with pain management is concurrent tranquilization and sedation. Most of the drugs used by veterinarians usually produce concurrent sedation. As mentioned previously, opioids have the greatest potential of producing dysphoria instead of sedation. Dysphoria becomes more likely when cats are administered canine doses of opioids and when a patient is already experiencing high anxiety in the hospital. Dysphoric patients can sometimes be treated simply by petting and soothing or by helping a patient to change position. Low-dose acepromazine (Table 3) administered intravenously or intramuscularly is reasonable drug therapy for dysphoria. Although acepromazine does not treat pain, it calms anxious patients well and also makes them care less about their pain. For patients in which acepromazine is contraindicated, such as those with bleeding disorders, the benzodiazepines (see Table 2) diazepam and midazolam often calm patients. Benzodiazepines should not be used by themselves in most alert patients because they frequently cause excitement. Combined with opioids, sedation usually results. In patients that are hemodynamically stable, a microdose of dexmedetomidine (0.0005–0.001 mg/kg administered intravenously) or medetomidine (0.001–0.002 mg/kg administered intravenously) administered intravenously or intramuscularly also can decrease dysphoria and increase analgesia.

Patients that develop dysphoria after oral analgesic medications often respond well to oral acepromazine or diazepam. It is important to discern whether the opioid dose is effective before changing the analgesia regimen, because dysphoria may occur with too high, too low, or an appropriate analgesic dose of the opioid.
Alprazolam at a dosage of 0.1 to 0.5 mg/kg/d administered orally can be given as an anxiolytic. Diazepam and midazolam can be administered as alternative therapy for animals in which acepromazine is contraindicated.

**ANTICONVULSANTS**

Gabapentin is a structural analogue of \( \gamma \)-aminobutyric acid (GABA)\(^{49} \) and was originally introduced as an antiepileptic drug. The mechanism of action of gabapentin is unclear and elusive. Although gabapentin is related to GABA, it does not seem to have any analgesic effect at GABA receptors. Several rat studies have investigated the effects of gabapentin on signs of neuropathic pain, such as hyperalgesia and allodynia. Other studies indicate a role for gabapentin in decreasing incisional pain and arthritis. Although the exact indications and efficacy for gabapentin have not yet been determined, it seems to be useful for neuropathic cancer pain. When gabapentin is added to an opioid regimen for patients that are only partially opioid responsive, they experience significantly better analgesia.

### Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog Dose</th>
<th>Cat Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acepromazine</td>
<td>0.025–0.1 mg/kg; maximum of 4 mg IV, SC, IM</td>
<td>0.05–0.1 mg/kg; maximum of 1 mg IV</td>
</tr>
<tr>
<td></td>
<td>0.5–2 mg/kg PO</td>
<td>0.1–2.0 mg/kg PO</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.025–0.1 mg/kg q 8 h</td>
<td>0.0125–0.025 mg/kg q 12 h</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.0005 mg/kg/h IV (preanesthetic)</td>
<td>0.0010 mg/kg/h IV (preanesthetic)</td>
</tr>
<tr>
<td></td>
<td>0.0005–0.002 mg/kg IV bolus (short-term sedation/analgesia)</td>
<td>0.0010–0.004 mg/kg IV bolus (short-term sedation/analgesia)</td>
</tr>
<tr>
<td></td>
<td>0.0005–0.001 mg/kg/h IV (extended sedation/analgesia-CRI)</td>
<td>0.0010–0.002 mg/kg/h IV (extended sedation/analgesia-CRI)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.1–0.5 mg/kg IV, IM</td>
<td>0.05–0.4 mg/kg IV, IM</td>
</tr>
<tr>
<td></td>
<td>0.5–2.2 mg/kg PO</td>
<td>0.5–2.2 mg/kg PO</td>
</tr>
<tr>
<td>Medetomidine</td>
<td>0.01–0.02 mg/kg IM</td>
<td>0.015–0.03 mg/kg IM</td>
</tr>
<tr>
<td></td>
<td>0.005–0.01 mg/kg IV (sedation/analgesia)</td>
<td>0.01–0.015 mg/kg IV (sedation/analgesia)</td>
</tr>
<tr>
<td></td>
<td>0.005–0.01 mg/kg IM</td>
<td>0.01–0.01 IM</td>
</tr>
<tr>
<td></td>
<td>0.003–0.005 mg/kg IV (preanesthetic)</td>
<td>0.005–0.01 mg IV (preanesthetic)</td>
</tr>
<tr>
<td></td>
<td>0.01–0.02 mg/kg/h IV (supplemental CRI during inhalant anesthesia)</td>
<td>0.003–0.010 IV bolus (short-term sedation/analgesia)</td>
</tr>
<tr>
<td></td>
<td>0.001–0.003 mg/kg IV bolus (short-term sedation/analgesia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.001–0.002 mg/kg/h IV (extended sedation/analgesia CRI)</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1–0.25 mg/kg IV, IM</td>
<td>0.05–0.25 mg/kg IV, IM</td>
</tr>
<tr>
<td>Xylazine</td>
<td>1.1–2.2 mg/kg IM, SC</td>
<td>1.1 mg/kg IM, SC</td>
</tr>
<tr>
<td></td>
<td>0.05–0.1 mg/kg IV prn</td>
<td>0.05–0.1 mg/kg IV prn</td>
</tr>
<tr>
<td></td>
<td>0.2 mg/kg SC, IM q 1–2 h</td>
<td>0.2–0.4 mg/kg SC, IM q 1–2 h</td>
</tr>
</tbody>
</table>

*Abbreviations: CRI, constant rate infusion; h, hours; IM, intramuscular; IV, intravenous; PO, per os; prn, as needed; q, every; SC, subcutaneous.*
These patients also experience less allodynia. Burning and lancinating pain is also more likely to respond to gabapentin compared with dull aching pain.

Although dosing has not been established in dogs or cats, the following recommendations are extrapolations from human beings. It is important to remember that there are no controlled or evidence-based studies in dogs and cats using gabapentin. Gabapentin has been investigated as an antiepileptic drug in dogs, with dosing between 800 and 1500 mg/d. Initial doses for pain range from 2.5 to 10 mg/kg administered orally two or three times daily but can be escalated up to 50 mg/kg administered orally two to three times daily depending on the analgesic effect achieved. Gabapentin may need to be compounded for smaller patients.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants, such as amitriptyline, clomipramine, and imipramine, block the reuptake of serotonin and norepinephrine in the central nervous system (see Table 3). They also have antihistaminic effects. These drugs have been used in human patients for the treatment of chronic and neuropathic pain at doses considerably lower than those used to treat depression.50 Despite the lack of studies verifying the use of tricyclic antidepressants in this manner, clinical experience by many practitioners would substantiate this analgesic use in dogs and cats.

LOCAL ANESTHETICS

The use of local and regional anesthetic techniques in small animals was common in the early twentieth century. There has recently been increased interest in these techniques, probably because of their ability to provide pre-emptive analgesia and decrease wind-up.51,52 Local anesthetic techniques can be used instead of general anesthesia in selected cases or, more commonly, in combination.

The most commonly used local anesthetics include lidocaine and bupivacaine. Lidocaine has a short onset (<1 minute) and lasts approximately 60 to 90 minutes. Doses of 1.5 to 2.0 mg/kg are safe in dogs and cats. Signs of toxicity are manifested as nausea and vomiting, followed by neurologic changes, including seizures. Bupivacaine takes approximately 20 minutes to take effect but may last for 5 to 8 hours. Although lidocaine has antidyssrhythmic effects at low to moderate intravenous doses, bupivacaine has cardiotoxic effects when administered intravascularly. Inadvertent intravenous administration can result in death.53,54 Epinephrine may be added to bupivacaine in a 1:200,000 dilution to cause local vasoconstriction and prolonged duration. Epinephrine should not be used for peripheral blocks, because there may not be collateral circulation to provide adequate perfusion to distal tissues. Combinations of lidocaine and bupivacaine are often used to achieve quick onset and long duration. This is especially necessary when using local anesthetics interpleurally. Because of its long onset, bupivacaine causes stinging discomfort. Lidocaine administered concurrently limits the discomfort to a period of seconds. When bupivacaine is used alone, a ratio of 1:10 sodium bicarbonate (1 mL) to bupivacaine 0.5% (10 mL) has been shown to reduce but not eliminate the discomfort of bupivacaine.

There are numerous uses for local anesthetics. They are often used epidurally to produce better analgesia in low doses or as anesthesia for caudal procedures in higher doses. They may be used interpleurally for thoracic and cranial abdominal pain. Intercostal nerve blocks are easily performed for lateral thoracotomy pain. Brachial plexus infiltration provides anesthesia for the proximal and distal forelimb. Maxillary, infraorbital, mandibular, and mental nerve blocks are commonly used for procedures involving the face and mouth. Local infiltration is common for procedures
involving the ear. Ring blocks have also been used for distal limb and digit amputations. Many of these techniques have been well described.55

The 5% lidocaine patch produces local tissue concentrations far lower than those capable of producing toxicity but high enough to produce clinically effective local analgesia for periods of up to 24 hours without complete sensory block. The patches have been used to provide analgesia for skin abrasions, lacerations, and severe local skin irritation and itching (hot spots), and they are likely useful for localized pain related to cancer.

**Epidural Drug Administration**

Epidural administration of drugs requires additional skill and expertise that may not be available in all clinical settings. Details of the procedure are described in the companion article elsewhere in this issue. Epidural morphine is commonly administered in the perioperative period to provide analgesia but not anesthesia in the abdomen or more caudally. In some instances, analgesia may be effective for the thorax and forelimb. This analgesia may last up to 24 hours.56 Local anesthetics may also be administered epidurally as a low dose to augment epidural morphine-induced analgesia or at a higher dose to produce anesthesia.

A catheter can also be placed in the epidural space for severe pain that may be intractable in the caudal portion of the body. Maintenance of this catheter requires veterinarian and client vigilance to ensure cleanliness and prevent infection migrating to the spinal cord. With proper care, an epidural catheter can remain in place for days to weeks.

**OTHER PAIN-RELIEVING MODALITIES**

Local or whole-body radiation can enhance analgesic drug effectiveness by reducing metastatic or primary tumor bulk.57 The radiation dose should be balanced between the amount necessary to kill tumor cells and that which would affect normal cells. Mucositis of the oral cavity and pharynx can develop after radiation to the neck, head, or oral cavities, resulting in impaired ability to eat and drink. Mucositis therapies include analgesics, green tea rinses, sucralfate, 2% viscous lidocaine, and a 1:1 combination of 2% lidocaine viscous to aluminum hydroxide, 64 mg/mL (commonly referred to as “Pink Lady”). A mix of 50 mL of each for a total volume of 100 mL can be sent home with the patient. This mixture tends to assist adherence of the lidocaine to the lesions. When local anesthetics are used orally, the maximum dose of lidocaine should not be exceeded. Just enough should be given to coat the inside of the mouth to avoid swallowing and coating the pharynx, because this can desensitize the area, potentially predisposing to aspiration.

Osteosarcoma and bony metastases are common causes of pain in advanced cancer. Some tumors cause osteoblastic metastases, but most can cause osteolytic lesions. Administration of bisphosphonates, such as pamidronate, reduces pain and pathologic fractures in human beings.58 Bisphosphonates accumulate on bone surfaces and inhibit osteoclast-induced resorption, favoring bone formation. This therapy is now reasonably priced and should be available to all veterinary clients. Pamidronate (1–2 mg/kg) is diluted in saline and administered intravenously over a 2- to 4-hour period at 3- to 5-week intervals. It decreases pain and potentially increases survival in dogs that have osteosarcoma.59 A potential oral alternative to pamidronate is alendronate. Alendronate inhibits cell migration through mechanisms that depend on calcium.60 It has been studied specifically in dogs and has been shown to have an antiosteosarcoma effect.61 At reasonable doses, it has also been shown to have no significant adverse effects over a 3-year period.62 Although alendronate therapy
Acupuncture can be used as a pain-relieving modality, often in conjunction with other therapy or when conventional therapy does not work. In conjunction with other therapy, it can allow administration of lower doses of drugs that may have significant side effects. Although some practitioners have difficulty in accepting acupuncture because of traditional Chinese medical explanations, which may be scientifically untenable, it is important to remember that there exists well-documented physiologic theory and evidence for its clinical effects. Electroacupuncture can be useful for cancer-related bone pain. In general, acupuncture analgesia is extremely useful for pelvic, radius or ulna, and femoral bone pain in addition to cutaneous discomfort secondary to radiation therapy. Acupuncture also helps to increase appetite and alleviate nausea associated with chemotherapy and some analgesics in addition to promoting general well-being. For details, please refer to the article by Gaynor.

**SPECIFIC PAIN PROBLEMS**

When developing a plan for alleviating pain in a patient that has cancer, it helps to have a paradigm to follow. A simple flow chart (Fig. 2) can help with the sequence of activities related to pain assessment and management. This flow chart emphasizes the use of multiple modalities, beginning therapy with the least invasive methods and advancing treatment to meet the patient’s needs. Although not all types of pain can be addressed here, pain relief should be considered achievable by following recommendations and paradigms in this article.

**SURGICAL CASE EXAMPLES**

The following generic examples, in conjunction with the flow chart, present useful approaches to specific types of pain encountered in oncology practice. The examples recommend specific techniques for the procedure rather than a complete analgesia program. Implicit in the recommendations is an appropriate opioid and an NSAID if not contraindicated.

- **Lateral thoracotomy**
  - Intercostal nerve block
  - Interpleural (intrapleural?) local anesthetic
  - Opioid epidural

- **Sternotomy**
  - Intercostal nerve block
  - Opioid epidural

- **Forelimb amputation**
  - Brachial plexus nerve block
  - Opioid epidural

- **Rear limb amputation**
  - Opioid epidural

- **Cranial mandibular surgery**
  - Mandibular nerve block
  - Mental nerve block

- **Upper lip and nose (nasal?) procedure**
  - Infraorbital nerve block

- **Maxillary surgery**
  - Maxillary nerve block
For all these procedures, the addition of an NSAID administered intravenously, subcutaneously, or intramuscularly as is species and drug appropriate is an extremely valuable adjunct to the regimen.

Midcaudal abdominal surgery
   - Opioid epidural (local anesthetic also if caudal abdomen)
Cranial abdominal surgery
   - Interpleural local anesthetic
   - Opioid epidural

Although not all types of pain can be addressed, pain relief should be considered achievable by following recommendations and paradigms in this article.

**Outpatient Case Examples**

Osteosarcoma (assuming the patient does not have an amputation)
   - Initial therapy with an approved NSAID for mild to moderate pain
Continuous therapy with amantadine to treat and prevent wind-up
Pamidronate, a bisphosphonate, every 3 to 4 weeks to decrease osteoclast function
Tramadol with the NSAID for moderate to severe pain
Oxycodone to replace tramadol as the pain gets worse
Chondrosarcoma
Initial therapy with an approved NSAID for mild to moderate pain
Gabapentin in progressively increasing doses for analgesia and to help prevent wind-up
Transitional cell carcinoma
This is the only tumor that has been definitively identified as being responsive to piroxicam. Hence, piroxicam should be administered for anticancer effects and for analgesia. The patient’s packed cell volume (PCV) should be monitored closely, because piroxicam is a nonspecific COX-1/COX-2 inhibitor, predisposing to moderate to severe ulceration and the potential for gastrointestinal bleeding.

SUMMARY
Control of cancer pain is within the capabilities of most veterinarians and is achievable in most animal patients that have cancer with techniques that are currently available. Once veterinarians and technicians gain a good knowledge base about pain and its therapy, pain control should be achievable by following these simple ABCs:

A. Assess the pain. Ask for the owner’s perceptions.
B. Believe the owner. The owner sees the pet each day in its own environment.
C. Choose appropriate therapy following the World Health Organization ladder and other more specific paradigms.
D. Deliver therapy in a logical coordinated manner.
E. Empower the clients to participate actively in their pet’s well-being.

Great satisfaction can be derived from not only treating the pet’s cancer but its pain. Incorporating pain management into oncology practice is good for the well-being of the pet, the owner, the staff, the veterinarians, and the practice.

REFERENCES
