





CONTINUING EDUCATION

PAIN MANAGEMENT

Gabapentin and Amantadine for Chronic Pain: Is Your Dose Right?

Tamara Grubb, DVM, PhD, DACVAA

Associate Professor, Anesthesia and Analgesia

*Washington State University, College of Veterinary Medicine
Pullman, Washington*

Pain is not always a bad thing, and all pain is not the same. Acute (protective) pain differs from chronic (maladaptive) pain in terms of function and treatment. This article describes the types of pain, the reasons why chronic pain can be difficult to treat, and the use of gabapentin and amantadine for treatment of chronic pain.

ACUTE PAIN

Acute pain in response to tissue damage is often called protective pain because it causes the patient to withdraw tissue that is being damaged to protect it from further injury (e.g., a dog withdrawing a paw after it steps on something sharp) or to become less active to protect tissue that is already damaged but healing (e.g., a cat sleeping frequently after abdominal surgery). A commonly used definition of acute pain reflects its normal role in tissue protection and healing: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.”¹ Protective pain (also called adaptive or nociceptive pain) is normal and a necessary adaptation for survival, but even protective pain causes adverse effects, and pain that exceeds the level needed for protection

should be treated. Untreated or undertreated pain can cause myriad adverse effects, including but not limited to insomnia, anorexia, immunosuppression, cachexia, delayed wound healing, increased pain sensation, hypertension, and behavior changes that can lead to changes in the human–animal bond.² Hence, we administer analgesic drugs to patients with acute pain, not to eliminate the protective portion but to control the pain beyond that needed for protection (i.e., the pain that negatively affects normal physiologic processes and healing). This latter type of pain decreases quality of life without providing any adaptive protective mechanisms and is thus called maladaptive pain. It serves no protective purpose but can cause the pain-mediated adverse effects previously mentioned.

CHRONIC PAIN

Chronic pain falls largely into the maladaptive pain category. This pain is often not protective because chronic pain is generally not caused by conditions that require rest for tissue healing, even if an acute injury that might have healed actually started the pain process. A common definition of chronic pain reflects

SENIOR PATIENTS DEALING WITH CHRONIC PAIN

The most common cause of chronic maladaptive pain is osteoarthritis, or degenerative joint disease.

its lack of a role in tissue protection and healing: “pain that has persisted beyond the normal tissue healing time ... pain without apparent biological value.”¹ As with acute pain, chronic pain can cause the pain-mediated adverse effects previously mentioned and thus requires analgesic treatment.

Components of Chronic Pain

The most common cause of chronic maladaptive pain in mammals is osteoarthritis, or degenerative joint disease, and the second most common cause is cancer. The overall sensation of pain from any cause is multifactorial, and pain from either osteoarthritis or cancer generally has both inflammatory (which can be protective if not excessive) and neuropathic (which is always maladaptive) components.³

Inflammatory Pain

Inflammatory pain is a very common component of most pain syndromes, making the inclusion of anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or piperazines [grapiprant]) an integral component of chronic pain therapy for all patients, unless use of these drugs is contraindicated (e.g., gastrointestinal ulceration, renal dysfunction, or hepatic dysfunction). However, anti-inflammatory drugs alone may not completely alleviate pain that is moderate to severe and/or longstanding. It isn't that anti-inflammatories don't work; rather, it is that they can't control pain from other sources, like neuropathic pain. For adequate control of moderate to severe chronic pain, multimodal analgesia (i.e., use of more than 1 mode of treatment) is almost always necessary.

Neuropathic Pain

Neuropathic pain is commonly defined as “pain caused by a disease or lesion which leads to damage or dysfunction of the somatosensory (pain) system.”⁴ Neuropathic pain is maladaptive and can be fairly intense; pain impulses are often described by people as “lightning bolts” or “stabbing pain.” Components of neuropathic pain include peripheral sensitization (increased pain stimuli from peripheral tissues) and central sensitization (increased activity of the pain pathway at the dorsal horn neurons of the spinal cord, often referred to as windup). Neuropathic pain also often includes ectopic firing of nociceptors, which normally do not fire unless stimulated, and down-regulation of opioid receptors, making

drugs in this class largely ineffective for treating this pain syndrome. Pain is naturally controlled to some extent by the descending inhibitory limb of the pain pathway; however, this limb is often dysfunctional in patients with neuropathic pain.

These pathologies in the pain pathway can lead to abnormal pain sensations such as hyperalgesia (exaggerated pain sensation from a mildly painful stimulus) and allodynia (pain sensation from a nonpainful stimulus). Examples of neuropathic pain commonly encountered in veterinary medicine include nerve entrapment, nerve damage after surgery or trauma, amputations, tumors associated with or impinging on nerves, lumbosacral disc disease/ degeneration, discospondylitis, feline lower urinary tract disease, chronic changes associated with osteoarthritis (degenerative joint disease) (**FIGURE 1**), and many others.^{3,5,6} It is intuitive that neurologic injury or damage can lead to neuropathic pain but

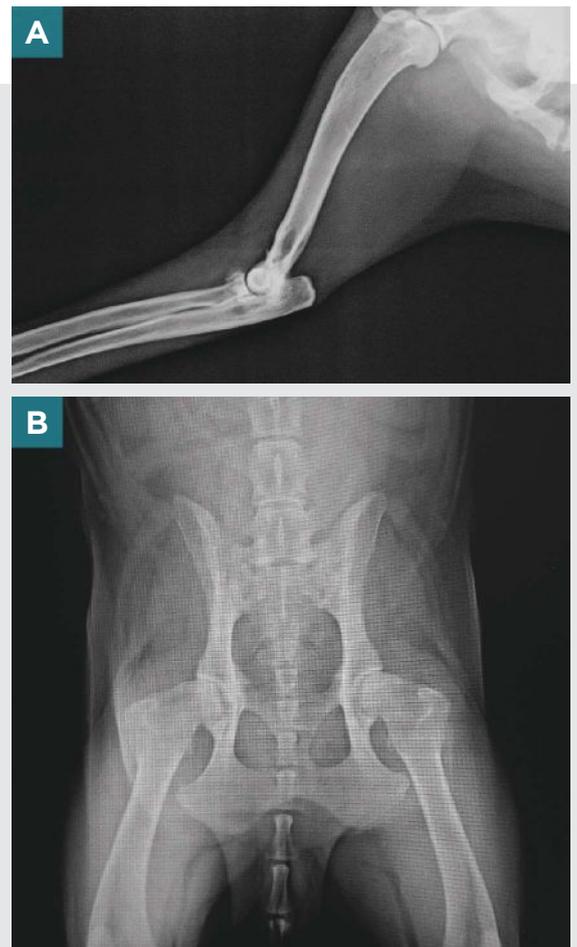


FIGURE 1. Degenerative joint disease in the cubital joint of a cat (**A**) and the coxofemoral joints of a dog (**B**).

perhaps not as clear how diseases like osteoarthritis can lead to neuropathic pain; this lack of clarity has contributed to the undertreatment of this condition. Although osteoarthritis and other chronic pain conditions may not involve direct nerve damage, chronic pain (especially if untreated or undertreated) can lead to pain pathway changes that are inherent to neuropathic pain, including ectopic activity in afferent nerves, peripheral sensitization, central sensitization, impaired inhibitory modulation, and pathologic activation of cells that are normally not active in the pain process.⁶ Adding to the potential for undertreatment of chronic pain is the fact that these changes make chronic pain difficult to treat. The pain often no longer results from the inciting cause but rather results from these changes in the pain pathway.³

Treatment of Chronic Pain

Unfortunately, the changes that lead to chronic pain are neither predictable nor consistent, making pain a truly individual sensation that often requires individual therapy. However, we have a variety of drugs that may effectively treat chronic pain in general and some that treat neuropathic pain in particular.^{3,5,6,7} This article focuses on 2 attainable and affordable options, gabapentin and amantadine, which are not only fairly specific for neuropathic pain, but are also nonopioid drugs. The opioid shortage has not threatened the supply of these drugs and diversion for human abuse is probably nonexistent. Neither drug is controlled by the Drug Enforcement Administration (DEA).

Gabapentin and amantadine each has a greater potential than tramadol for effectively treating chronic pain because of their mechanisms of action. Tramadol, a class IV DEA-controlled drug, is commonly used in veterinary medicine yet is unlikely to be effective when used alone for treatment of either acute or chronic pain; it was recently shown to be ineffective for treatment of osteoarthritis pain in dogs.⁸ This finding is not surprising because the opioid effects of tramadol in dogs are minimal.⁹ However, tramadol may provide some mild analgesia that would be useful in a multimodal protocol because of tramadol's role as a serotonin and norepinephrine reuptake inhibitor, which may provide analgesia through modulation of the descending inhibitory limb of the pain pathway. Tramadol effectively treats osteoarthritis pain in cats,¹⁰ but those who have tried administering this drug to cats know that it can be difficult because its taste seems to be especially noxious to cats.

GABAPENTIN

What Is Gabapentin?

Gabapentin is a drug in the anticonvulsant class that is approved by the Food and Drug Administration (FDA) for treatment of seizures and certain neuropathic pain conditions in humans. It is commonly used off-label to treat seizures (not described in this article) and neuropathic pain in animals. The drug is structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which explains its name but not its mechanism of action. Although not completely defined, the primary mechanism of action is presynaptic inhibition of calcium channels (specifically the alpha-2-delta-1 subunit) and subsequent calcium influx, which leads to decreased release of excitatory neurotransmitters (**FIGURE 2**). This is the mechanism for both seizure control and pain relief.

Why Use Gabapentin?

Gabapentin is useful because chronic pain commonly has a neuropathic component that

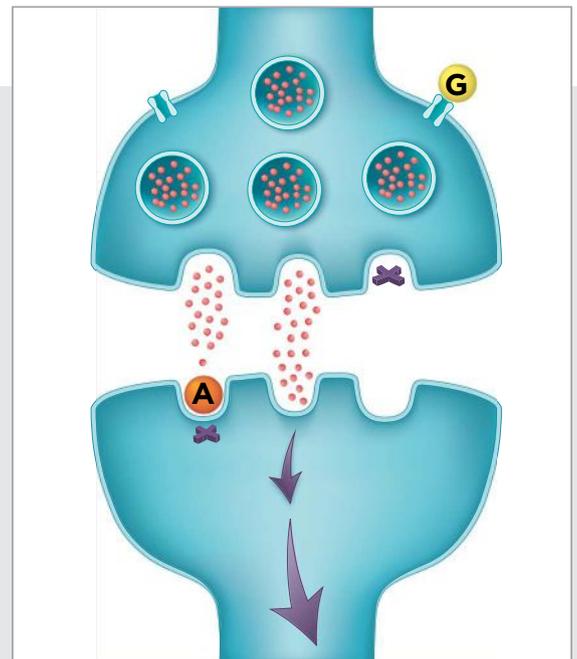


FIGURE 2. Sites of action of gabapentin and amantadine at the neuronal synaptic cleft. During depolarization, calcium enters the presynaptic membrane to cause the release of excitatory transmitters. Gabapentin (G) blocks the influx of calcium; thus, no neurotransmitters are released. Amantadine (A) antagonizes the N-methyl-D-aspartate (NMDA) receptor on the postsynaptic side of the cleft, thereby blocking transmission of pain signals from those receptors. Both of these actions decrease the number of pain impulses that are transmitted from the spinal cord to the brain.



is not controlled by anti-inflammatory drugs, opioids, or other drugs/drug classes.

Which Patients Should Receive Gabapentin?

Gabapentin should be administered to patients with a known neuropathic lesion (e.g., extruded disc, nerve injury), suspected neuropathic lesion (e.g., painful back, neck), or chronic pain that is not controlled by anti-inflammatory drugs or for which these drugs are contraindicated.

What Is the Dosage for Gabapentin?

Gabapentin is often overlooked because it has a reputation for a prolonged onset of action and/or ineffectiveness. Both of these characteristics can be true, but both may also result from inadequate dosing or dosing regimens, and it is my experience that inadequate dosing is very common. Most of us learned to prescribe gabapentin at 5 mg/kg PO q12h; however, although this regimen may be effective for some patients, neither the dose nor administration frequency is adequate for many patients. Dose and administration frequency can vary among individuals, meaning that we may have to work a little bit to find each patient's optimal dose (**BOX 1**). But finding the optimal dose is not all that hard to do; we just need to understand the pharmacokinetics of the drug—and enlist the pet client's help.

Why is the dose so variable? To answer that, let's first look at data from human medicine, for which the pharmacokinetics are better defined. After oral administration, gabapentin is absorbed from the gastrointestinal tract via an L-amino acid transport system, which is saturable, meaning that as the dose of gabapentin increases, the serum concentration does not increase linearly. In humans, as the dose increases from 900 to 3600 mg/day, the bioavailability of gabapentin drops from 60% to 33%.¹¹ We know that this same pharmacokinetic phenomenon also occurs in dogs,¹² and we presume that it occurs in cats, although this phenomenon has yet to be studied in cats. What we do know about cats is that the bioavailability of gabapentin is highly variable, at least in nonfasted cats.¹³ This finding means that dosages that provide serum concentrations of gabapentin adequate for analgesia may be higher and more variable among patients than we once thought. The dose range has long been reported as 3 to 20 mg/kg, but use of doses

Working with the client, choose a reasonable endpoint for determining effective pain relief (e.g., taking longer walks, climbing stairs) and discuss the signs of sedation.

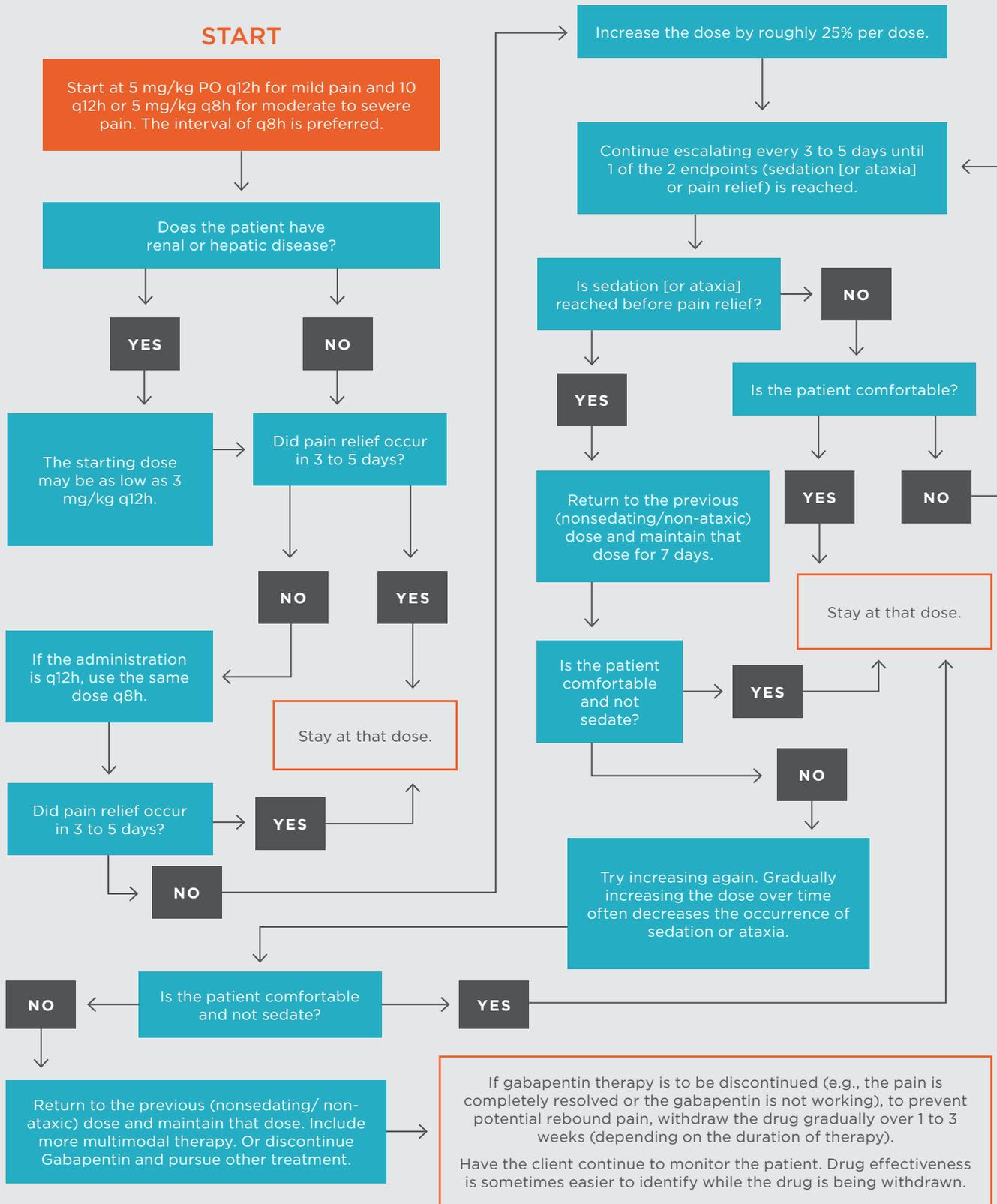
as high as 50 mg/kg has been anecdotally reported. Although your initial dose may not be 50 mg/kg, you may eventually reach that dose as you challenge the effective dose for any individual patient.

In addition to escalating doses, more frequent administration may be necessary. The pharmacokinetics for dogs¹² and cats¹³ indicate that gabapentin administration every 6 to 8 hours, rather than every 12 hours as commonly used, may be needed to provide serum concentrations of gabapentin that are adequate for analgesia. Thus, for each patient, both the dose and the administration frequency may need to be explored, for which we need to engage the client/caregiver. Mild sedation, which can be easily recognized by clients, can be used to guide the need for dosage changes. Working with the client, choose a reasonable endpoint for determining effective pain relief (e.g., taking longer walks, climbing stairs) and discuss the signs of sedation. Then choose a starting dose and, by placing frequent phone calls to the client to check on progress, guide the client on titrating the dose of gabapentin until either endpoint—sedation or decreased pain—is reached. Clients should also be advised that ataxia might occur at higher dosages, especially in large breed dogs and/or dogs with decreased muscle mass. If ataxia occurs, the same guidelines as described for the occurrence of sedation (e.g., decreasing the dose) should be followed.

What Efficacy Data Are Available for Gabapentin?

No controlled research studies on the use of gabapentin for the treatment of chronic pain in dogs and cats have been performed. Unfortunately, lack of research is a common problem for most methods of chronic pain treatment in veterinary medicine. Several case reports note analgesia when gabapentin was used for treatment of chronic pain.^{14,15} And in a clinical study

BOX 1 Recommended Gabapentin Treatment Guidelines





on postoperative pain in dogs undergoing mastectomy, although pain scores did not differ, dogs receiving NSAIDs plus gabapentin required fewer opioid rescue doses than dogs receiving NSAIDs alone; thus, the gabapentin did seem to have an effect.¹⁶ When looking at chronic conditions, among dogs with Chiari-like malformation and syringomyelia, pain scores did not differ among those receiving gabapentin and those receiving topiramate (an anticonvulsant and treatment for migraines in humans), but quality of life scores were better for the dogs receiving gabapentin.¹⁷ However, dogs receiving gabapentin immediately after surgery for herniated disc extrusion, which would be a mix of chronic pain from the disc and acute pain from the surgery, demonstrated no significant pain relief with gabapentin compared with placebo.¹⁸ The fact that the results between these studies are mixed is probably explained by 2 factors: 1) chronic pain has many facets, and pain from sources other than neuropathic were probably present; and 2) doses of gabapentin were low (5 to 10 mg/kg q12h) and perhaps ineffective, which actually makes the fact that any improvement was seen quite encouraging. More appropriate dosing, as defined by patient-specific dose and administration-interval adjustments, could potentially provide analgesia.

In a thermal research model, gabapentin seems to provide minimal benefit for control of acute pain caused by heat.¹⁹ However, because acute pain is not often neuropathic pain, the lack of evidence does not mean that gabapentin is not effective. Even in chronic pain studies, results for gabapentin may be mixed in terms of provision of analgesia because chronic pain is complicated and no one drug will work for all types of chronic pain in all patients. However, gabapentin is a common addition to analgesic protocols and, based on its mechanism of action, effectiveness can be anticipated if the dose and diagnosis (that the source of pain is actually neuropathic pain) are correct.

What Are the Adverse Effects of Gabapentin?

The primary side effect (not necessarily an adverse effect!) of gabapentin therapy in dogs and cats is sedation. This side effect is generally dose-related and usually alleviated by decreasing the dose. If sedation occurs and the dose is reduced, sedation can often be avoided if the dose is slowly titrated back up to its original high/therapeutic level over several weeks. Sedation is more common in patients receiving other sedating drugs (e.g., tramadol). Dose-dependent ataxia

and weakness can occur, especially in older patients with decreased muscle strength. In rats and humans, gabapentin is primarily cleared by the kidneys; in dogs, it is also metabolized by the liver.²⁰ In cats, the route of clearance is unknown but is presumed to be primarily renal. Thus, gabapentin may undergo more rapid accumulation, and thus more rapid onset of adverse effects, in cats and dogs with renal disease and dogs with hepatic disease. For these patients, a lower starting dose and slower dose escalation is recommended.

How Is Gabapentin Supplied and What Does It Cost?

Gabapentin is available as a generic drug in tablets and capsule of various strengths. It is also available as a liquid, but some liquid formulations contain a low concentration of xylitol. The liquid can be compounded without xylitol. Gabapentin is not a DEA-controlled drug and is not expensive.

Are There Any Other Drugs in This Class (Anticonvulsants) That Are Used for Pain Relief?

Pregabalin is FDA-approved for the treatment of numerous neuropathic pain syndromes in humans. Dosing at 1 to 2 mg/kg PO q12h is supported by pharmacokinetic studies in dogs²¹ and cats.²² Pregabalin is DEA class V and fairly expensive.

NOTE: Gabapentin is also commonly used for behavior modification, especially in cats, before stressful events such as trips to a veterinary clinic.²³ The dosage for this indication is 50 to 150 mg/cat PO at least 2 hours before the scheduled stressor will occur. In very anxious or fractious cats, the same dose is often administered the night before the stressor will occur.

AMANTADINE

What Is Amantadine?

Amantadine is a very interesting drug with multiple uses stemming from varied mechanisms of action. Amantadine is FDA-approved for the treatment of influenza virus A infection and Parkinson's disease in humans. The mechanisms of action by which amantadine treats those 2 conditions differ, and the mechanism by which it contributes to analgesia differs yet again. In its role in pain management, amantadine antagonizes N-methyl-D-aspartate (NMDA) receptors

in the central nervous system (**FIGURE 2**), a mechanism akin to that of ketamine, which reverses or prevents central sensitization. A key component of central sensitization is the opening of NMDA receptors with subsequent transmission of excitatory electrical signals.

Why Use Amantadine?

Amantadine plays a role in pain control because central sensitization, often called central plasticity,³ can be a stand-alone component of moderate to severe and/or undertreated pain and is a major component in the development of neuropathic pain.

Your first choice for known nerve damage should be gabapentin, and your first choice for pain that is suddenly worse than expected with no signs of worsening disease should be amantadine.

Which Patients Should Receive Amantadine?

Amantadine should be considered as part of the initial multimodal therapy for any patient that has moderate to severe chronic pain and as an add-on drug for patients that have worsening chronic pain despite presumably adequate pain control and no worsening of the inciting disease.

What Is the Dosage for Amantadine?

Because amantadine's contribution to pain relief is not really analgesia (it is technically called antihyperalgesia), the drug must be used as part of a multimodal protocol with true analgesic drugs like NSAIDs, opioids, and gabapentin. The dosage for dogs and cats is 3 to 5 mg/kg PO q24h to q12h, with q12h preferred. Data from recent pharmacokinetic studies indicate that twice daily dosing is probably more effective than the traditional once daily dosing in dogs²⁴ and cats.²⁵ To

decrease the central sensitization component of chronic pain, treatment duration probably needs to be long; thus, the current minimum duration recommended is 21 days.²⁶ Longer durations may be necessary, and many patients may need amantadine for life.

What Efficacy Data Are Available for Amantadine?

Less information is available about the use of amantadine than use of gabapentin for the treatment of chronic pain in veterinary patients, but 1 controlled research study of dogs with chronic refractory hindlimb osteoarthritis has been reported.²⁶ In that study, dogs receiving NSAIDs plus amantadine (3 to 5 mg/kg PO q24h for 21 days) were more active and scored lower on a lameness scale than dogs receiving NSAIDs alone. Researchers of a study of heat-induced pain in cats receiving oxymorphone concluded that "amantadine might decrease the antinociceptive (analgesic) dose of oxymorphone in some but not all cats."²⁷ These results are not surprising because the mechanism of action of amantadine is more likely to be effective in animals with central sensitization, which was not caused in this research model. As stated in the discussion of gabapentin, there is a scarcity of studies on treating chronic pain with any drug or modality in veterinary patients.

What Are the Adverse Effects of Amantadine?

No adverse effects or drug interactions in dogs or cats receiving amantadine have been reported.⁷

How Is Amantadine Supplied and What Does It Cost?

Amantadine is moderately expensive. Amantadine is supplied as tablets and capsules of various strengths and can be compounded as a liquid without xylitol.

Are There Any Other Drugs in This Class (NMDA-Receptor Antagonists) That Are Used for Pain Relief?

Ketamine, which is used as an infusion to provide analgesia, is used for acute pain relief, and reports from human medicine show that it can be used to treat some forms of chronic pain.²⁸ Methadone, a potent opioid, also has some NMDA-receptor antagonistic effects. Other oral drugs in this class

include memantine, dextromethorphan, and a few others,²⁹ none of which have been studied for relief of neuropathic pain in veterinary patients.

CONCLUSION

Although research evidence is currently lacking, the scientific mechanisms of gabapentin and amantadine support their use as part of analgesic protocols for chronic pain relief in dogs and cats. Each can effectively treat chronic pain when the dose, administration frequency, and duration of treatment are correct. When to choose one drug over the other? That choice is somewhat personal preference but also based on disease progression. Either or both can be part of initial therapy for chronic osteoarthritis pain. I often use both (usually with no dosage adjustments) if pain is severe. Your first choice for known nerve damage should be gabapentin, and your first choice for pain that is suddenly worse than expected with no signs of worsening disease should be amantadine. But you really cannot go wrong; grab one of them—or both of them—and try! Gabapentin and amantadine are best used as part of a multimodal protocol, especially when pain is moderate to severe. **TVP**

References

- Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle: International Association for the Study of Pain Press; 1994.
- Muir WW. Pain and stress. In: Gaynor JS and Muir WW, eds. *Handbook of Veterinary Pain Management*. 3rd ed. St Louis: Mosby; 2014:42-60.
- Adrian D, Papich M, Baynes R, Murrell J, et al. Chronic maladaptive pain in cats: a review of current and future drug treatment options. *Vet J* 2017;230:52-61.
- Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. *Pain* 2011;152(10):2204-2205.
- Mathews KA. Neuropathic pain in dogs and cats: if only they could tell us if they hurt. *Vet Clin North Am Small Anim Pract* 2008;38(6):1365-1414.
- Moore SA. Managing neuropathic pain in dogs. *Front Vet Sci* 2016;3(12):1-8.
- KuKanich B. Outpatient oral analgesics in dogs and cats beyond nonsteroidal antiinflammatory drugs: an evidence-based approach. *Vet Clin North Am Small Anim Pract* 2013;43(5):1109-1125.
- Budsberg SC, Torres BT, Kleine SA, et al. Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. *JAVMA* 2018;252(4):427-432.
- KuKanich B, Papich MG. Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *Vet Pharmacol Ther* 2004;27(4):239-46.
- Monteiro BP, Klinck MP, Moreau M, et al. Analgesic efficacy of tramadol in cats with naturally occurring osteoarthritis. *PLoS One* 2017;12(4):e0175565.
- Bockbrader HN, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010;49(10):661-669.
- Kukanich B, Cohen RL. Pharmacokinetics of oral gabapentin in greyhound dogs. *Vet J* 2011;187(1):133-135.
- Siao KT, Pypendop BH, Ilkiw JE. Pharmacokinetics of gabapentin in cats. *Am J Vet Res* 2010;71(7):817-821.
- Lorenz ND, Comerford EJ, Iff I. Long-term use of gabapentin for musculoskeletal disease and trauma in three cats. *J Feline Med Surg* 2013;15:507-512.
- Vettorato E, Corletto F. Gabapentin as part of multi-modal analgesia in two cats suffering multiple injuries. *Vet Anaesth Analg* 2011;38:518-520.
- Crociolli GC, Cassu RN, Barbero RC, et al. Gabapentin as an adjuvant for postoperative pain management in dogs undergoing mastectomy. *J Vet Med Sci* 2015;77:1011-1015.
- Plessas IN, Volk HA, Rusbridge C, Vanhaesebrouck AE, Jeffery ND. Comparison of gabapentin versus topiramate on clinically affected dogs with Chiari-like malformation and syringomyelia. *Vet Rec* 2015;177:288.
- Aghighi SA, Tipold A, Piechotta M, Lewczuk P, Kastner SB. Assessment of the effects of adjunctive gabapentin on postoperative pain after intervertebral disc surgery in dogs. *Vet Anaesth Analg* 2012;39:636-646.
- Pypendop BH, Siao KT, Ilkiw JE. Thermal antinociceptive effect of orally administered gabapentin in healthy cats. *Am J Vet Res* 2010;71:1027-1032.
- Vollmer KO, von Hodenberg A, Kölle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. *Arzneimittelforschung* 1986;36(5):830-839.
- Salazar V, Dewey CW, Schwark W, Badgley BL, Glead RD, Horne W, Ludders JW. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. *Vet Anaesth Analg* 2009;36(6):574-580.
- Esteban MA, Dewey CW, Schwark WS, et al. Pharmacokinetics of single-dose oral pregabalin administration in normal cats. *Front Vet Sci* 2018;20;5:136.
- van Haften KA, Forsythe LRE, Stelow EA, Bain MJ. Effects of a single preappointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination. *JAVMA* 2017;251(10):1175-1181.
- Bleidner WE, Harmon JB, Hewes WE. Absorption, distribution and excretion of amantadine hydrochloride. *J Pharmacol Exp Ther* 1965;150:484-90.
- Siao KT, Pypendop BH, Stanley SD. Pharmacokinetics of amantadine in cats. *J Vet Pharmacol Ther* 2011;34:599-604.
- Lascelles BD, Gaynor JS, Smith ES, et al. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. *J Vet Intern Med* 2008;22(1):53-59.
- Siao KT, Pypendop BH, Escobar A, et al. Effect of amantadine on oxymorphone-induced thermal antinociception in cats. *J Vet Pharmacol Ther* 2012;35(2):169-174.
- Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol* 2014;77(2):357-367.
- Aiyer R, Mehta N, Gungor S, Gulati A. A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. *Clin J Pain* 2018;34(5):450-467.



Tamara Grubb

Dr. Grubb is a board certified veterinary anesthesiologist with a strong clinical interest and research focus in pain management. She is a certified acupuncturist and a consultant in a private small animal veterinary practice. She is also a member of the board of directors of the International Veterinary Academy of Pain Management (IVAPM). Her most notable achievement was winning the Carl J. Norden Distinguished Teaching Award, which has been awarded to her from students at two universities.

Gabapentin and Amantadine for Chronic Pain: Is Your Dose Right?

LEARNING OBJECTIVES

Readers will be able to compare protective pain and maladaptive pain, discuss the reasons that chronic pain can be difficult to treat and the need for multimodal analgesia, describe the role of gabapentin and amantadine in the treatment of chronic pain, and prepare treatment protocols.

TOPIC OVERVIEW

This article describes the complexity of chronic pain, the need for multimodal therapy, and the use gabapentin and amantadine at correct dosages and administration frequencies in treatment protocols.

The article you have read has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment when approval has been received. To receive credit, take the approved test online for free at vetfolio.com/journal-ce. Free registration on VetFolio.com is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

- 1. What is another name for acute pain in healing tissue?**
 - a. Maladaptive
 - b. Neuropathic
 - c. Protective
 - d. Osteoarthritic
- 2. Define maladaptive pain.**
 - a. Pain lasting more than 30 days
 - b. Pain without biological value (not protective)
 - c. Joint pain that develops from mild osteoarthritis
 - d. Pain that prevents further damage to injured tissue
- 3. How does chronic pain with no physical neurologic damage become neuropathic pain?**
 - a. Damage occurred at some point in the pain syndrome, which led to neuropathic pain.
 - b. Sensory pathway changes in response to chronic moderate/severe stimulus are essentially pathology of the nervous system.
 - c. Neuropathic and chronic pain are equal.
 - d. Cancer pain can become neuropathic if the tumor impinges on nerves.
- 4. Why is it important to adequately treat pain?**
 - a. Pain causes adverse effects that can negatively affect the patient's overall health.
 - b. Untreated pain can get worse as changes occur in the pain pathway.
 - c. Pain can decrease the patient's quality of life.
 - d. All of the above.
- 5. Assuming no contraindication, which one should generally be the first choice in treatment and why?**
 - a. Gabapentin; chronic pain is always neuropathic pain, even if it is only mild.
 - b. Amantadine; the NMDA receptors are always activated in chronic pain, making chronic pain very difficult to control.
 - c. Opioids; only opioids control excruciating pain.
 - d. Anti-inflammatory drugs; inflammation pain is a common source of chronic pain.
- 6. In which of these patients would you have the client increase the dose of gabapentin right now?**
 - a. Experiencing mild sedation at the current dose.
 - b. Renal disease patient still showing some signs of pain despite a dose increase in the past 24 hours.
 - c. Experiencing no sedation and still exhibiting pain despite a dose increase 3 days previously.
 - d. Exhibiting no signs of pain despite being on a low dose of gabapentin administered q12h.
- 7. What role does amantadine play in pain relief?**
 - a. Antihyperalgesia
 - b. Anti-inflammation
 - c. Calcium channel blockade
 - d. NMDA-receptor agonist
- 8. Current pharmacokinetic data for gabapentin and amantadine support a dosing interval of:**
 - a. At least q8h for gabapentin and q12h for amantadine
 - b. Q12h for gabapentin and q24h for amantadine
 - c. Q24h for gabapentin and q12h for amantadine
 - d. At least q8h for gabapentin and once every 21 days for amantadine
- 9. Amantadine and gabapentin can be administered concurrently.**
 - a. True
 - b. False
- 10. Which patient would be least likely to benefit from gabapentin or amantadine? A patient:**
 - a. With chronic untreated otitis that snaps if touched, even gently.
 - b. With worsened elbow arthritis despite no evidence of worsening.
 - c. Hit by a car and in extreme pain.
 - d. After a forelimb amputation secondary to a painful nonunion of a radius-ulna fracture.