While osteoarthritis (OA) may be the most commonly recognized cause of chronic pain in dogs and cats, other pain syndromes exist. The following scenarios, when evaluated together, may have a prevalence approaching that of OA:

1. Chronic or chronic–active inflammatory pain
2. Maladaptive chronic pain

Treatment of these pain phenomena has not been investigated in depth, so therapeutic rationale must be inferred from disease pathophysiology and existing evidence regarding individual treatment modalities.

**CHRONIC OR CHRONIC–ACTIVE INFLAMMATORY PAIN**

A growing body of evidence suggests that peripheral and central sensitization not only exists in chronic inflammatory disease states (Table 1) but may actually advance pathologic abnormalities through proinflammatory neurogenic mechanisms.

Few studies have assessed the management of nonOA chronic inflammatory conditions, and such studies may be difficult to perform. However, a treatment sequence for this category of chronic pain can be inferred, in the following approximate order:

1. Anti-inflammatory medications: nonsteroidal anti-inflammatory drug (NSAID) or corticosteroid
2. Treatment of underlying disease or aggravating comorbidities
3. Neuromodulatory analgesic drugs, such as gabapentin, tramadol, and amitriptyline
4. Weight optimization.

---

**TABLE 1. Examples of Chronic & Chronic–Active Inflammatory Pain**

<table>
<thead>
<tr>
<th>Chronic periodontal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feline lymphocytic–plasmacytic stomatitis</td>
</tr>
<tr>
<td>Idiopathic feline lower urinary tract disease*</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Meningoencephalitides</td>
</tr>
<tr>
<td>Otitis externa</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

* Feline interstitial cystitis is increasingly being considered a somatic pain syndrome.†
Maladaptive pain occurs through the process of peripheral and central sensitization. Its features include pain that is protracted in duration, exaggerated in severity (hyperalgesia, allodynia), and expanded in field, and can occur in the absence of obvious tissue pathology. These types of disease states (Table 2) include many poorly understood pain syndromes.

**NSAIDs**

To the degree that inflammation is considered a component of the underlying pathologic abnormality activating nociceptive pathways, NSAIDs can be considered a first-line drug. However, many maladaptive chronic pain states have progressed to, or are intrinsically, a neuropathic state. In these cases, NSAIDs may contribute a less robust analgesic effect.

**Other Analgesic Therapies**

In humans, systematic reviews of neuropathic pain recommend the following drugs: tricyclic antidepressants, gabapentin, and opioids. While these papers are drawn mainly from trials involving diabetic neuropathy and postherpetic neuralgia—clinical conditions not identified in animals—these drugs commonly play a more prominent role in managing maladaptive pain than NSAIDs.

- **Gabapentin** can be considered a relatively well-tolerated, inexpensive, easy-to-administer, and effective pain medication in dogs and cats, with efficacy supported by numerous case reports. Use of the tricyclic antidepressant **amitriptyline** for pain has been described in canine and feline case reports and for feline interstitial cystitis.
- **Oral opioids** may also have a role in treating these syndromes.

Additional medications that have been used in humans for maladaptive pain states include:

- **Other anticonvulsants** (pregabalin, lamotrigine)
- **Ion channel blockers** (mexiletine, infusions of systemic lidocaine, ketamine)
- **Selective serotonin-norepinephrine reuptake inhibitors** (duloxetine, venlafaxine).

However, lack of experience with, and data on, these agents for pain in animals limits their use at this time.

**Additional Therapies**

As adipose tissue is the body’s largest endocrine organ and secretes a witches brew of degradative enzymes and pro-inflammatory cytokines, weight optimization may have the same important role to play in managing nonOA chronic pain as it does in OA. In elderly humans, central obesity (abdominal fat) doubles the risk for chronic pain from any cause.

Table 3 outlines therapeutic options for maladaptive chronic pain.

---

**TABLE 2. Examples of Potential or Existing Maladaptive Chronic Pain**

<table>
<thead>
<tr>
<th>Central nervous system lesions, including post-trauma or vascular accidents, intracranial masses, and congenital defects (eg, syringomyelia)</th>
<th>Chronic intervertebral disk disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td>Feline hyperesthesia syndrome</td>
</tr>
<tr>
<td>Feline orofacial pain syndrome</td>
<td>Postperipheral nerve injury (eg, trauma, amputation)</td>
</tr>
<tr>
<td>Postsurgical conditions (eg, fractures, hernia repair)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3. Management of Maladaptive Pain: Therapies to Consider**

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Neuromodulatory Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>• Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>• Gabapentin preferred in dogs</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>• Possible role for pregabalin</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>• Tricyclic antidepressant</td>
</tr>
<tr>
<td>Tramadol</td>
<td>• Pharmacokinetics of oral tramadol do not favor its use for pain in dogs</td>
</tr>
<tr>
<td></td>
<td>• It may have better results in cats</td>
</tr>
<tr>
<td>Amantadine</td>
<td>• NMDA receptor antagonist</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>• Selective serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td></td>
<td>• Oral venlafaxine has approximately 50% bioavailability in dogs, with half-life of 3 h</td>
</tr>
<tr>
<td></td>
<td>• Duloxetine has poor oral bioavailability in dogs</td>
</tr>
<tr>
<td>Acetaminophen + hydrocodone or codeine</td>
<td>• Consider judicious use, especially for breakthrough pain in dogs</td>
</tr>
<tr>
<td></td>
<td>• The dog does not appear to demonstrate a special proclivity toward hepatotoxicity, but methemoglobinemia and anemia are reported with overdosage and long-term use. Complete blood count monitoring is recommended.</td>
</tr>
<tr>
<td></td>
<td>• Pharmacokinetic, but not clinical, data support the utility of codeine and hydrocodone in the dog</td>
</tr>
</tbody>
</table>

(Table continued on page 42)
Cancer Pain

Any primary neoplasm or cancer metastasis to bone, including osteosarcoma (OSA), causes a chronic pain condition in dogs and cats; pain is due to many unique factors to this disease (Table 4).

Table 4. Factors That Cause Chronic Cancer Pain

| Action of osteoclasts | Local necrosis | Lymphatic obstruction | Neurochemical blend of bi-active, proinflammatory cytokines, which distinctly sustain and enhance nociceptive pathways | Upregulation of cyclooxygenase (COX) enzymes |

Palliative Care

For patients whose owners have opted for palliative care—pain management and disease control versus amputation or chemotherapy—inadequate pain control, rather than the disease itself, will probably be the terminal event leading to euthanasia. Once a collaborative decision is made between the veterinarian and pet owner that pain can no longer be sufficiently managed, humane euthanasia should quickly follow.

In these difficult cases, it is important to access the entire pain management arsenal because undermanaging these patients’ pain is inhumane and results in death (euthanasia). OSA and other bone cancers warrant a multimodal polypharmacy approach to treatment, while paying attention to the potential for adverse drug reactions and interactions.

Therapeutic Approach

A recent review in the human literature evaluated the number needed to treat: number needed to harm ratio for treatment of cancer pain. The authors cited gabapentin, pregabalin, and strong opioids as the most effective and best-tolerated drugs, while amitriptyline, trameadol, and NSAIDs elicited less effect or had a more unfavorable safety profile.

See Medications for Cancer Pain in Dogs & Cats for further information.

Conclusion

The treatment of chronic pain in dogs and cats remains a vast and largely unexplored frontier, but provides enormous opportunities for positive outcomes for patients, pet owners, veterinary teams, and practices themselves. With focus, continued learning, and leadership, this arena of veterinary medicine is a means for personal and professional growth and, ultimately, compassionate care of companion animal populations.

References

Medications for Cancer Pain in Dogs & Cats

1. NSAIDs
   The antineoplastic effects of certain NSAIDs in humans and dogs are well established, and appear to be mediated through the upregulation and overexpression of COX-2 enzymes by some neoplasms. However, the spectrum of NSAIDs, species, and neoplasms for which this effect might occur is unknown.

   Most tumors evaluated in cats have little, if any, COX-2 expression. That said, the upregulation of COX enzymes and presence of perineoplastic inflammation warrant use of NSAIDs, whether or not they exhibit an antineoplastic effect.

2. Opioids
   While long-term use of oral opioids in animals with cancer pain is limited, canine patients may benefit from codeine or hydrocodone as these drugs have the most favorable pharmacokinetic profile in dogs. Transmucosal buprenorphine may be used in cats.

   In addition, a recent rat study suggested that bone cancer pain may respond better to delta-receptor active opioids than to mu-receptor active opioids. Fentanyl patches in humans are labeled for use in cancer breakthrough pain, as are some buprenorphine patches, but their efficacy in animals is questionable.

   Newer extended-release oral and transmucosal opioids—combined with peripheral opioid-receptor antagonists (to minimize gastrointestinal side effects) and, in the future, gial inhibitors—may ultimately play a greater role in palliative care and breakthrough cancer pain in pets.

3. Neuromodulatory Agents
   - Gabapentin or pregabalin: No studies yet exist in the veterinary literature, but several systematic reviews in humans support the use of gabapentin for cancer related pain.
   - Tricyclic antidepressants: Such as amitriptyline
   - Tramadol: See Table 3
   - Amantadine: Although not used for human cancer pain, its NMDA receptor antagonist activity may make it worthy of consideration.

   - Acetaminophen: May be used for breakthrough pain in dogs but cannot be used in cats; a literature search for toxicity in dogs revealed no special predisposition to adverse effects or toxicity. It remains a first-line therapy for acute and chronic pain in elderly humans.

   - IV CRI of ketamine, lidocaine, opioids, or combination: Can be used for a 24- to 48-hour pain holiday, and to reduce central sensitization; this approach has been anecdotally used for severe neuropathic pain states in humans but has not yet been investigated in canine and feline OSA-related pain.

4. Bisphosphonates
   These compounds may palliate OSA related pain by decreasing osteoclast activity and inhibiting calcium and phosphorus dissolution, and appear most effective when administered as part of multimodal therapy. Pamidronate is the bisphosphonate most commonly used in dogs. IV infusions are administered Q 3 to 4 weeks in patients whose owners elect to forego surgery and chemotherapy. Anecdotally, 60% of dogs respond favorably, and the dosing cycle is repeated until the drug is no longer effective for bone pain. Nephrotoxicity is a dose-limiting adverse effect.

5. Lidocaine Patch
   Anecdotal experience suggests pain relief with use of lidocaine patches applied to the skin over the site of the OSA. Patches are considered safe because they elicit very low plasma levels. However, they must be secured properly in order to prevent ingestion by the patient.

6. Energy-Based Biophysical Modalities
   These modalities (eg, therapeutic laser, shock wave therapy, electromagnetic field) are generally considered contraindicated in neoplasia due to possible adenosine triphosphate production and activation of cell division.


33. Personal communication, Louis-Philippe de Lorimier, Hôpital Vétérinaire Rive-Sud, Brossard, Québec, September 2007.


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