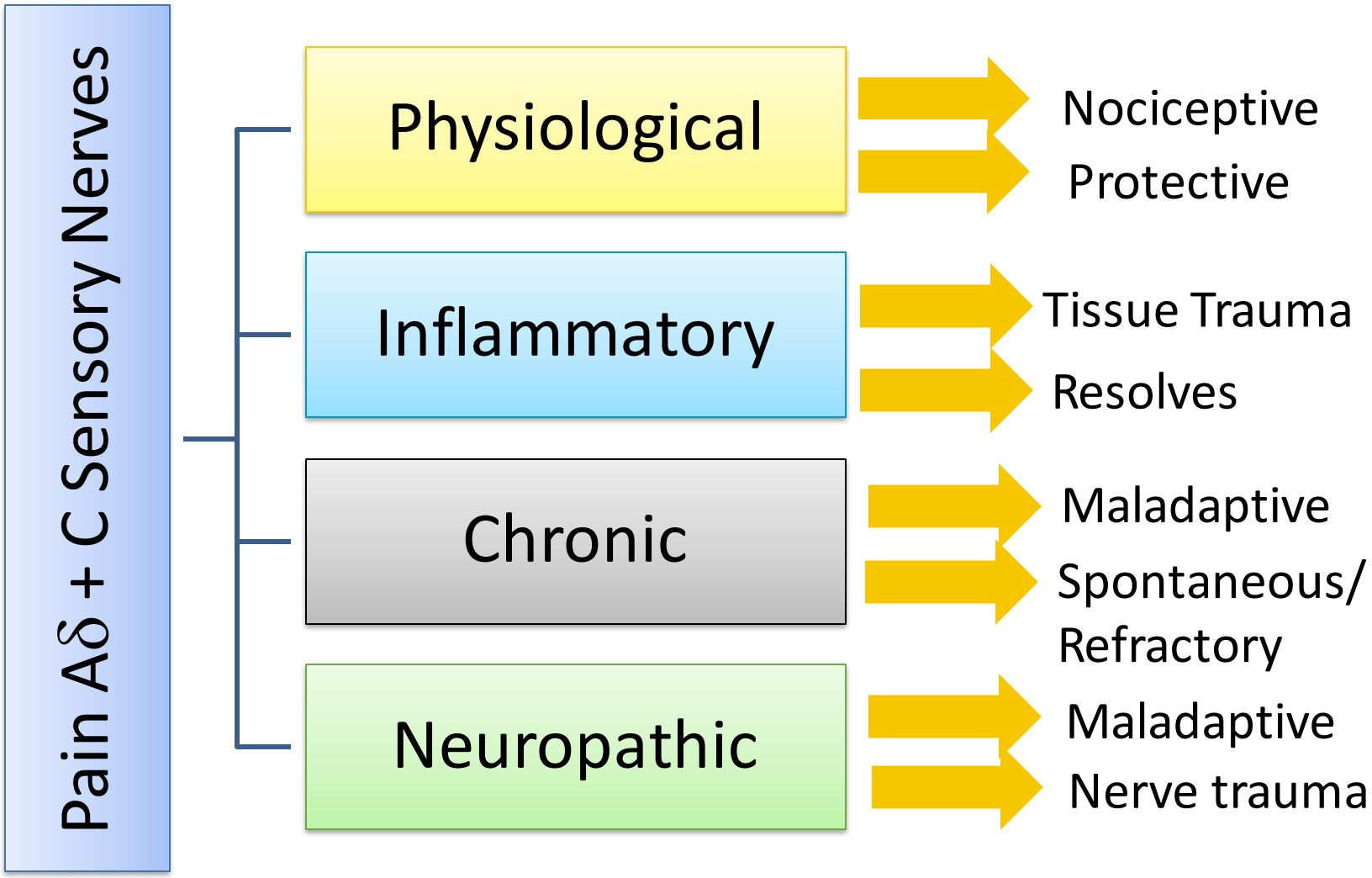
Nonsteroidal Anti-inflammatory Drugs:
A Tool for Managing Pain

April 29, 2018

Sharon L. Campbell, DVM, MS, DACVIM

Classification of Pain



1. Costigan M. *Ann Rev Neuro.* 2009.

THE CLASSICAL "PAIN PATHWAY"

1 TRANSDUCTION

- A sufficiently intense physical pain stimulus causes initiation of an action potential by either Aδ or C nociceptors.
  - A non-electrical stimulus is transduced into an electrical potential.

2 TRANSMISSION

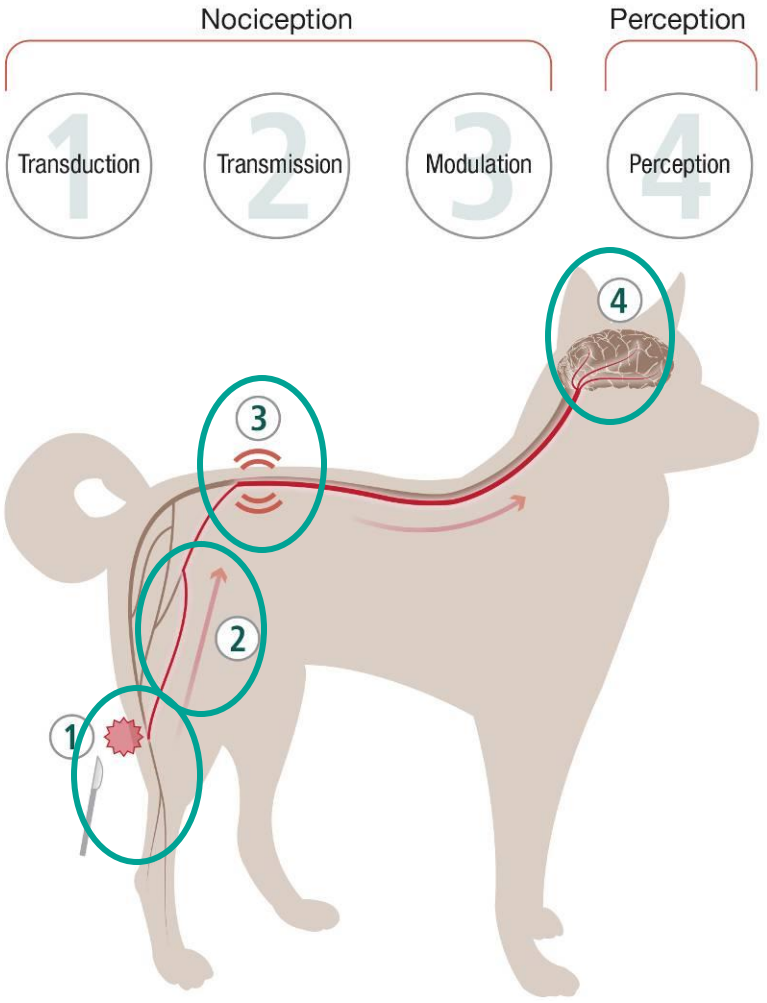
- The signal is transmitted along the peripheral sensory nerve to the dorsal horn of spinal cord.

3 MODULATION

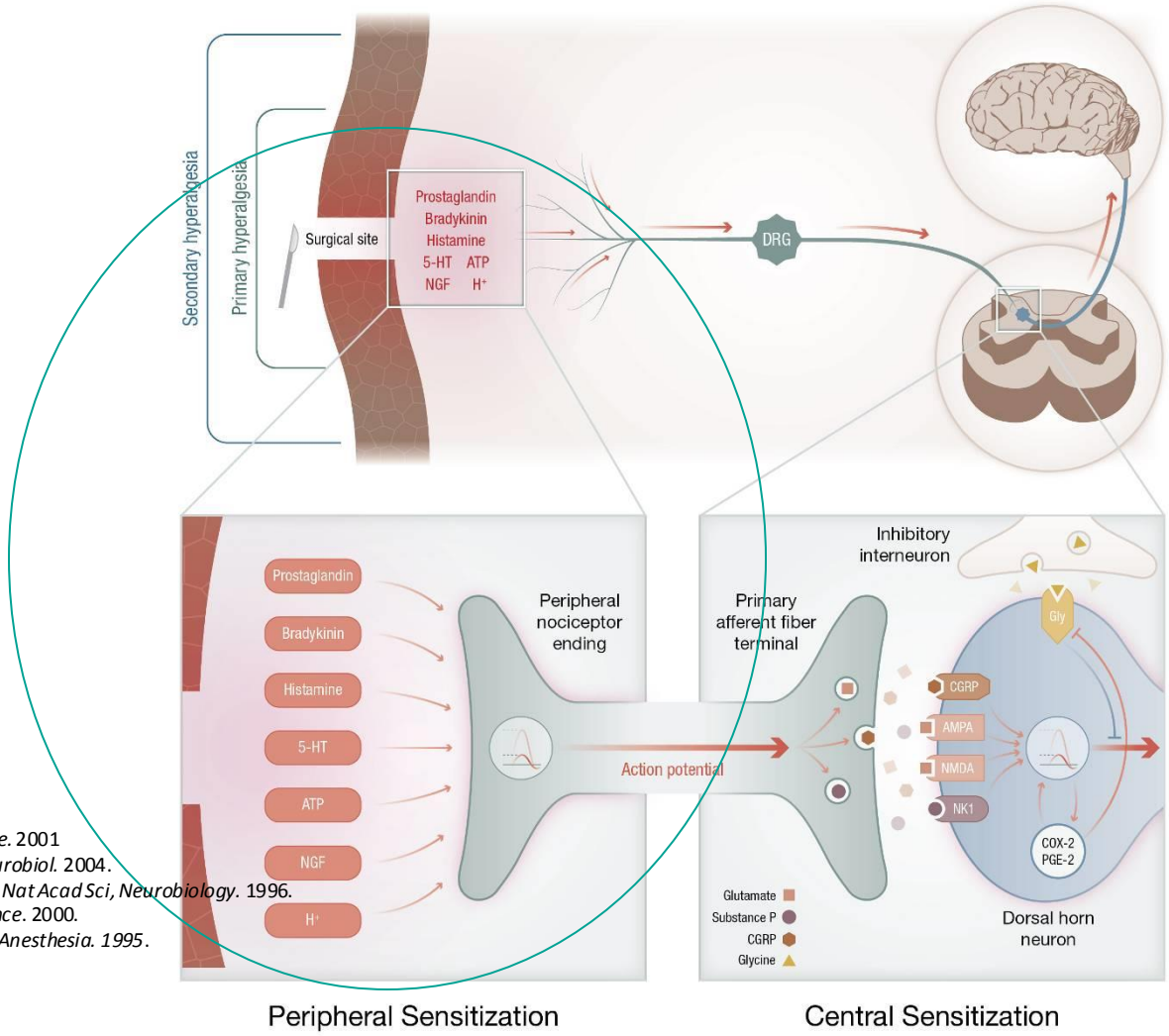
- The peripheral sensory nerve synapses with neurons in the dorsal horn.
- The pain signal is modulated by interneurons and is either enhanced or diminished.

4 PERCEPTION

- The peripheral sensory nerve synapses with second-order neurons of specific ascending spinal tracts within the dorsal horn.
- The pain signal is projected to different areas within the brain where it is perceived as pain.



Inflammatory Pain Lowers Threshold of Nociceptors: Peripheral Sensitization



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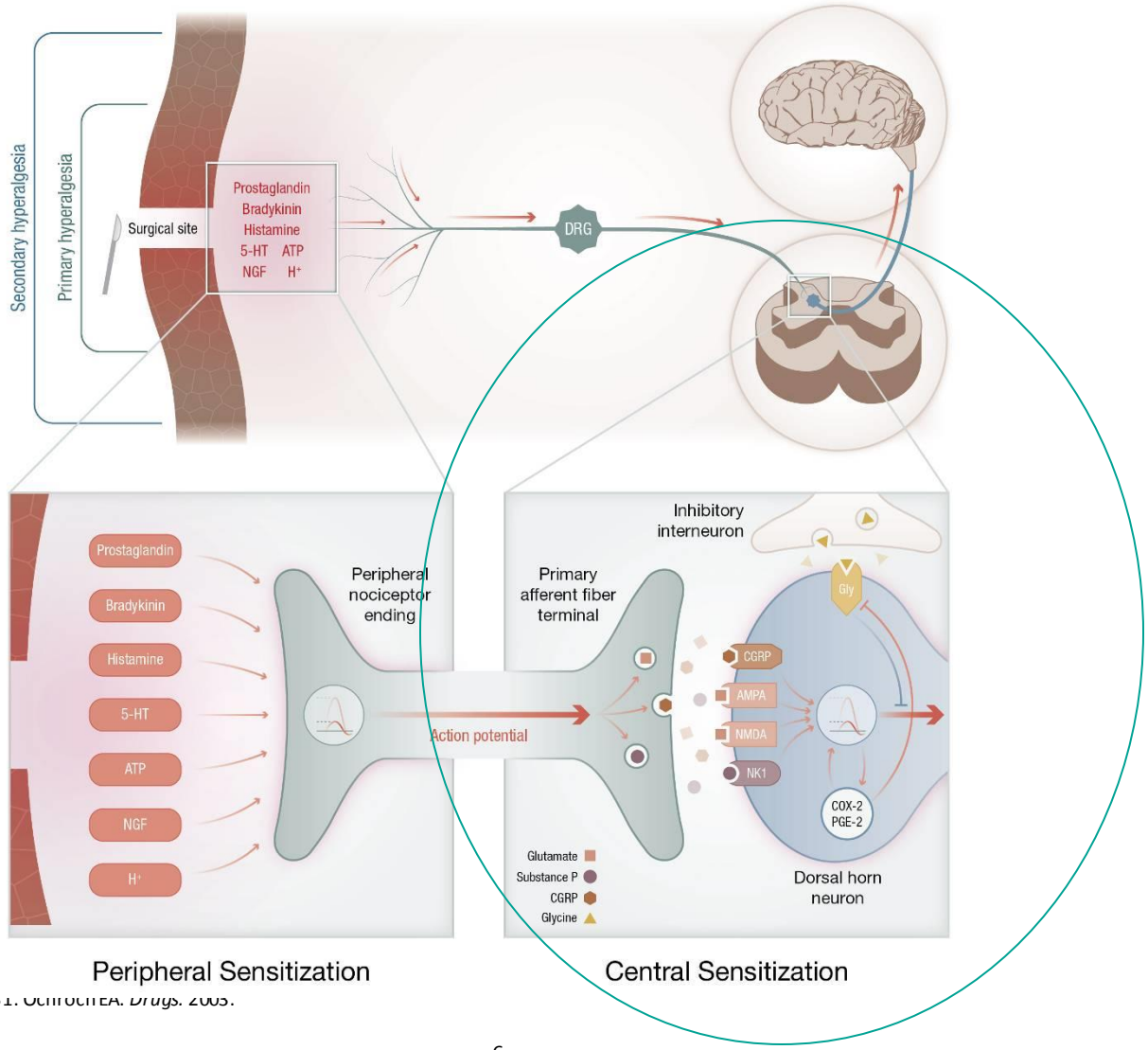
2) Bhave G. *J Neurobiol.* 2004.
3) Gold MS. *Proc Nat Acad Sci, Neurobiology.* 1996.
4) Woolf CJ. *Science.* 2000.
5) Woolf C. *Brit J Anesthesia. 1995.*

Central Sensitization: Modulation and Modification of the Dorsal Horn Neurons



27. Woolf CJ. *Science*. 2000.

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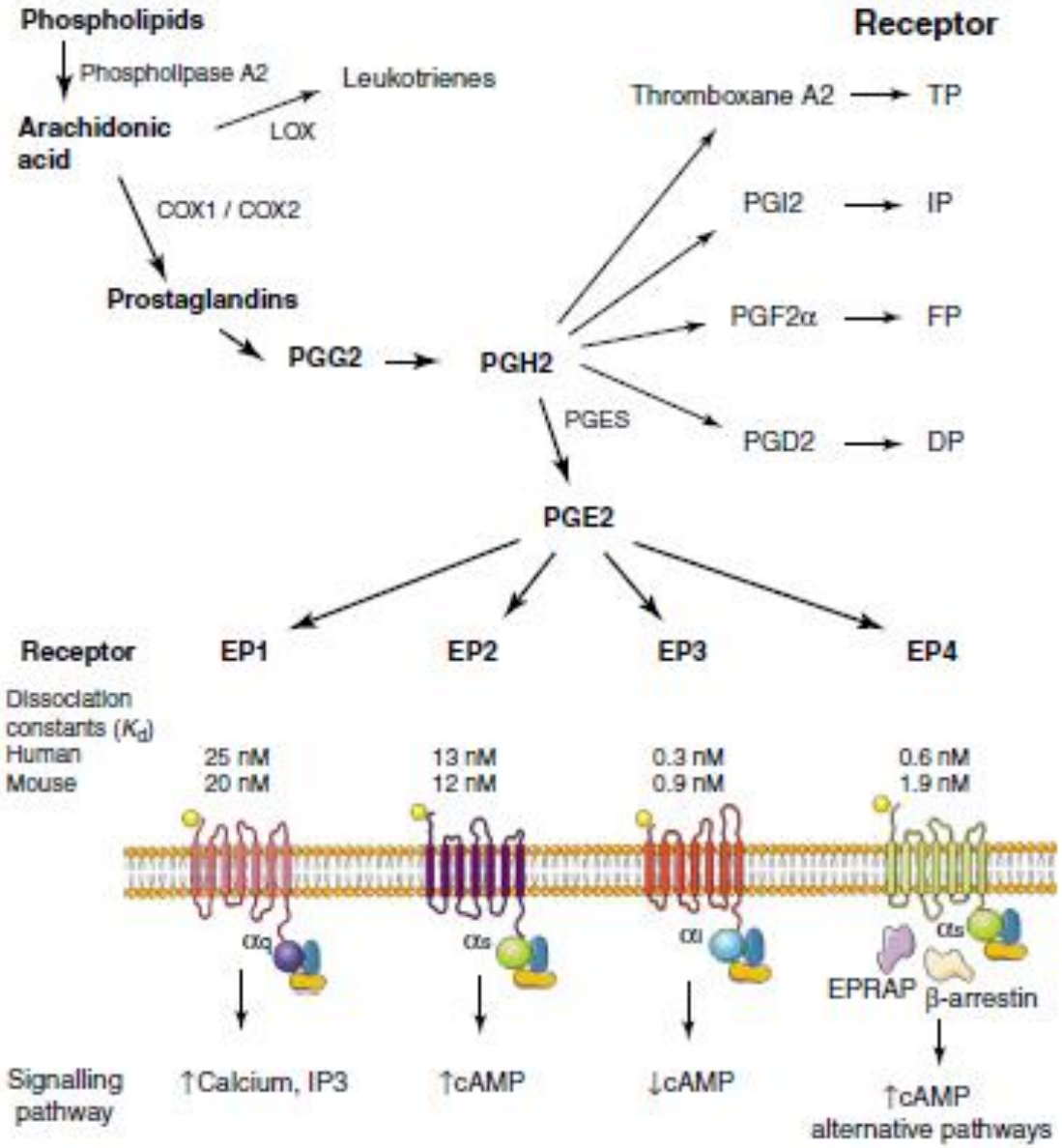
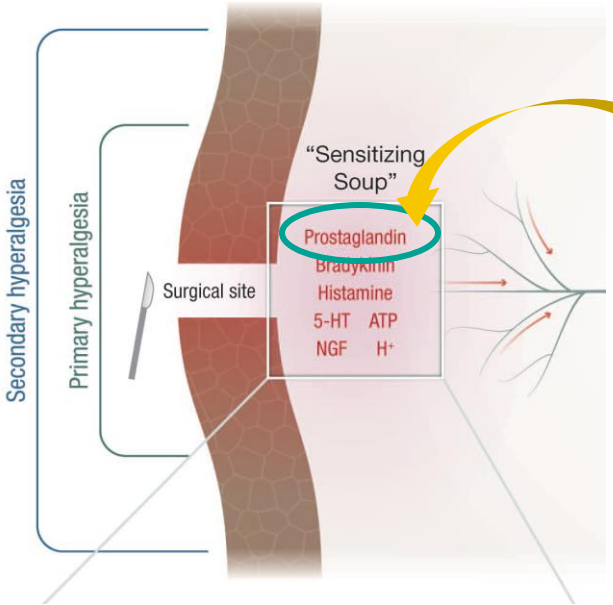
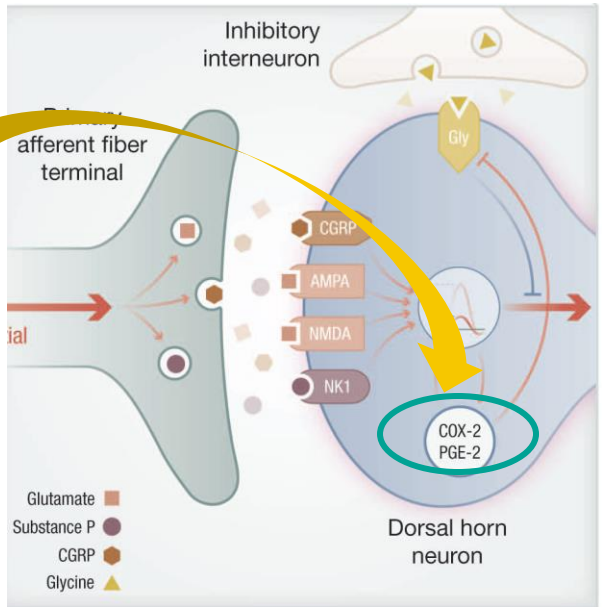


Markovic T, Jakopin Z, Dolenc ME st al. Drug Discovery Today. 22:57-71; 2017.

Surgical Site and in the Dorsal Horn



NSAIDS[1]



1) COX-2 enzymes are up-regulated at the surgical → prostaglandin (PG) synthesis
2) Increased COX-2 derived PGs correlated with increase post-op pain[2]

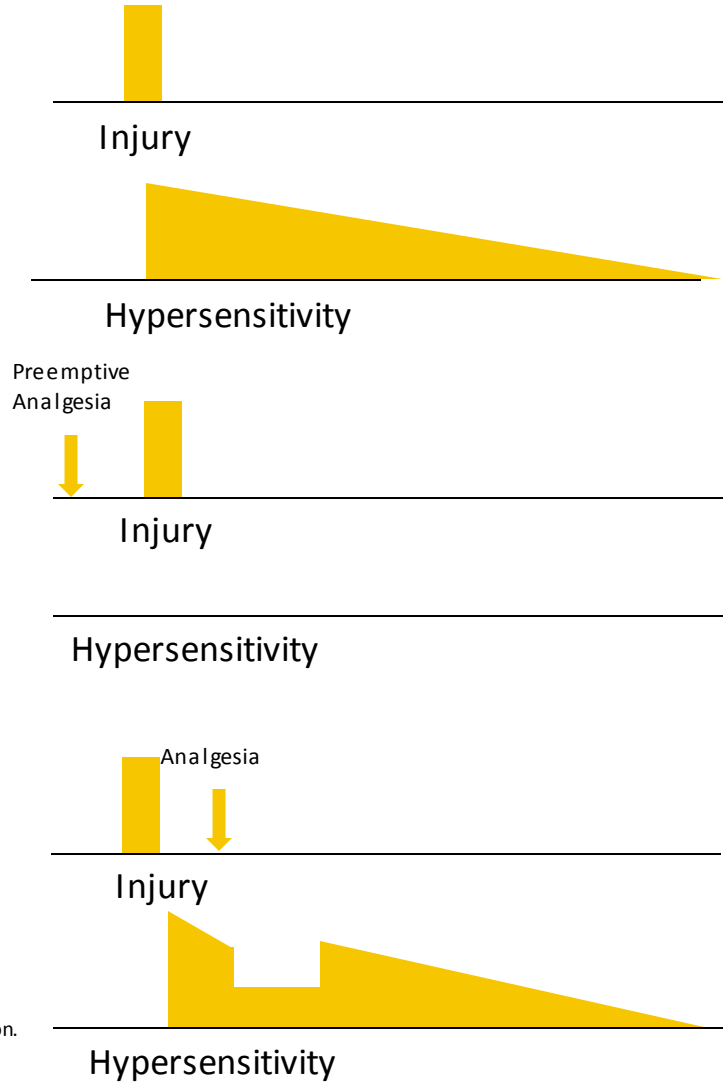
1) COX-1 and COX-2 enzymes are constitutively expressed in dorsal root ganglia and spinal cord.[3]
2) COX-2 enzymes up-regulation during pain[4-6]
3) Circulating TNF-α and IL-1β can also up-regulate COX-2 [4-6]

Rimadyl Reduces Development of Peripheral And Central Sensitization[7]
General Anesthetic Drugs Do Not

1) Malmgren AB. *Science*. 1992 2) Buvanendran A. *Anesthesiology*. 2006. 3) Svensson CI. *Ann Rev Pharmacol Toxicol*. 2002. 4) Samad TA. *Nature*. 2001
5) Beiche F. *Inflamm Res*. 1998. 6) Maihofner C. *Neuroscience*. 2000. 7) Lascelles BDX, et al. *Vet Surg* 1998.

PREEMPTIVE TO PREVENTIVE ANALGESIA

- ***Preemptive analgesia:*** pain medication administered prior to painful injury
  - Treat post-op pain by preventing establishment of central sensitization[1]
- ***Preventive analgesia:*** includes any analgesic that is administered during the entire perioperative period
  - Goal: prevent peripheral and central sensitization.
  - Include:
    - Initiating analgesia early
    - Ensuring degree of analgesia = degree of pain
    - Continuing analgesia until pain has subsided [2]
  - Research confirms preventive analgesia as the preferred approach for acute post-operative analgesia and to prevent chronic post-operative pain.[3]



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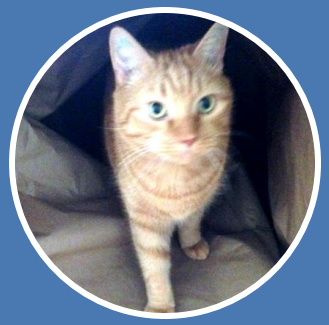
2) Pogatzki-Zahn EM, Segelcke D, Schug SA. *Postoperative Pain*. 2006.
3) Katz J. *Current Opin Anaesth*. 2002.

Current FDA approved NSAIDS For Dogs and Cats

Rimadyl®
Metacam®
Derramaxx®
Previcox®
Onsior®
Galliprant®



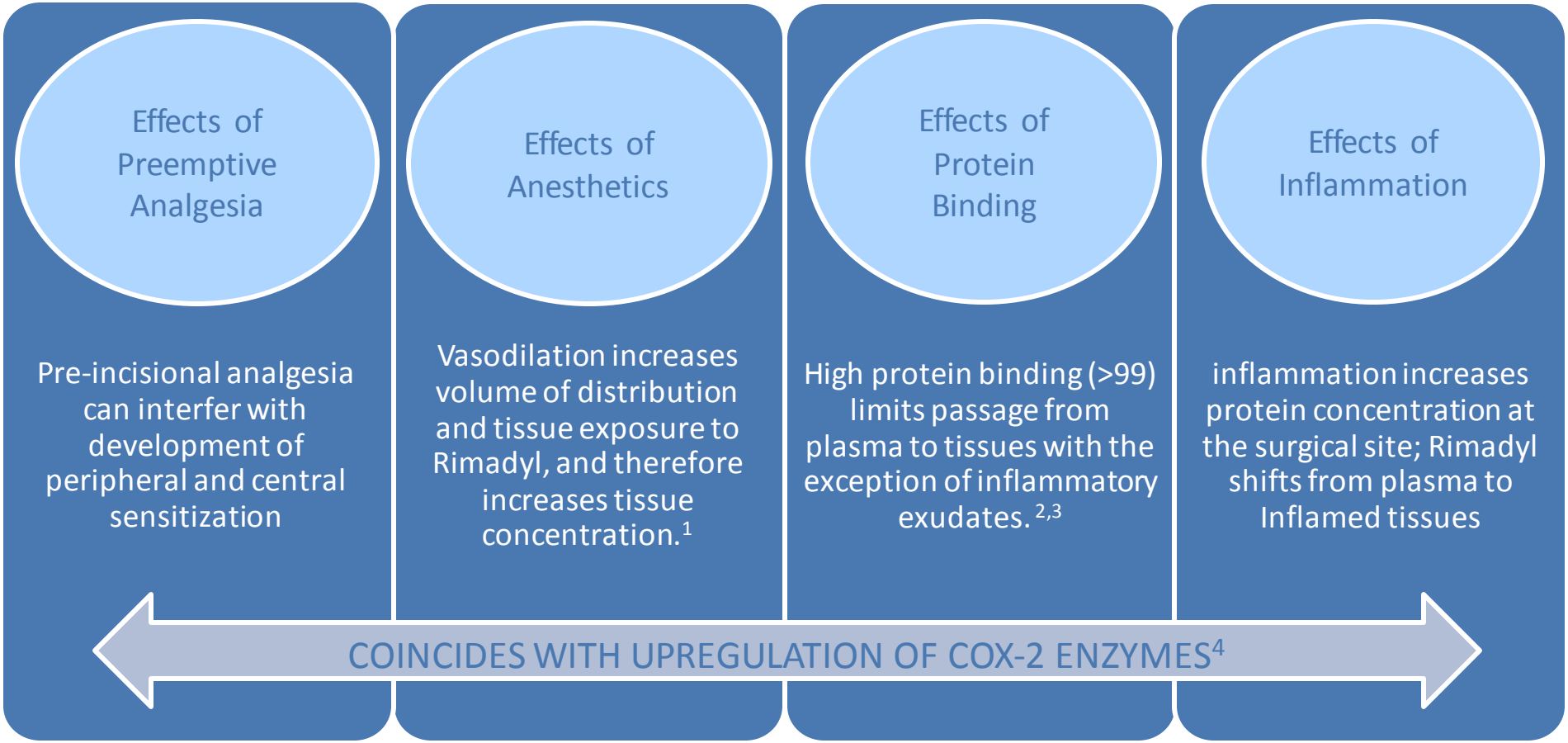
Metacam®
Onsior®

FDA Claims for Canine and Feline NSAIDs

NSAID	Postoperative Pain	Treatment of OA
Rimadyl®	✔	✔
Metacam®	✔ (cat)	✔ (dog)
Derramaxx®	✔	✔
Previcox®	✔	✔
Onsior®	✔	
Galliprant®		✔

PRE-OPERATIVE ADMINISTRATION OF NSAIDs PROVIDES BETTER IMMEDIATE POST-OP ANALGESIA

Surgical analgesia due to early Inhibition of inflammation



1) Lascelles BD. *Vet Surg.* 19931. 2) McKellar QA. *J Vet Pharm Therap*. 1994. 3) Riviere JE. *Veterinary Pharmacology and Therapeutics.* 2009.
4) Ochroch EA. *Drugs.* 2003.

Chronic verses Acute Pain Summary

Acute Pain	Chronic Pain
Peripheral & Central Hypersensitization	Peripheral & Central Hypersensitization
Modulation of Pain Pathway	Modification of Pain Pathway – Prostaglandins One of the Mediators
Changes Are Temporary, Pain Resolve When Injury/ Inflammation Resolves	Changes Are Long Lasting, Pain Does Not Resolve When Injury/Inflammation Resolves
Pain is Associated with a Defined Stimulus	Pain Can Be Spontaneous, Intermittent, Difficult to Control

Do the Benefits of Using an NSAID Outweigh the Risks?

- There are risks and benefits with all commonly prescribed veterinary drugs, including NSAIDs
- All NSAIDs approved for oral use in dogs have been determined to be safe at the approved dose for the general population of dogs
- Adverse Events (reactions) or AEs (for all drugs) are divided into two groups:
  - Inducible
  - Idiosyncratic

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The Two Types of Drug Adverse Reactions

Inducible	Idiosyncratic
Reactions are dose-related	Not dose-related
Reactions are attributable to the mechanism of action of the drug	Not attributable to the mechanism of action of the drug
Predictable	Unpredictable and rare

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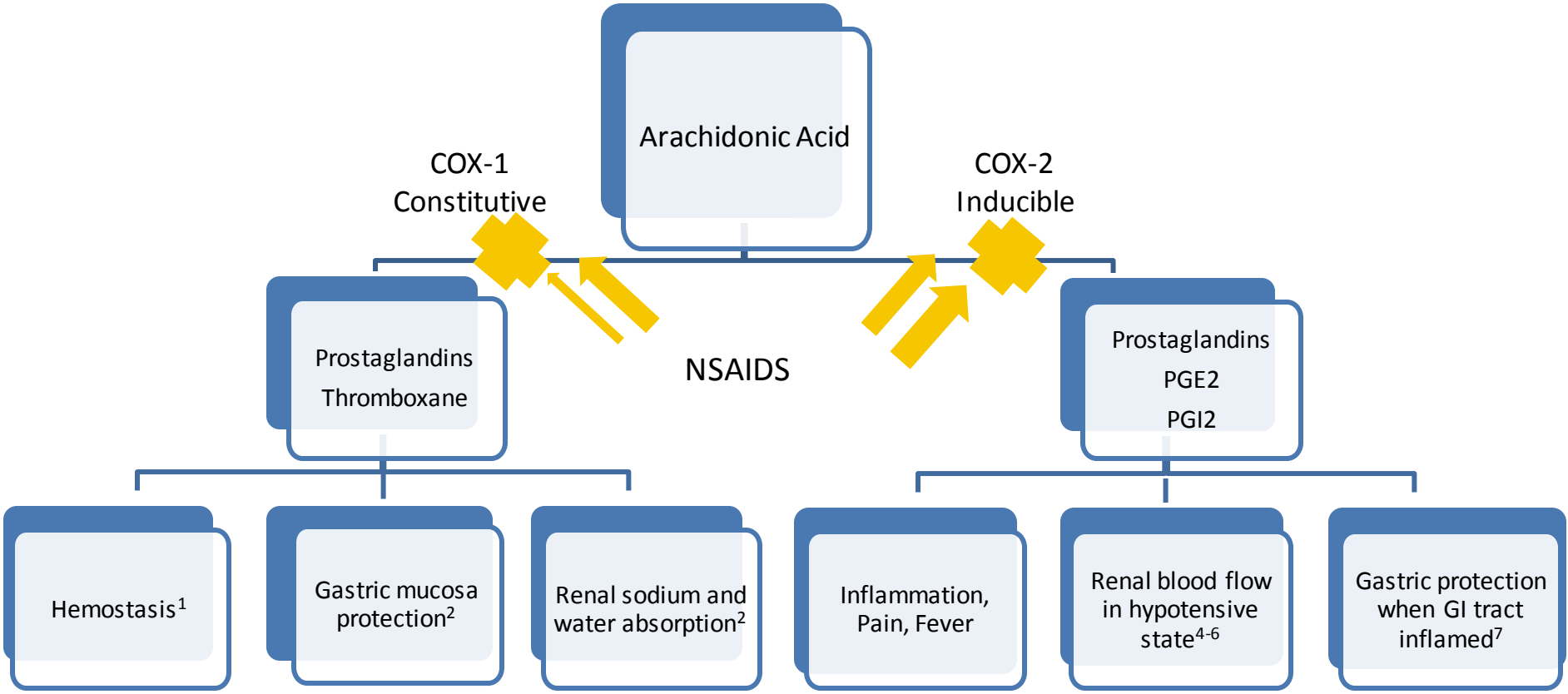
NSAID Mechanism of Action: Inhibition of Cyclooxygenase (COX) Enzymes



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5. Hartner A. *Hypertension.* 1998.
6. Miller SB. *Semin Arthritis Rheum.* 2006.
7. Brzozowski T. *Microscopy Res Tech.* 2001

The Risk of an Adverse Reaction is Greatest Early in Treatment (not with long-term use)

- The most common AEs seen with NSAIDs are inducible, and include GI irritation[19]
- Idiosyncratic reactions occur infrequently (1 in 10,000)[17,20]
- Idiosyncratic reactions are most likely to occur in the first 90 days of treatment[14,27]

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Clinical Considerations When Prescribing an NSAID

- Get a thorough history of previous medications and medical conditions
- Perform a thorough physical exam
- Screen patient for any underlying conditions
- Inform owner of potential risks and benefits
- Distribute Client Information Sheets
- Monitor and assess appropriately

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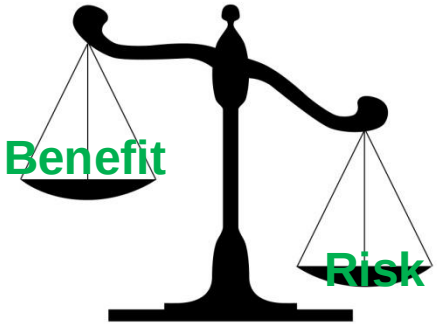
Misconceptions About NSAID Adverse Events



- Some DVMs perceive that the risks outweigh the benefits
- Many myths exist around NSAID adverse events
- By better understanding adverse events:
  - Veterinarians are able to minimize their occurrence
  - Better communicate the actual risks to pet owner

Benefits/Risk of Treating with an NSAID Should Be Evaluated on a Patient by Patient Basis

Benefits	Risks
Pain Relief	GI Signs
Relief of Inflammation	Renal Disease
Return to Function	Hepatic Disease
Re-establish Human–Animal Bond	Other Less Commonly Reported Signs

- Frequency is low for most adverse events and resolve with discontinuation and/or supportive treatment
- With appropriate patient selection and monitoring can maximize the benefits and minimize the risks

What are the Risks?

- Most common adverse reaction is GI, ranging from dyspepsia to GI perforation
- Renal Disease
- Hepatic Disease
- Other
- Frequency is low for most
- Can be minimized by appropriate patient selection and monitoring (See Risk Benefit discussion)

NSAIDs Removes Autoregulation of Blood Flow in the Kidneys

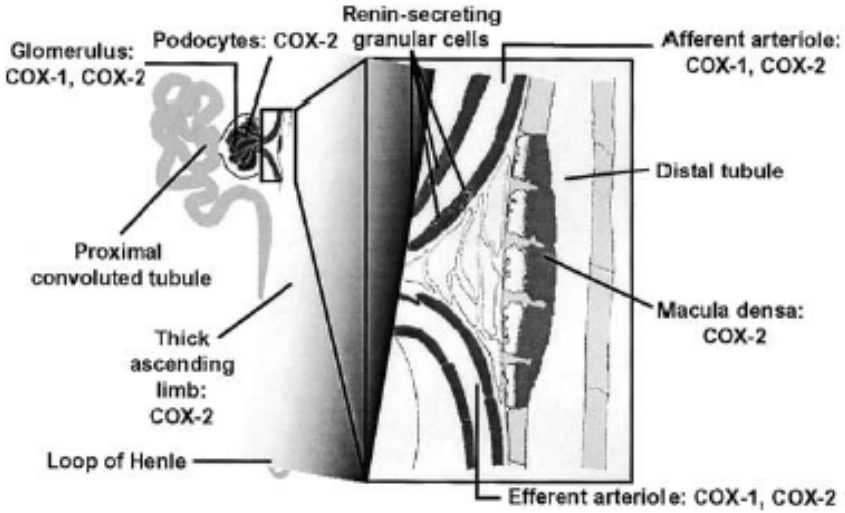


Fig. 1. Distribution of COX-1 and COX-2 in the human kidney.

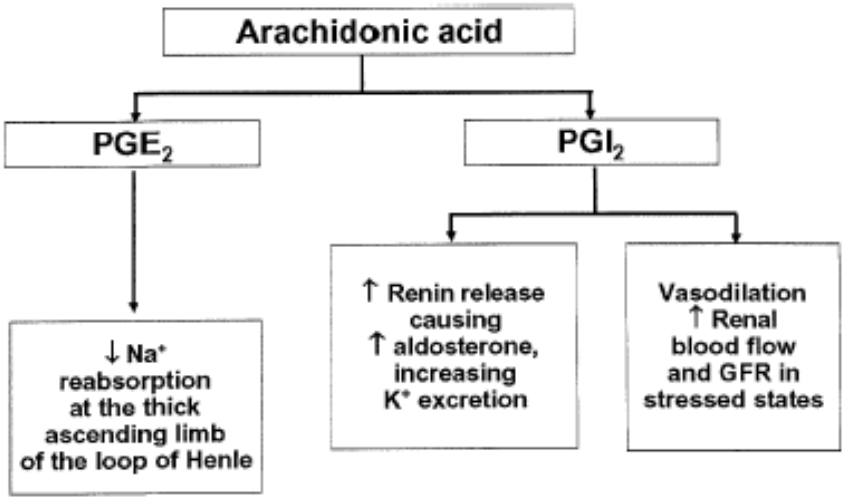
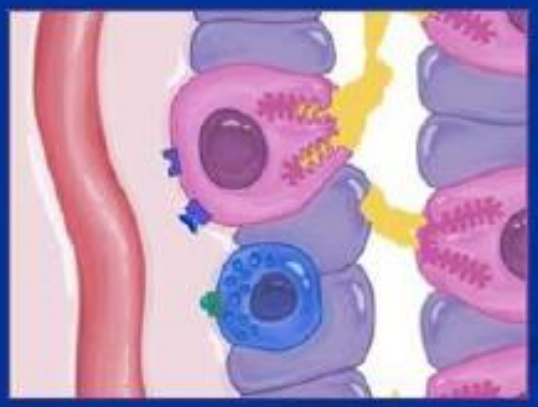


Fig. 2. Role of prostaglandins in the kidney.

NSAID Reduces the Protective Mechanisms of the Gastric Mucosa

Gastrointestinal (GI) Tract

- Upper GI complications have also occurred in pts treated with COXIBs
  - Perforation
  - Ulcers
  - Bleedings
  - PUBs



NSAIDs and Liver

- The liver is uniquely susceptible to damage by drugs
- Genetic polymorphism in hepatic enzymes involved in drug metabolism
  - Breed differences
  - Individual variation
- Idiosyncratic hepatoxicosis has been documented with the use of NSAIDs in the dog[1, 2]
  - Most occur within first 90 days
  - Most dogs recover with immediate discontinuation of the drug and appropriate support
- Educate pet owners; monitor appropriately

1. McPhail, C et al. *JAVMA* 1998. 212:189501901.
2. Webster, CRL. ACVIM Forum Proceedings. 2004: access from website 7/20/2011.

Elevated Liver Enzymes May or May Not Preclude the Use of NSAIDs

- Elevations of hepatic enzymes often reported in older dogs
- NSAIDs use in these patients depends upon cause of enzyme elevation
  - Benign conditions – Nodular hyperplasia, breed (Scottish Terrier)
  - Disease conditions – hepatic disease, endocrinopathies, drug induced (steroids, phenobarbital, etc.), pancreatitis, neoplasia, current drug therapy, infectious disease, etc.
- Certain breeds predisposed to liver disease[1]

Bedlington Terriers	**Doberman Pinchers**	**Cocker Spaniels**
Labrador Retrievers	**Dalmatians**	**West Highland White & Skye Terrier**

1. Willard M. Textbook of Veterinary Medicine., 7th edition. Ed Ettinger SJ and Feldman EC. Saunders Elsevier, St Louise Missouri; 1637-1642: 2010.

Tailor Work-up of Elevated Liver Enzymes to The Patient

Review CBC, Panel, UA

Review Medical History and Medications

Suggested Tests – Dependent Upon Signalment, History and Clinical Signs

- Hepatic Function Test
- Leptospirosis titers
- Pancreatic Lipase Immunoassay
- Abdominal Ultrasound
- Thyroid Panel
- Urine Cortisol/Creatinine
- Low Dose Dex/ ACTH Stimulation
- Liver Aspirate/Biopsy

If Only ALP is Elevated and the Dog is Asymptomatic

- Could be Benign Nodular Hyperplasia[1]
  - Is fairly common in older dogs
  - ALP can be 2.5x to >10x normal
  - Ultrasound and Bile Acids to rule out other disease
  - Additional diagnostic as needed
- Consider NSAIDs if no other underlying disease detected
- Monitor to ensure no further elevation or other abnormalities (within 10–30 days, then periodically)
  - Any further increases in hepatic enzymes warrants further evaluations[2]

1. Prause LC, Twedt DC. Kirk's Current Veterinary Therapy XIII, *Small Animal Practice*. ED Bonagura, JD. W. B. Saunders, Philadelphia, 675-676: 2000.
2. Papich MG.. *Vet Clin Am Small Anim Pract.* 38,1243-1266: 2008.

NSAIDs NOT RECOMMENDED if Patient Has:

- Pre-existing hyperbilirubinemia
- Elevated ALT, AST and GGT
  - If any of these are elevated alone on in combination, with or with our signs of hepatic disease
- Decreased albumin– Recommend workup for renal, GI or hepatic dysfunction
- Elevated ALP ***with*** clinical signs of liver or Cushing's disease

Labrador Retrievers, Liver and NSAIDs

- The Labrador Retriever Breed is overrepresented because:
  - Most popular breed

    and
  - Has a high incidence of OA
- Recently identified: Copper Associated Chronic Hepatitis(CACH) in Labrador Retrievers[1,2]
  - Dog can be asymptomatic
  - Females > males?; middle age to older dogs
  - Diagnosis: Elevation of ALT and ALP with a greater relative increase in ALT; histopathology with copper analysis
- Screening and monitoring NSAIDs use in Labs, since CACH may be asymptomatic

1. Hoffman G et al. JAVIM 2006, 20: 856-861.
2. Shih JL et al. JVIM, 2007: 21-33.

Minimizing the Risk: Patient Selection[1-6]

- All dogs should undergo a thorough history & physical examination before initiating NSAID therapy
- Appropriate hematological & serum baseline data is recommended prior to and periodically during administration
- Avoid in dogs with a history of renal disease
- NSAIDs are not recommended for dogs with bleeding disorder
- Dogs that have adverse reactions from other NSAIDs, may have adverse reactions with other NSAIDs
- Dogs at greatest risk
  - Dehydrated or on concomitant diuretic therapy
  - Dogs with renal failure, cardiovascular and or hepatic dysfunction

1. Deramaxx Package insert, NADA # 141-203, 2008 Novartis Animal Health.
2. Etodolac Package insert, NADA 141-108, 2008 Fort Dodge.
3. Metacam Package Insert, NADA 141- 213, 2010, Boehringer Ingelheim Vetmedica, Inc.
4. Prevacox package insert NADA 141-230, 2010, Merial.
5. Rimadyl Package insert, NADA 141- 111, 2007 Pfizer Animal Health,
6. http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm, FDA Website.

Minimizing the Risk: Concurrent Medications[1-6]

- Concomitant use of NSAIDs with other anti-inflammatory drugs such as corticosteroids and other NSAIDs should be avoided
  - Pet owners may not disclose that they are treating dogs with aspirin
    - 7% veterinarians recommend aspirin to treat canine osteoarthritis[7]
    - 28% of pet owner indicated that they use aspirin to treat their dogs osteoarthritis[7]
- Studies to determine the activity of NSAIDs when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted
- Drug compatibility should be monitored closely in patients requiring cardiac, anticonvulsant and behavioral medications

1. Deramaxx Package insert, NADA # 141-203, 2008 Novartis Animal Health.
2. Etodolac Package insert, NADA 141-108, 2008 Fort Dodge.
3. Metacam Package Insert, NADA 141- 213, 2010, Boehringer Ingelheim Vetmedica, Inc.
4. Prevacox package insert NADA 141-230, 2010, Merial.
5. Rimadyl Package insert, NADA 141- 111, 2007 Pfizer Animal Health,
6. http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm, FDA Website.

Minimizing the Risk: Pet Owner Communication[1-6]

- Always provide a Client Information Sheet with prescription
- Pet owners should be:
  - Informed regarding potential adverse events
  - Advised to discontinue NSAID therapy if side effects occur and contact their veterinarian
  - Store palatable formulations out of reach of dogs, in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested
  - Made aware of the importance of periodic follow-up for
    - Safety, Efficacy, Compliance
    - Development of unrelated conditions

1. Deramaxx Package insert, NADA # 141-203, 2008 Novartis Animal Health.
2. Etodolac Package insert, NADA 141-108, 2008 Fort Dodge.
3. Metacam Package Insert, NADA 141- 213, 2010, Boehringer Ingelheim Vetmedica, Inc.
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5. Rimadyl Package insert, NADA 141- 111, 2007 Pfizer Animal Health,
6. http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm, FDA Website.

The Best Course of Action is to Focus on *Early* Diagnosis and *Consistent* Treatment!

- DVMs frequently limit NSAID use to moderate or late stage OA
- Some veterinarians use as last resort
- Intervention prior to the onset of pain in osteoarthritis is challenging
- Effective Treatment with NSAIDS
  - Reduces inflammation – slows or eliminates further progression
  - Prevents wind-up

Consequences of Waiting

"The changes associated with osteoarthritis ultimately have an impact on the patient through decrease ability to use the joint or the production o pain or both. Unfortunately once these changes are sever enough to be recognized clinically, they are likely to be irreversible with current treatments." [1]

"Because windup is more difficult to treat, one treatment modality may not control the multiple receptors that have been activated in chronic pain"[2]

1) Johnston SA. Vet Clin NA: SAP. 1997
2) Muir WW. Veterinary Pain Management, Gaynor, J and Muir WW. (Eds), Mosby, Columbus 2003.

Most Information for Treatment of Canine OA is on NSAIDS

- NSAIDs:
  - Improved activity and showed progressive improvement in clinical signs of OA with long term treatment[1,2,3]
  - NSAIDs break the progressive cycle of inflammation and pain by acting in both the joint and the dorsal horn.[4]
  - For most dogs, the benefits of using NSAIDs outweigh the risks.[2,3]

1) Brown, DC et al. *JAVMA*. 237: 66-70; 2010.
2) Autefage A, et al.. *Revue Méd. Vét*, 158; 119-127: 2007
3) Innes JF et al. *Vet Record*, 166; 226-230: 2010.
4) Camu F, Shi I, Vanlersberghe C. *Drugs*. 63 Suppl 1:1-7: 2003

More than "Just Pain Medicine"

The primary pharmaceutical therapy used for pain management of OA in dogs is NSAIDs

- Anti-inflammatory effects of NSAID may provide disease altering benefits in OA patients, improve recovery from surgery [1-3]
  - NSAID therapy provides analgesic benefits that allows appropriate exercise
  - Rehabilitation therapy & appropriate exercise enhance joint function, mobility, and maintenance of muscle tone
  - NSAIDs have been shown to effectively control the pain and inflammation associated with osteoarthritis and as a result activity[4,5]

1) Pelletier JP, et al. *J Rheumatol*. 27: 2893-2902; 2000.; 2) Dvorak LD, et al. *AJVR*, 63: 1363-1369; 2002; 3) Dassler CL, et al. *Vet Comp Ortho Traumatol,16*: 32-37; 2003 4) Brown, DC et al. *JAVMA*. 237: 66-70; 2010. 5) Autefage A, et al.. *Revue Méd. Vét*, 158; 119-127: 2007

Key Point to Consider When Choosing an NSAID

- Overall, all NSAIDs are equally efficacious for osteoarthritis and have similar safety profiles
- Choice is dependent on the individual patient
  - One drug maybe more effective than another drug
  - One drug may be better tolerated
  - Pharmacogenetics ?
- Start treatment using preferred NSAID
  - Pre-treatment blood work
- Monitor – efficacy and safety
- If need to switch – 3-5 days based on PK (not clinical studies)

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1) Autefage A, Gossellin J. Efficacy and safety of long-term oral administration of carprofen in the treatment of osteoarthritis in dogs. *Revue Med Vet. 2007;158(3):119-127.*

2) Brown DC et al. Use of activity monitor to detect response to treatment in dogs with osteoarthritis. *JAVMA. 2010; 237: 66-70.*

3) Camu F, Shi l, Vanlersberghe C. The role of COX-2 inhibitors in pain modulation. *Drugs. 2003;63 (Suppl 1):1-7.*

4) Dassler CL, et al. Histological features of osteoarthritic canine cartilage after prolonged administration of carprofen. *Vet Comp Ortho Traumatol,16*: 32-37; 2003

5) Dvorak LD, et al. Effects of carprofen and dexamethasone on canine chondrocytes in a three-dimensional culture model of osteoarthritis. *AJVR*. 2002; 63:1363-1369.

6) Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. *Vet Rec. 2010;166:226-230.*

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9) Juni P. Osteoarthritis: rational approach to treating the individual. *Best Prac & Resea Clin Rheumatol*, 2006; 20:721-740.

10) Konttinen YT et al. Pain fibers in osteoarthritis: a review. *Semin Arthritis Rheum. 1989;18(4 Suppl 2):35-40.*

11) Konttinen YT et al. Peripheral and spinal neural mechanisms in arthritis. *Arthritis Rheum*, 1994; 37:965-982.

12) Litman D. Maximizing success in osteoarthritis care: benefits of a comprehensive management approach. Int J Rheumatol. 2008; 5: 1-37.