Chronic Pain: Implications for Quality of Life and Strategies for Management

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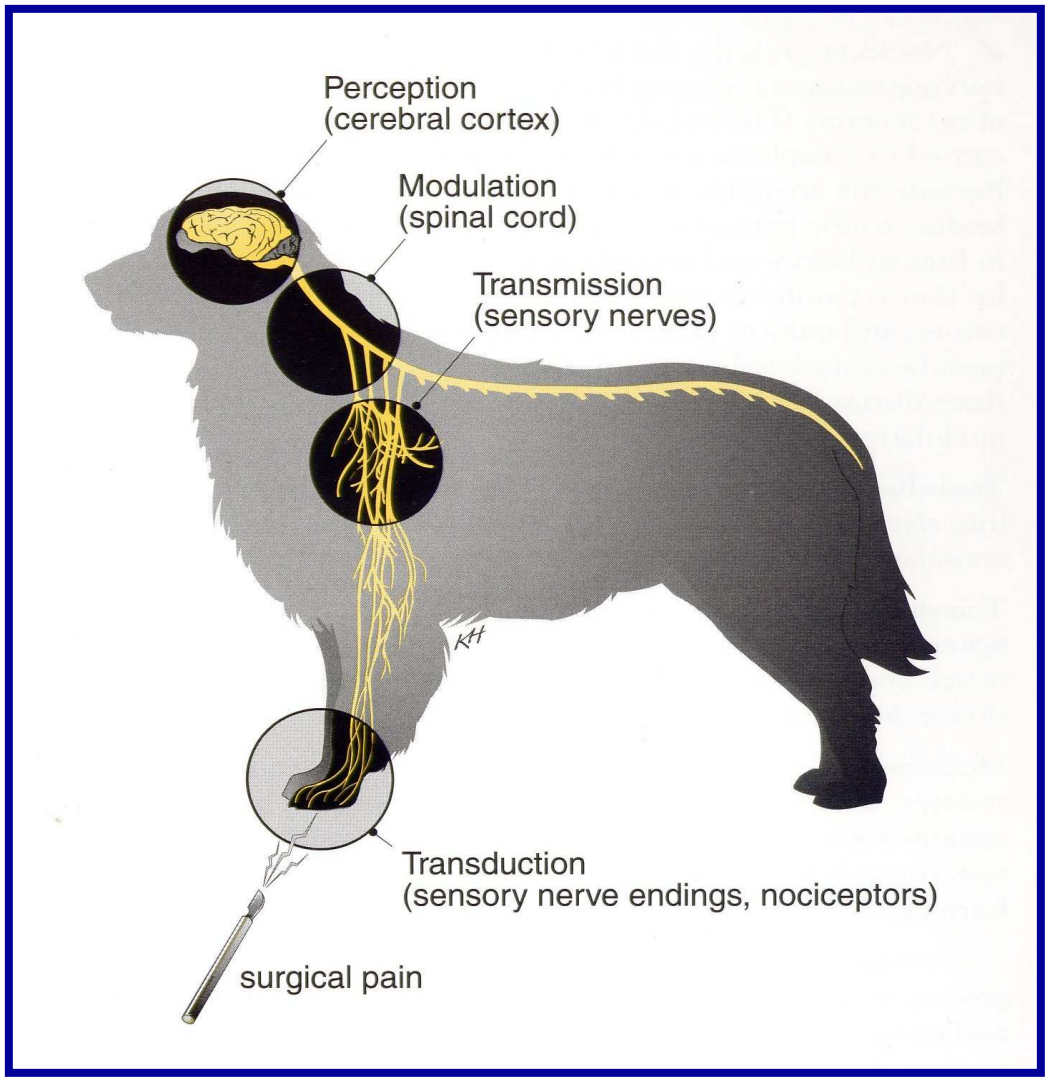
Overview

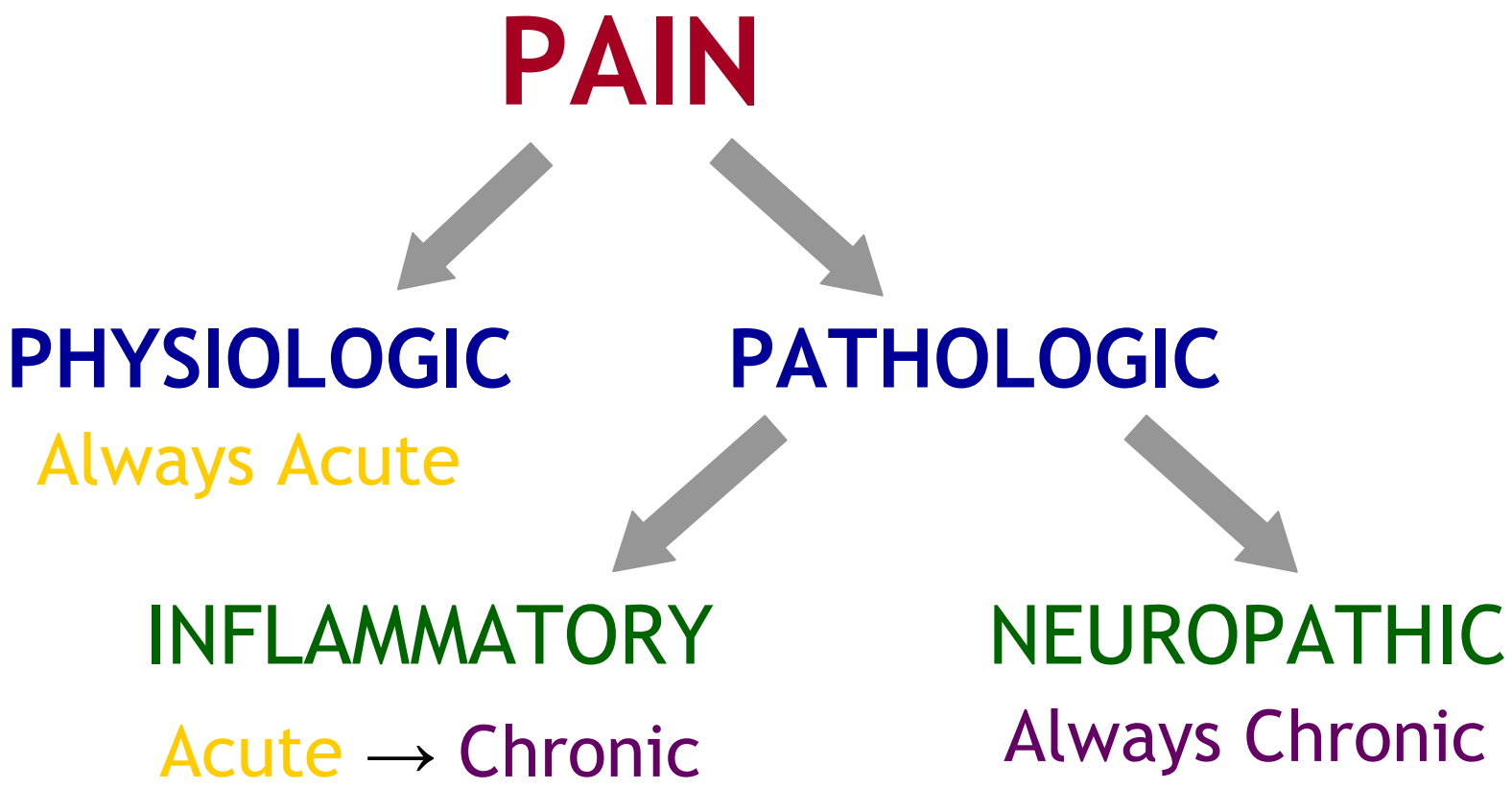
- Pathophysiology of chronic pain
- Recognizing pain and monitoring response to therapy
- Pharmacotherapy for chronic pain in dogs and cats
- Case Examples

Pain and Nociceptive Pathways

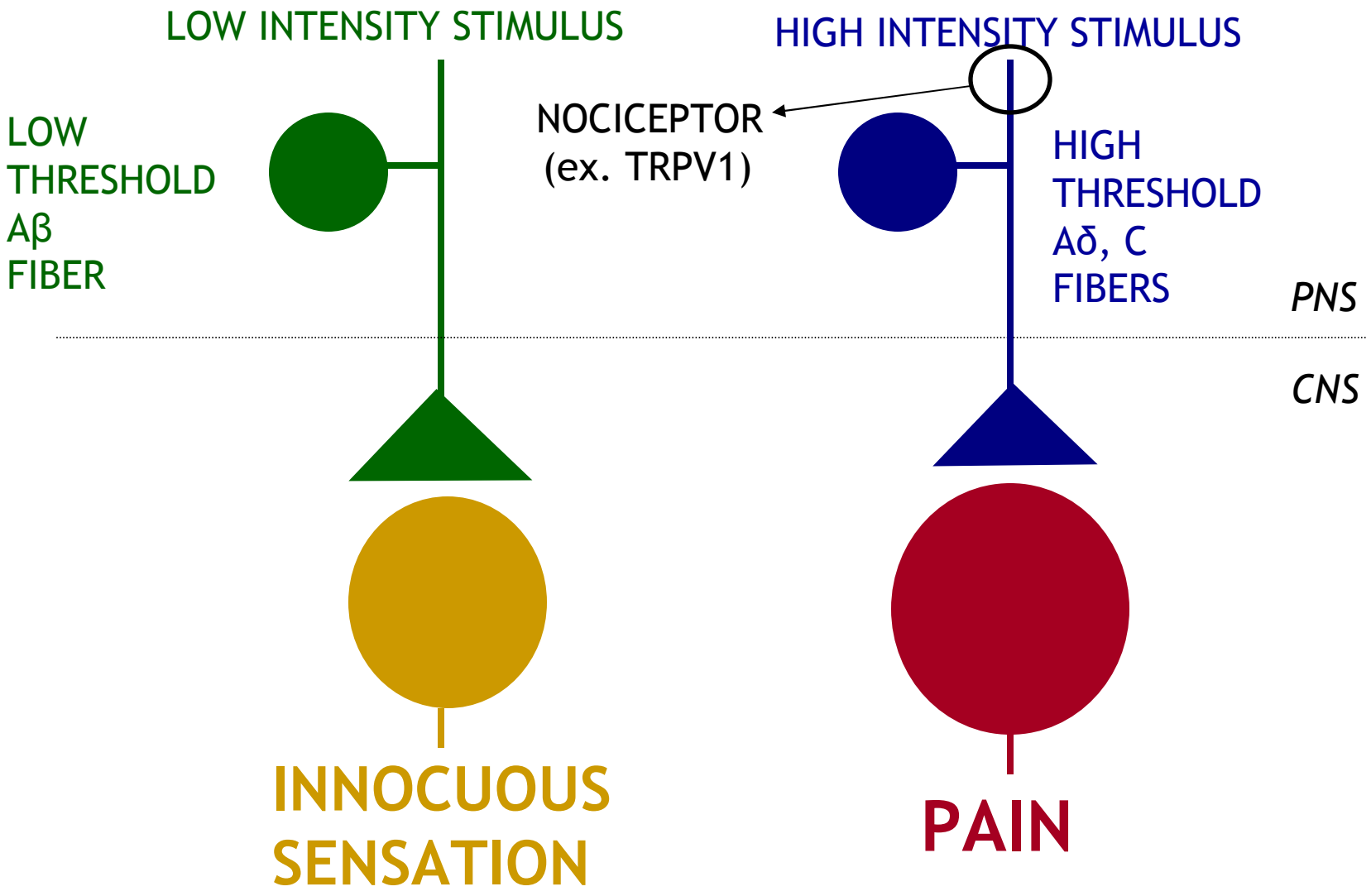


From:

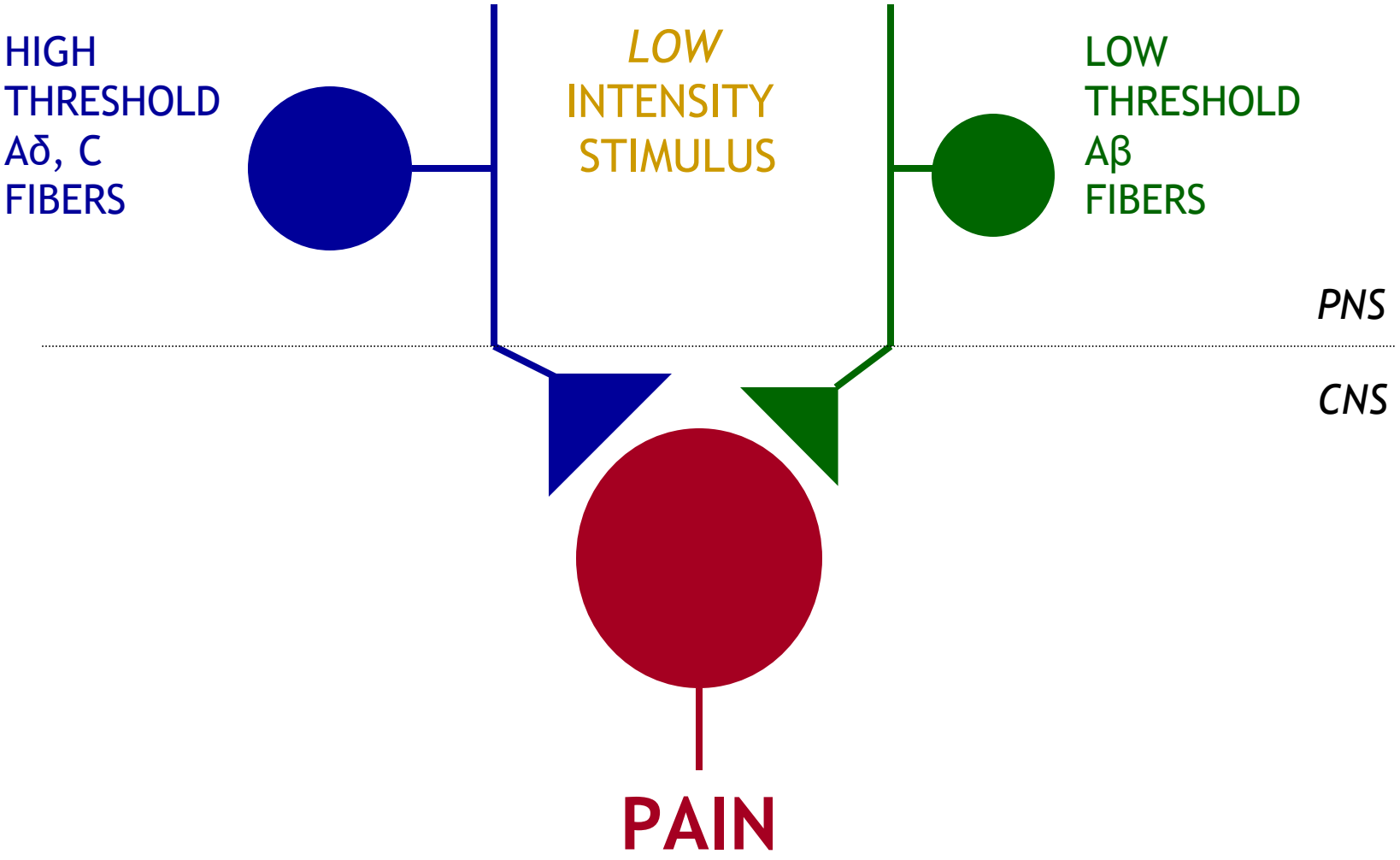
Pain Management for the Small Animal Practitioner, 2nd Edition


PAIN
PHYSIOLOGIC
Always Acute
PATHOLOGIC
INFLAMMATORY
Acute → Chronic
NEUROPATHIC
Always Chronic

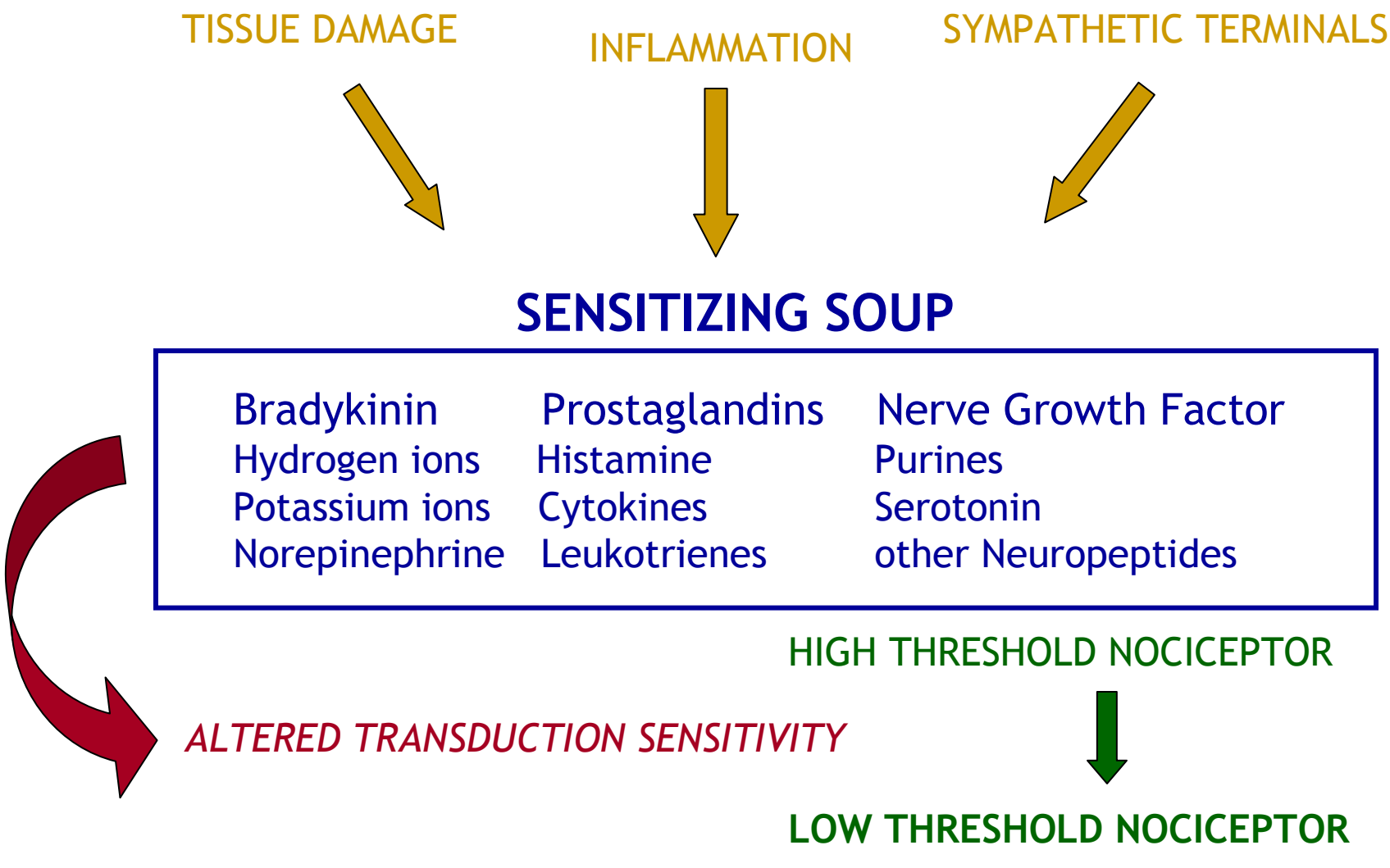
Physiologic Pain and the Sensory Nervous System



Pathologic Pain



Peripheral Sensitization



Central Sensitization

- increased excitability in dorsal horn nociceptive neurons
- changes are temporally related:
  - activity-dependent → triggered by nociceptor input
  - transcription-dependent → altered gene expression
- mechanisms similar to peripheral sensitization
- key neuromodulators:
  - glutamate activated NMDA receptors
  - substance P, BDNF
  - *glial cells*

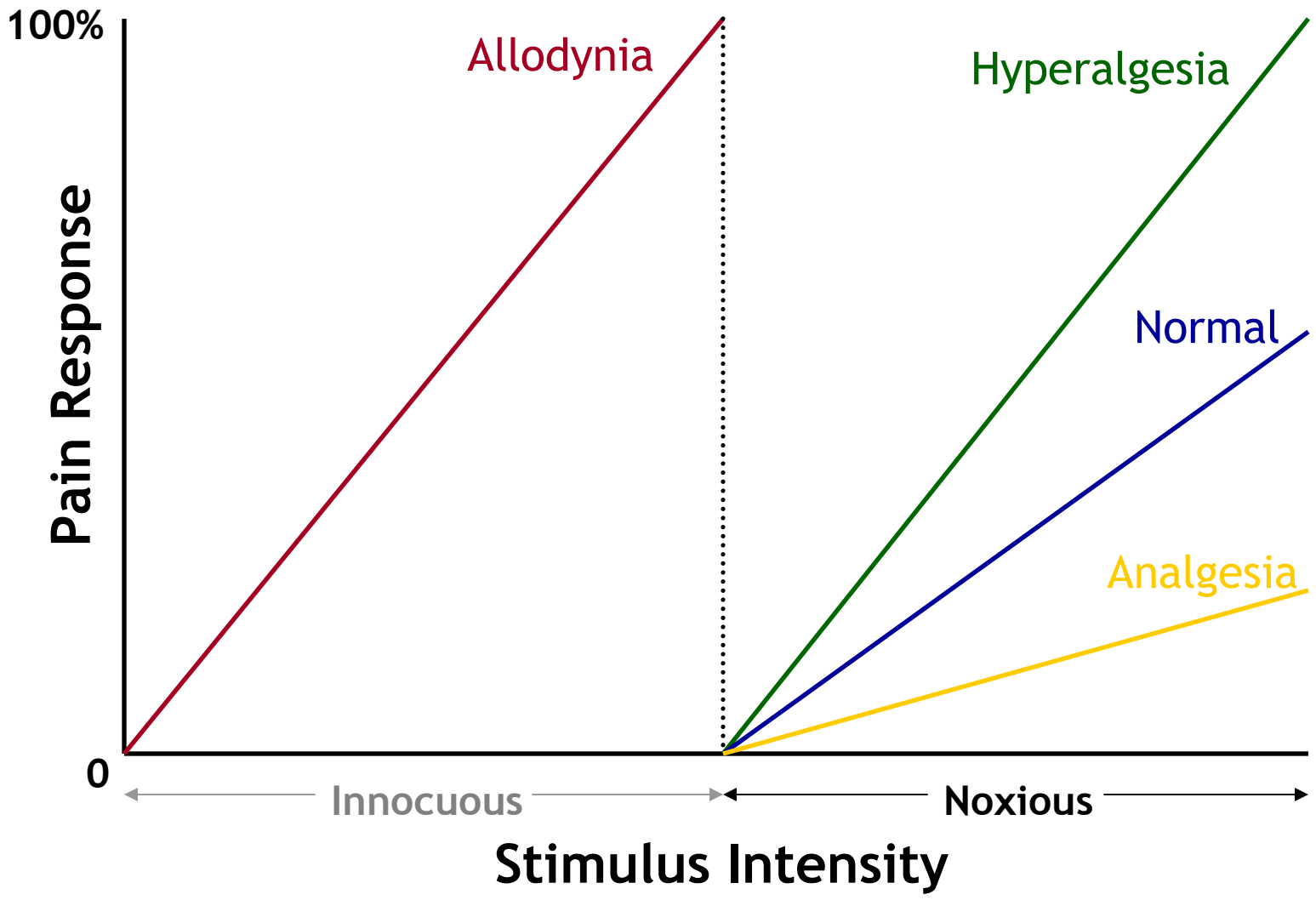
The Emerging Role of Glial Cells in Central Sensitization

- traditionally thought of as “housekeepers”
- recently recognized as key players in generation and maintenance of pathologic pain
- activation is secondary to nerve trauma or inflammation → release of proinflammatory mediators such as IL-1β, TNFα, IL-6
- glial cells also may compromise opioid efficacy for management of chronic pain

Chronic Pain

- end result of sensitizing changes in the CNS
  - alteration in cell phenotype
  - expression of novel proteins (receptors)
  - changes in neurotransmitter and ion channels
  - changes in neural structure (cell loss, synaptic reorganization)
- implies more than just duration
- serves no useful biologic or adaptive function
- nervous system itself becomes the focus of pathology

Clinical Manifestations of Chronic Pain



Chronic Pain in Humans

- major public health issue
- WHO/IASP report that *1 in 5 people* suffer from moderate to severe chronic pain worldwide
- hundreds of specific chronic pain syndromes are recognized in people:
  - low back pain, fibromyalgia, chronic pancreatitis, chronic active hepatitis, metastatic bone cancer pain, trigeminal neuralgia, postherpetic neuralgia, migraine, cluster headache, chronic pelvic pain, rheumatoid arthritis, osteoarthritis, phantom limb pain, reflex sympathetic dystrophy, diabetic neuropathy, giant cell arteritis, etc, etc, etc

Chronic Pain in Animals

- true incidence unknown
- specific chronic pain syndromes not as well-characterized as in humans
- pain a common reason for owners to seek veterinary care
- mild to moderate chronic pain may go unrecognized for extended periods as associated behavioural changes are often insidious and may evolve slowly over time
- veterinarians must be aware of conditions that *MAY* be associated with chronic pain so discussions regarding quality of life can be initiated with owners early in the disease process

Conditions Associated with Chronic Pain in Dogs and Cats

CONDITION	*EXAMPLES*
Cancer	osteosarcoma, chondrosarcoma, nerve sheath tumour
Chronic Inflammatory Disease	chronic otitis, chronic pancreatitis, feline interstitial cystitis
Chronic Orthopedic Disease	osteoarthritis, lumbosacral instability
Chronic Soft Tissue Injury	degloving injury, radiation-induced pain
Nervous Tissue Injury	post-amputation pain, post-thoracotomy pain, intervertebral disc disease

Recognizing Pain in Dogs and Cats

"You see only what you look for, you recognize only what you know."

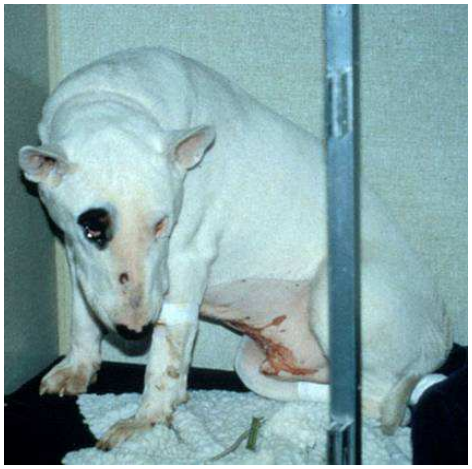
Merrill Sosman

Pain Recognition

- recognition and evaluation are the first steps toward effective treatment of pain
- no “gold standard”
- must rely on recognition and interpretation of *behaviours* by a care-giver

Variability in Pain-associated Behaviours

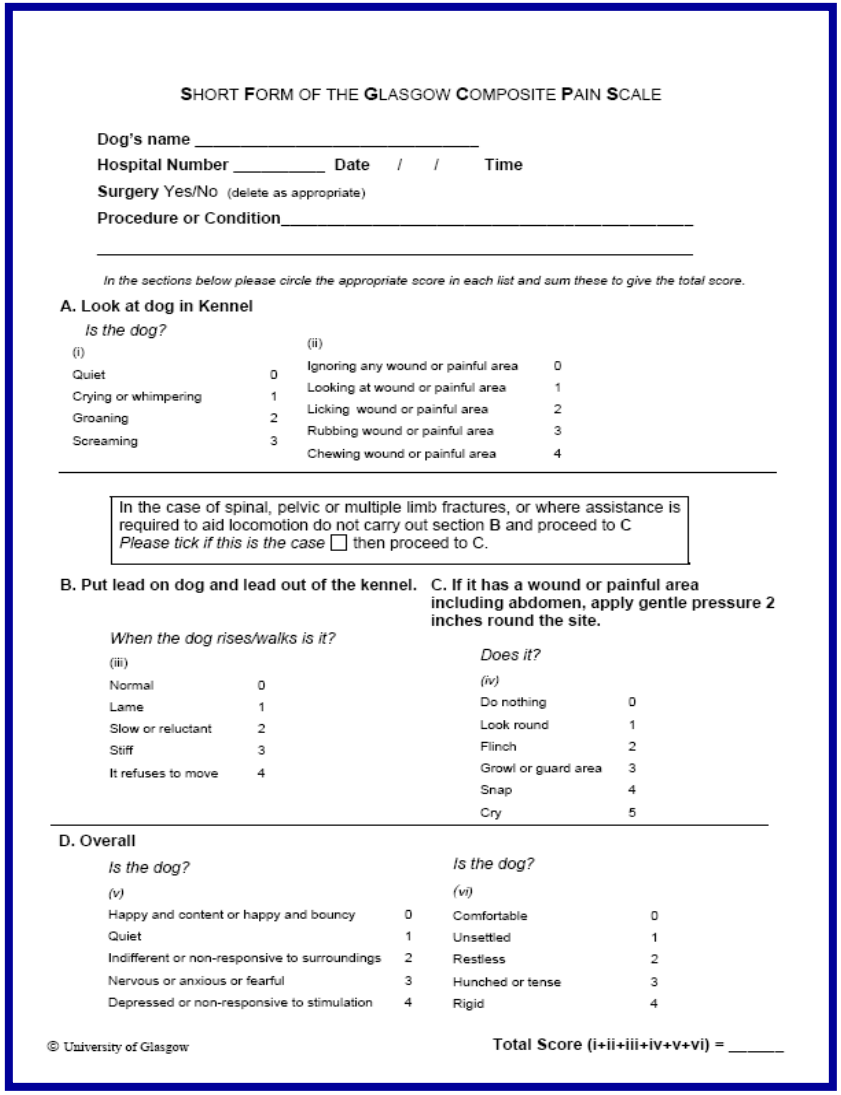
- type of pain
- intensity of pain
- duration of pain
- species
- breed
- individual animal
- setting



Pain Scales

- several species-specific scales have recently been developed and validated
- the intent of such scales is to ensure that pain is specifically assessed and treated in every patient on a systematic basis
- *ALL* pain scales have inherent limitations

Short-form of the Glasgow Composite Pain Scale (SF-GCPS)



SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ Date / / Time

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)

Quiet	0
Crying or whimpering	1
Groaning	2
Screaming	3

(ii)

Ignoring any wound or painful area	0
Looking at wound or painful area	1
Licking wound or painful area	2
Rubbing wound or painful area	3
Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section B and proceed to C
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)

Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)

Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog?

(v)

Happy and content or happy and bouncy	0
Quiet	1
Indifferent or non-responsive to surroundings	2
Nervous or anxious or fearful	3
Depressed or non-responsive to stimulation	4

Is the dog?

(vi)

Comfortable	0
Unsettled	1
Restless	2
Hunched or tense	3
Rigid	4

Total Score (i+ii+iii+iv+v+vi) = _____

- questionnaire format
- dogs only
- 5 sets of behavioural categories
- specific word descriptors
- utilizes psychometric principles and interval-level scaling model

Reid et al., VAA 32(6):7; 2005

Are Pain Scales Useful for Assessing Chronic Pain?

NO

- currently available pain scales are not useful for recognizing or assessing chronic pain

What about Chronic Pain?

- complex experience
- significant impact on *Health-related Quality of Life (HRQOL)* in animals
- owners are best equipped to recognize and report information regarding behavioural changes associated with chronic pain in their pets

Traditional Tools for Owner Assessment of Chronic Pain

Name _____ Treatment Week _____

Please fill in this chart each evening before going to bed. Record your estimation of your pet's pain intensity and the amount of pain relief. If your pet had any side-effects please note them in the side-effects box.

	Date							
Pain Intensity How bad was your pet's pain today?	Severe							
	Moderate							
	Mild							
	None							
Pain relief How much pain relief has the medication given your pet today?	Complete							
	Good							
	Moderate							
	Slight							
	None							
Side-effects Has the treatment upset your pet in any way?								

How effective was the treatment this week?

Poor Fair Good Very Good Excellent

please circle one choice

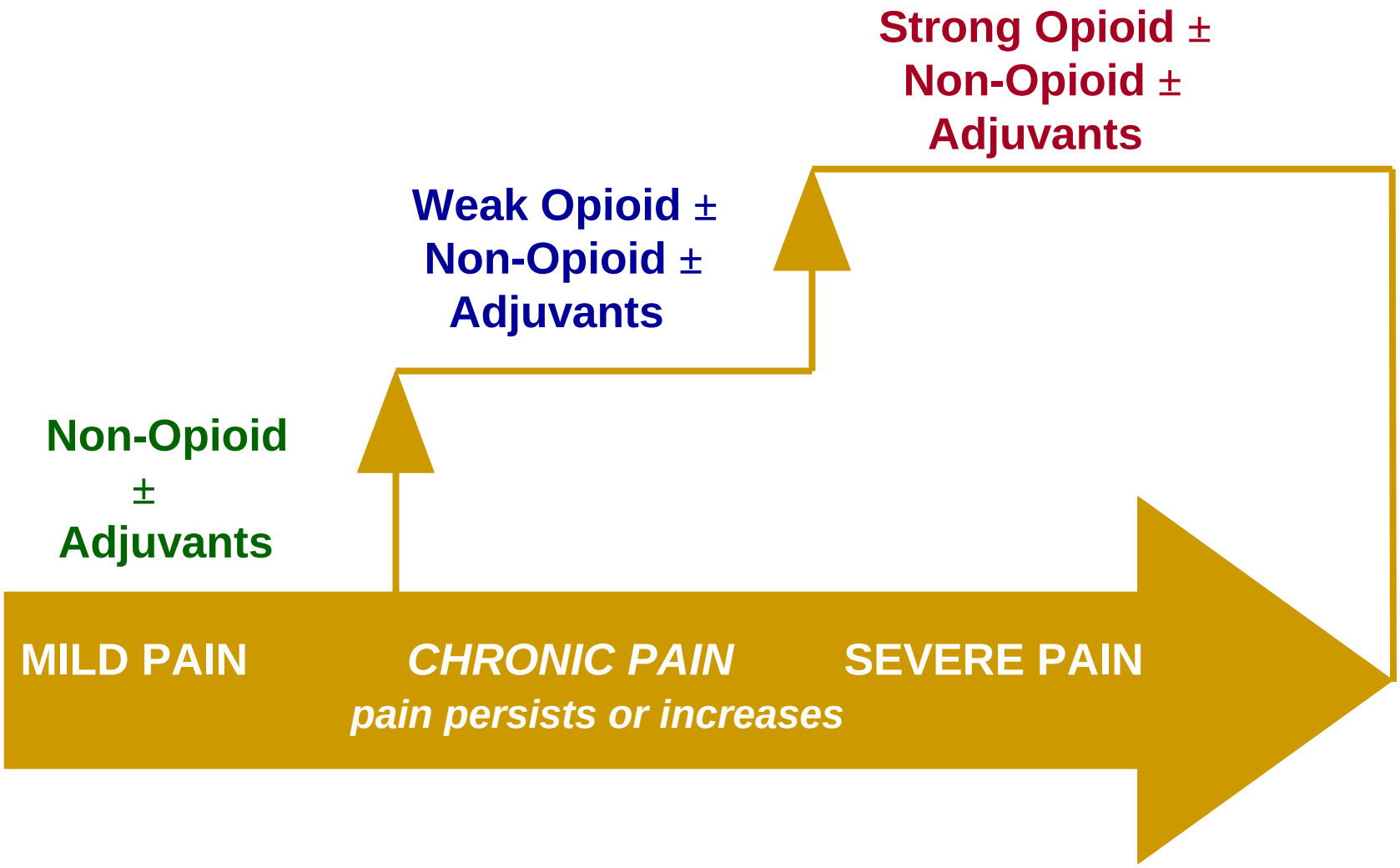
New Directions in HRQOL Assessment

- development of structured, validated, reliable and sensitive psychometric tools will help veterinarians improve clinical decision-making
- numerous publications within the last 5 years are moving toward this goal
- examples:
  - *Glasgow University Health-related Dog Behaviour Questionnaire, Wiseman-Orr et al., AJVR 2006*
  - *Canine Brief Pain Inventory, Cimino Brown et al., JAVMA 2008*
  - *Helsinki Chronic Pain Index, Hielm-Bjorkman et al., AJVR 2009*

General Guidelines for Management of Chronic Pain

1. Identify the underlying cause of pain
2. Treat the specific disease
3. Introduce physical medicine modalities
4. Prescribe appropriate analgesic agents
5. Incorporate alternative analgesic techniques, such as acupuncture where appropriate
6. Continue to document underlying disease and its progression over time

WHO Ladder for Cancer/Chronic Pain Management



Overview of Analgesic Agents Useful for Management of Chronic Pain

1. Nonsteroidal Antiinflammatories (NSAIDs)
2. Adjunctive Agents
3. Opioids

NSAIDs: Mechanism of Action

- NSAIDs bind to and inhibit *cyclooxygenase enzymes (COX)* peripherally and centrally
- this blocks the first step in prostaglandin synthesis and decreases release of inflammatory mediators known to sensitize nociceptive neurons
- net result is diminished perception of pain
- "newer" NSAIDs have greater specificity for the inducible form of COX, *COX-2*, which may reduce adverse side effects

NSAIDs: Classification

Salicylic Acids
- aspirin

Para-Aminophenol
- acetaminophen

Fenamic Acids
- flunixin meglumine
- tolfenamic acid

Pyrazolones
- dipyrone
- phenylbutazone

Propionic Acids
- carprofen
- ketoprofen
- ibuprofen
- naproxen

Oxicams
- meloxicam
- piroxicam

Acetic Acids
- ketorolac
- etodolac

Coxibs
- deracoxib
- firocoxib

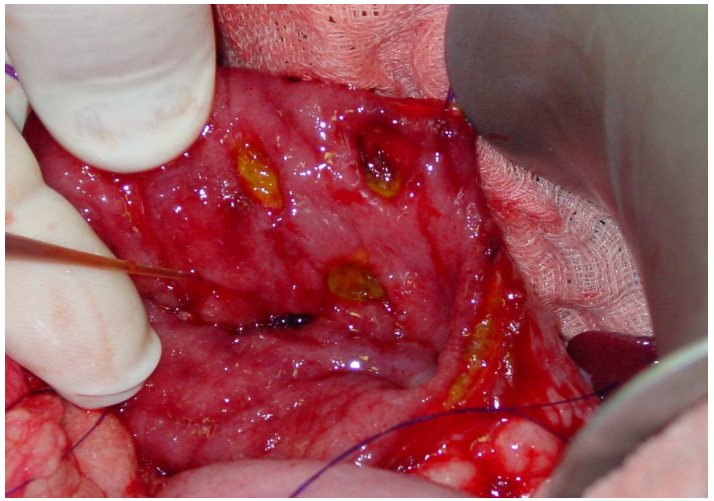
Dual Inhibitors
- tepoxalin

NSAIDs: Clinical Use for Chronic Pain

- first line treatment for OA and other types of chronic pain in dogs and possibly cats
- traditionally believed to be *less effective* for noninflammatory/neuropathic pain → this assumption has been questioned in recent human literature
- adverse side effects are major factor that may limit chronic use in certain patients
- increasing the dose administered beyond the label range is *NOT* recommended

NSAIDs: Patient Related Considerations

- GI compromise (mucosal damage)
- Renal compromise
- Hepatic compromise
- Hemostatic dysfunction
- Uncontrolled hemorrhage
- Dehydration
- Hypotension/Hypovolemia
- Concurrent corticosteroids
- Other NSAIDs concurrently



NSAIDs: Clinical Use for Chronic Pain

- currently available veterinary products appear to have similar analgesic efficacy
- a less than optimal response to treatment with one NSAID does *NOT* mean that other drugs in this class will be ineffective
- a trial and error approach is often necessary to identify the best treatment plan for a particular patient
- veterinarians need to have multiple NSAID options available when designing chronic pain treatment plans

Adjunctive Analgesics

- diverse group of drugs
- have primary indications other than pain, but are analgesic in certain situations
- enhance analgesia by binding CNS receptors and modifying neurotransmitter release or by altering nerve conduction processes
- especially useful in management of numerous types of chronic pain
- dose adjustments are often necessary during treatment to optimize analgesia and manage side effects

Adjunctive Analgesics: Classification

Drug:	Class:
Medetomidine	Alpha$_2$ agonist
Ketamine	Dissociative agent/NMDA antagonist
Gabapentin	Anticonvulsant
Amantadine	Antiviral/NMDA antagonist
Amitriptyline	Tricyclic Antidepressant
Mexiletine	Oral local anesthetic
Pamidronate	Osteoclast inhibitor

Adjuvant Analgesics: Considerations before Initiating Therapy

1. Approved indications in humans and/or animals
2. Indications for analgesia in humans and/or animals
3. Common/uncommon side effects in species of interest
4. Important pharmacokinetic features in species of interest
5. Specific dosing guidelines for pain in species of interest

Gabapentin: Mechanism of Action

- binding of *$a_2\delta_1$ subunit of voltage-gated calcium channels*
- ↓ Ca^{2+} currents at spinal and supraspinal levels → ↓ release of excitatory neurotransmitters→ ↓ development of central sensitization → ↓ hyperalgesia, allodynia
- also activates descending analgesic pathways and stimulates release of spinal NE → α_2-adrenoceptor activation → analgesia

Gabapentin: Clinical Use for Chronic Pain

- traditionally recommended for neuropathic pain but may have other chronic pain applications (ex. OA pain)
- often combined with NSAIDs and/or opioids but may be used alone in certain patients
- dosing based on anecdotal reports in dogs and cats
- no clinical trials evaluating analgesic efficacy
- large margin of safety
- dose limiting side effect is usually sedation
- 5 – 10 mg/kg PO q8 to 12 hrs

Amantadine: Mechanism of Action

- stabilizes NMDA channels in the closed state → anti-NMDA effects → ↓ development of central sensitization → ↓ hyperalgesia, allodynia

- most evidence of analgesic efficacy is in humans with chronic neuropathic pain

Amantadine: Clinical Use for Chronic Pain

- recent veterinary study (randomized, blinded, placebo-controlled):

  Amantadine beneficial when combined with an NSAID (meloxicam) for management of chronic OA pain in dogs;

  Lascelles et al., J Vet Intern Med, 2008

- often in combination with NSAIDs and/or opioids
- dosing based largely on anecdotal reports
- 3 – 5 mg/kg PO q24 hrs

Opioids: Mechanism of Action

- bind receptors in both the CNS *and* the PNS
- *pre-synaptic binding* causes decreased release of excitatory neurotransmitters in the dorsal horn
- *post-synaptic binding* causes hyperpolarization of nociceptive neurons
- net result is diminished perception of pain
- different opioids have different binding characteristics at mu, kappa and delta receptor subtypes

Opioids: Classification

Pure Agonists	
oxycodone	PO; fewer side effects than morphine
morphine	PO; sustained-release formulation
fentanyl	transdermal patch formulation
tramadol	PO; weak mu agonist; pharmacokinetics in dogs?
codeine	PO; also available with acetaminophen
methadone	PO not recommended; poor oral bioavailability
Partial Agonists	
buprenorphine	transmucosal administration in cats (not Canada)
Agonist-Antagonists	
butorphanol	PO; less intense analgesia; very short duration

Tramadol: Mechanism of Action

- classified as an “atypical opioid” due to its weak effects at mu receptors
- *NOT* classified as a controlled substance
- inhibits re-uptake of norepinephrine and serotonin and may facilitate serotonin release → primary mechanism of analgesia
- *in humans*, principle active metabolite (M1) has much greater potency at mu receptors → contributes significantly to tramadol’s analgesic effect

Tramadol: Drug Formulations

1. Immediate Release (IR) Tablets
   - available in the US
   - *NOT* commercially available in Canada
   - commonly prepared from tramadol powder by compounding pharmacies
2. In Combination with Acetaminophen
   - Tramacet® (37.5mg tramadol with 325mg acetaminophen)
   - *CONTRAINDICATED in cats*
   - in dogs, base dose on acetaminophen (10-15mg/kg q8-12hrs)
3. Extended Release (ER) Tablets
   - available in US and now in Canada

Tramadol: Species-Specific Pharmacokinetic Considerations

Oral Bioavailability:

- Tramadol IR (not available commercially in Canada)
  - Humans 68%
  - Dogs 65%
  - Cats 93%
- Tramadol ER (available in Canada)
  - Humans ~70%
  - Dogs 10%
  - Cats?

Metabolism of Parent Drug:

- Humans significant production of M1 (active metabolite)
- Dogs minimal production of M1
- Cats significant production of M1

Tramadol: Pharmacokinetic Considerations

Elimination and Clearance of Parent Drug and Metabolites:

- Tramadol IR
  - Humans $t_{1/2}$ 5.5hrs / slow clearance
  - Dogs $t_{1/2}$ 1.7hrs / rapid clearance
  - Cats $t_{1/2}$ 3.4hrs / intermediate clearance
- Tramadol ER
  - Humans $t_{1/2}$7.9hrs / slow clearance
  - Dogs $t_{1/2}$1.9hrs / rapid clearance
  - Cats ?
- M1
  - Humans $t_{1/2}$ 6.7hrs / slow clearance
  - Dogs $t_{1/2}$ 2.2hrs / rapid clearance
  - Cats $t_{1/2}$ 4.8hrs / intermediate clearance

Tramadol: Bottom Line

- anecdotal clinical evidence suggests oral tramadol is useful for management of chronic pain in dogs and cats
- no clinical trials evaluating analgesic efficacy
- at this time, there is no evidence to suggest that tramadol ER is suitable for q24hr dosing
- for tramadol IR: 2 – 5 mg/kg PO q6 to 8hrs (longer dosing interval recommended in cats)
- many practitioners claim success with q12hr dosing of the IR formulation in dogs(?)

Case Examples

6 yr old, 38kg, FS German Shepherd dog

- bilateral degenerative joint disease of both coxofemoral joints
- chronic osteoarthritis pain for ~ 3 years
- receiving deracoxib 50mg PO q24hrs with good results until recently
- pain intensity appears to have increased over the past month despite continued treatment
- thorough examination including orthopedic evaluation → no significant changes from previous

Bilateral Coxofemoral OA

- Pain Description
  - chronic inflammatory and neuropathic pain
  - moderate intensity

- Recommendation #1:
  - switch NSAID to carprofen 150mg PO q24hrs
  - sometimes switching to a different drug from the same general class can improve analgesia

Bilateral Coxofemoral OA

- Outcome #1:
  - dog became more comfortable and activity level increased after 3 days on carprofen
  - improvement was maintained for 4 months
  - resumption of clinical signs despite continued treatment
- Recommendation #2:
  - start amantadine 100mg PO q24hrs to treat potential central sensitization
  - continue carprofen

Bilateral Coxofemoral OA

- Outcome #2:
  - comfort level improved significantly within 2 days of initiating amantadine treatment
  - amantadine was continued for 21 days and then discontinued
- Longterm Therapy and Outcome:
  - carprofen continued at 150mg PO q24hrs
  - pain continues to be well-managed on carprofen alone 8 months later

12 yr old, 4kg, MN DSH

- owners report that, over the past year, the cat has gradually stopped playing and jumping
- thorough diagnostic workup → bilateral degenerative joint disease of both stifle joints
- chronic osteoarthritis pain is suspected
- CBC and complete biochemical profile revealed no abnormalities

Bilateral Stifle OA

- Pain Description
  - chronic inflammatory and neuropathic pain
  - moderate intensity

- Recommendation #1:
  - initiate meloxicam 0.4mg PO once then…
  - 0.2mg PO for 4 days then…
  - 0.1mg PO for 4 days then titrate down to lowest effective dose

Bilateral Stifle OA

- Outcome #1:
  - cat became more comfortable and activity level increased after 2 days on meloxicam
  - after day 9, the 0.1mg dose was reduced from q24hrs to q48hrs
  - CBC and biochemical profile were re-checked after two weeks of therapy → no abnormalities
  - cat remained comfortable on the 0.1mg q48hrs dose and was continued on this treatment
  - CBC and biochemical profile to be re-checked every 3 to 6 months as indicated

12 yr old, 18kg, FS mixed dog

- presented for weakness, apparent back pain and progressive inactivity over a 2 month period
- on initial physical examination → severe pain and hypersensitivity on palpation of lumbar spine with proprioceptive deficits
- thorough diagnostic evaluation → multiple myeloma with metastasis to lumbar spine
- chemotherapeutic treatment initiated (melphalan and prednisone)

Multiple Myeloma

- Pain Description
  - chronic inflammatory pain secondary to boney metastasis
  - chronic neuropathic pain secondary to nerve root entrapment
  - severe intensity
- Recommendation #1:
  - initiate carprofen 75mg PO q24hrs
  - initiate gabapentin 100mg PO q8hrs
  - initiate tramadol IR 100mg PO q8hrs

Multiple Myeloma

- Outcome #1:
  - good response to chemotherapy
  - pain management plan also effective and owners report much improved HRQOL for ~ 4 weeks
  - at this point, pain returned despite clinical evidence of remission
- Recommendation #2:
  - continue carprofen at 75mg PO q24hrs
  - increase gabapentin to 200mg PO q8hrs
  - switch to oxycodone IR 5mg PO q8hrs

Multiple Myeloma

- Outcome #2:
  - comfort level improved significantly within 2 days of increasing gabapentin and adding oxycodone
  - oxycodone was continued for 21 days, then reduced to q12hr dosing, then q24hr dosing, and then stopped
- Longterm Therapy and Outcome:
  - carprofen continued at 75mg PO q24hrs
  - gabapentin continued at 200mg PO q8hrs
  - pain continued to be well-managed for ~ 9 months when relapse of the neoplasm occurred
  - euthanasia at ~ 10 months post-diagnosis

Chronic Pain Resources

- Veterinary Clinics of North America Small Animal Practice, Update on Pain Management. Mathews KA, ed. 38(6), 2008.
- Handbook of Veterinary Pain Management 2nd edition. Gaynor JS and Muir III WW, eds. Mosby Elsevier, 2009.
- Nonsteroidal Antiinflammatory Drugs in Cats: a Review. Lascelles BDX et al. Veterinary Anesthesia and Analgesia, 34:228–250, 2007.

Questions?