



## Pain Management

Peter J. Pascoe



International Academy of Veterinary Pain Management  
<http://www.cvms.colostate.edu/ivapm/>

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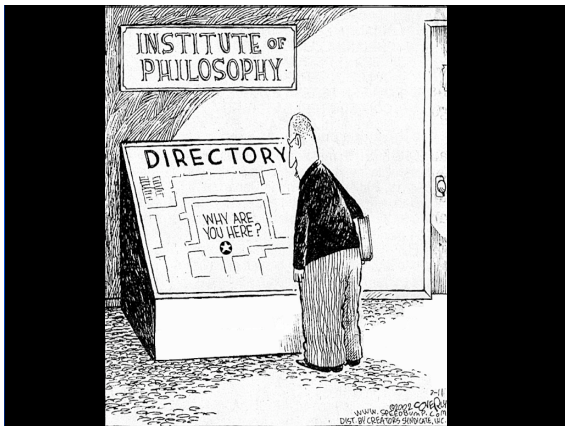
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## Pain Management

### Acute Pain (Physiologic pain)

- Usually of short duration and tied to an injury - serves the physiologic purpose of getting the animal to protect or treat the injury

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## Pain Management

### Chronic Pain (Pathologic pain)

- Pain that persists beyond the period of normal tissue healing or that arises from a pathologic process.
- In people chronic pain has been defined on a time line - e.g. pain lasting longer than x weeks.



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## Pain Management

### Neuropathic Pain

- Pain initiated or caused by a primary lesion or dysfunction in the nervous system

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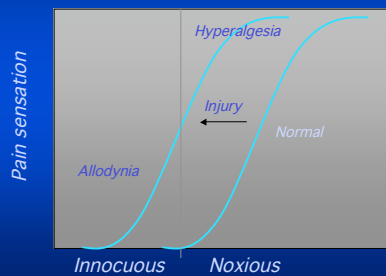
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## Effects of injury on pain



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## Pain Management

Human Medicine

- Undertreated
  - Patient expectations
  - Lack of knowledge
  - Concern for side effects & addiction
- Pain is of secondary concern
  - Mask clinical signs
  - Expected to resolve

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## Chronic pain

- Osteoarthritis
- Cancer
- Injury
- Visceral disorders
- Muscle disorders
- Nerve damage

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## Chronic pain after surgery

- Chronic pain occurs after surgery with incidences as high as 50%
- Factors
  - Presurgical pain
  - Nerve damage at surgery
  - Perioperative pain management
  - Preoperative susceptibility to pain

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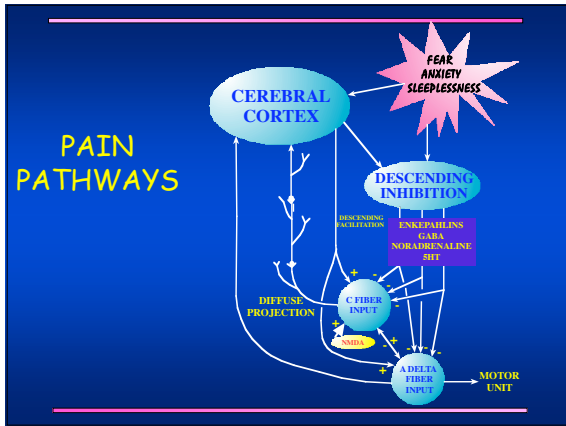
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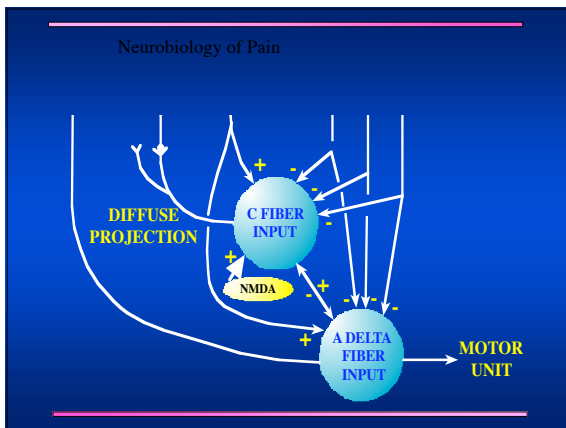
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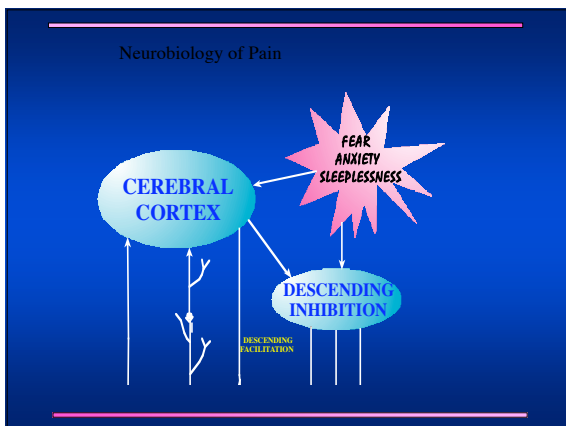
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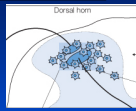
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## Synaptic Plasticity



- Microglial changes
  - Pain facilitation involves activation of microglia and astrocytes
  - Disruption of glial activation prevents or reverses pain facilitation
    - Minocycline better at preventing than reversing facilitation
  - Antagonism of substances released by activated glia blocks or reverses pain facilitation

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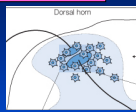
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## Synaptic Plasticity



### Microglial changes

- Proinflammatory cytokines (TNF and IL-1) critical
- Injection of activated glia will facilitate pain
- Blockade of glial activation does not affect nociceptive thresholds
- Blockade of glial activation does not provide analgesia

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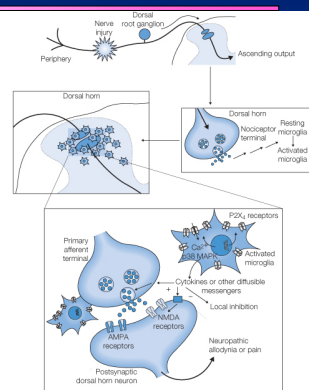
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## Synaptic Plasticity

### Microglial changes




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## Benefits of pain control

- Effect of local nerve block vs epidural vs PCA on postop pain and knee rehabilitation after arthroplasty
- Noted significantly lower incidence of side effects with local block
- Better knee flexion (up to 6 weeks post surgery)
- Faster ambulation and shorter hospital stay.

*Singelyn et al. Anesth Analg 1998;87:88-92*

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## Benefits of pain control

- Effect of epidural morphine/bupivacaine vs morphine vs bupivacaine vs IV morphine on postoperative pain and rate of recovery after colon surgery
- Noted significantly lower incidence of side effects with morphine/bupivacaine
- Groups MB and B had faster return of GI function and were discharged 1.5 days sooner than the other 2 groups

*Liu et al. Anesthesiology 1995;83:757-765*

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## Comfort as the primary goal in veterinary medical practice

FD McMillan

JAVMA 1998;212:1370-1374

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## A world of hurts - is pain special?

FD McMillan  
JAVMA 2003;223;183-186

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### Pleasant Feelings

- Joy
- Play
- Social companionship
- Mental stimulation
- Physical contact
- Taste, eating
- Smell
- Nurturing young
- Sexual activity
- Control



Quality of Life

### Unpleasant Feelings

- Fear
- Anxiety
- Boredom
- Loneliness
- Separation anxiety
- Grief
- Depression
- Frustration
- Anger
- Hypoxia
- Pain
- Thirst
- Hunger
- Cough
- Dizziness
- Full bladder
- Constipation
- Nausea
- Pruritus

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## Assessment of pain

- Method should be simple, reliable and repeatable
- Take little time to carry out
- Be applicable to a broad range of clinical situations or be readily adaptable to different conditions

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## Assessment of pain

- Visual analog scale
- Numeric scale using simple descriptors
- Descriptions of behavior
- Objective measurements
  - Heart rate, respiration rate, blood pressure
  - Response to a measurable stimulus
  - Cortisol
- Complex integrated scales using objective and subjective data

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## Assessment of pain

- Chronic pain
  - Chronic pain assessment can utilize other measures
    - Activity, comfort, appetite, extroversion-introversion, aggression, anxiety, alertness, dependence, contentment, consistency, agitation, posture-mobility, compulsion.
    - Health-related quality of life (HRQL) questionnaire developed by University of Glasgow (GUVQuest®)

Wiseman-Orr et al. AJVR 2004 and 2006

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## Pain management



- Opioid for moderate to severe pain, ± non-opioid ± adjuvant
- Opioid for mild to moderate pain, ± non-opioid ± adjuvant
- Non opioid ± adjuvant

*WHO's pain relief ladder*

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## BALANCED ANALGESIA

- Use of several different drugs to block different components of a nociceptive stimulus
- Smaller doses of each mean less likelihood of individual toxicity
- More drugs means more interactions and more chance of negative effects
  - Opioid = central and peripheral analgesia
  - Local anesthetics = block the nociceptive input into the central nervous system
  - NSAID = reduce the peripheral sensitization of nociceptors by prostaglandins
  - NMDA antagonists (ketamine) = reduce central facilitation (wind-up)
  - Alpha-2 agonists = enhance descending inhibition and reduce peripheral sensitization by catecholamines

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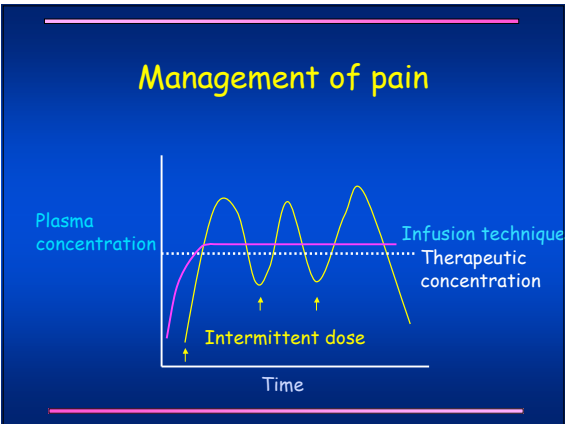
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## Pain Management

- Drugs and Techniques
  - Manage primary condition
    - Surgical
    - Medical
  - Weight loss
  - Non-steroidal anti-inflammatory drugs
  - Opioids
  - Cyclohexanones
  - Alpha-2 agonists
  - Local anesthetics
  - Antidepressants
  - Complementary therapies

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## Non-Steroidal Anti-Inflammatory Drugs

- Drugs
  - Aspirin, phenylbutazone, flunixin, meclofenamic acid, acetaminophen, dipyron, ibuprofen, indomethacin, naproxen
  - Carprofen, ketoprofen, ketorolac, piroxicam, meloxicam, etodolac, deracoxib, tepoxalin, diclofenac, firocoxib

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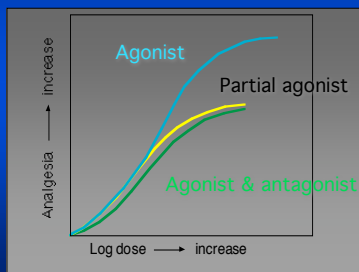
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## Opioids

- Classification - Effect



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## Opioid Administration

- Injected - SC, IM, IV
- Transdermal
- Transmucosal
- Oral
- Intra-articular
- Epidural or spinal
- Local injection

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## Systemic Opioid Administration

- Preanesthetic administration
  - Sedation, preemptive analgesia
- Intraoperative administration
  - Blunts autonomic responses to noxious stimuli
  - MAC reduction
  - Better hemodynamic stability
- Postoperative administration
  - Analgesia

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## Oral opioids

- Morphine (sustained release)
  - About 20% bioavailable in dogs
  - Peak plasma concentration at around 6 hours
  - Vomition in healthy dogs
  - Rectal administration - about the same uptake as oral

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## Oral opioids

- Codeine
  - About 6.5% bioavailable in dogs
  - In people 10% metabolized to morphine (the effective part)
  - In dogs and cats <1.5% converted to morphine

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## Oral opioids

- Oxycodone
- Hydromorphone
  - Bioavailability 25% in dogs
- Oxymorphone (Opana®)
  - Available as an immediate and extended release tablet
  - Bioavailability poor in people (~10%)
- Butorphanol
  - Bioavailability around 20-30%?

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## Tramadol

- Weak opioid agonist ( $\mu$ )
  - 1/6000th affinity for  $\mu$  receptor compared with morphine
  - O-desmethyl metabolite 1/30th affinity for  $\mu$  receptor compared with morphine
- Not a Scheduled drug

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## Tramadol

- Inhibits reuptake of norepinephrine and serotonin so some analgesia is caused by alpha-2 mechanism

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## Tramadol

- Supplied as 50 mg tablets
- Not licensed for animal use
- No studies in dogs reporting clinical efficacy
- Clinical doses vary from 2-5 mg/kg BID to TID
- Often being used in conjunction with NSAID for chronic pain conditions

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## Tramadol

### *Pharmacokinetics*

- Bioavailability = ~65%
- Peak plasma concentration at 0.5-2 hours
- Elimination half life 1.7 hours (5.5 h in people)
- 16% of dose metabolized to M1
- Elimination half-life of M1 2.2 hours (6.7 h in people)

Kukanich et al 2004

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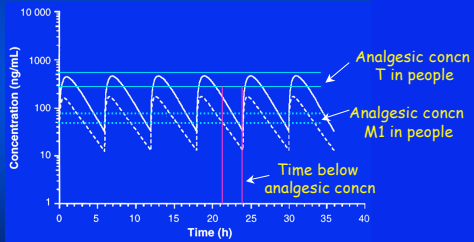
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## Tramadol

Pharmacokinetics 5 mg/kg Q 6 hours



Kukanich et al 2004

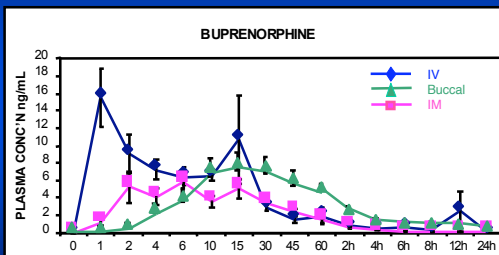
## Oral opioid administration

- Oral buprenorphine - 10  $\mu\text{g}/\text{kg}$
- Peak effect in 2 hours
- High bioavailability



## Oral opioid administration

- *Transmucosal*



Robertson et al, 2001

## Oral opioid administration

- *Transmucosal in dogs*
  - With a spray formulation got about 20% bioavailability with rapid clearance of the drug from the mouth
  - Using the injectable drug formulation peak plasma concentrations were reached by 30 minutes

*Mama et al. 2007, McInnes et al. 2008*

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## Cyclohexanones

- NMDA antagonists so should affect windup.
- Adjunct to therapy with other drugs
- Low doses used that do not induce sedation or dysphoria
- Pretreatment with ketamine prevented fentanyl induced hyperalgesia in carageenan treated rats.

*Rivat et al. Anesthesiology, 2002;96:381-91*

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## Cyclohexanones

- Ketamine (2.5 mg/kg) given pre or postoperatively in dogs undergoing OVH.
- Post operative ketamine gave lower pain scores at 20 minutes
- Preoperative ketamine gave lower pain scores at 18 hours
- Wound threshold scores lowest for saline treated animals!

*Slingsby and Waterman-Pearson Res Vet Sci 2000;69:147-152*

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## Cyclohexanones

- Dogs undergoing forelimb amputation (n=27)
- Ketamine 10  $\mu\text{g}/\text{kg}/\text{min}$  intraop
- Reduced to 2  $\mu\text{g}/\text{kg}/\text{min}$  postop
- Fentanyl 2  $\mu\text{g}/\text{kg}/\text{h}$
- Lower pain scores at 12 and 18 hours postop and on 3rd day as assessed by owner.

Wagner et al 2002

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## Cyclohexanones

- Ketamine as an adjunct for dogs with burn injuries
- Used in 2 cases in addition to therapy with opioids
- Ketamine at 10-12  $\text{mg}/\text{kg}$  orally QID provided improved analgesia

Joubert, J South Afr Vet Med Assoc 1998;69:95-97

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## Morphine/lidocaine/ketamine

- MLK
  - 10 mg morphine
  - 150 mg lidocaine
  - 30 mg ketamine into 500 mL LRS
  - Run during surgery @ 10 mL/kg/hour
  - = 0.2  $\text{mg}/\text{kg}/\text{hr}$  morphine
  - = 50  $\mu\text{g}/\text{kg}/\text{min}$  lidocaine
  - = 10  $\mu\text{g}/\text{kg}/\text{min}$  ketamine
  - Taper fluids and therefore MLK post surgically

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## Morphine/ketamine/lidocaine

- MLK
  - Analgesia by three different mechanisms
  - Less respiratory depression?
  - Decreases wind-up/facilitation?
  - Less effect on GI function?
  - Use less of each drug

No clinical studies proving efficacy

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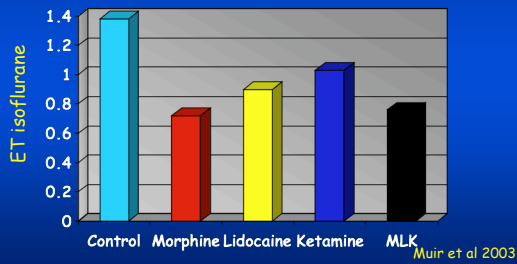
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## Morphine/ketamine/lidocaine

- Effect of MLK or individual components on MAC in dogs



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## Morphine infusions

- Dogs undergoing laparotomy (n=20)
- Morphine at 1 mg/kg q 4 h or
- CRI at 0.12 mg/kg/h
- No significant differences in pain scores

Lucas et al 2001

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## Lidocaine infusion

- Dogs undergoing eye enucleation (n=12)
- Lidocaine infusion intraoperatively 25  $\mu\text{g}/\text{kg}/\text{min}$  vs saline or morphine (0.1  $\text{mg}/\text{kg}/\text{h}$ )
- All saline dogs required rescue analgesics vs 50% of other 2 groups

Smith et al 2004

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## Amantadine & memantine

- NMDA antagonists
- Reduce facilitation
- May reduce doses needed of other drugs
- Good for neuropathic/chronic pain?

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## Amantadine

- Decreases reuptake of catecholamines
- Excreted unchanged in the urine in people. In dogs only 19% recovered unchanged but it appears to be metabolized rapidly
- Toxic dose >10 times usual oral dose
- Toxic signs of CNS stimulation (myoclonus, convulsions, salivation)
- High anxiety, restlessness and dry mouth at ~ 6  $\text{mg}/\text{kg}$

Bleiden et al. J Pharmacol Exp Ther, 1965

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## Amantadine

- Bioavailability is high
- Estimated half-life is around 5 hours
- Available as 100 mg capsules or a 10 mg/mL liquid

*Bleiden et al. J Pharmacol Exp Ther, 1965*

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## Amantadine

- Amantadine vs placebo in dogs with osteoarthritis
- 31 dogs treated with meloxicam (0.1 mg/kg SID) for 3 weeks and then amantadine (0.3-0.5 mg/kg SID) or a placebo was added for 3 weeks
- Both owners and clinicians agreed that there was an improvement on amantadine at 3 weeks

*Lascelles et al. JVIM 2008*

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## Alpha-2 agonists

- Analgesia appears to be mediated by the descending noradrenergic pathways
- The effects are antagonized by alpha-2 antagonists but not opioid antagonists
- There may be some "differential" analgesia
- Epidural or spinal administration can induce "surgical" analgesia
- Systemic alpha-2 agonists are not anesthetics

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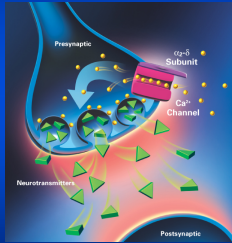
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## Gabapentin

- Originally marketed as an anti-seizure medication
- Mechanism involves alpha-2 delta subunit of the calcium channel
- Also may have an action through the alpha-2 adrenergic system (descending inhibition)



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## Gabapentin

- High bioavailability (95% +)
- Metabolized in the liver and excreted via the kidneys
- N-methylgabapentin is a metabolite
  - Hepatic toxicity?
- Half life is 3-4 hours
- Dose is 2.5-10 mg/kg BID or TID but individual patients have received up to 50 mg/kg

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## Gabapentin

- Useful adjunct for acute and chronic pain
  - Not an analgesic itself
- Decreases allodynia and hyperalgesia
- May cause significant sedation initially
- Dose per patient varies widely

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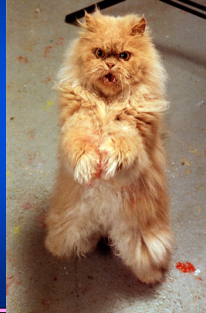
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## Local Anesthetics

- Drugs
  - Onset
  - Duration
  - Side effects
- Blocks
  - For surgery
  - Before surgery
  - After procedure
  - Pain from other causes



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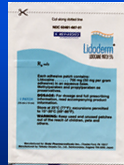
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## Local Anesthetics

- Transdermal
  - Lidocaine patch (Lidoderm®) 5%
  - Applied over an area of chronic or acute pain intermittently
  - Depth of penetration?



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## Local Anesthetics

- Nerve blocks
  - A single block may give relief of pain that outlasts the duration of action of the drug
  - Relief of sympathetic mediated pain
  - Development of formulations with a long duration of action (e.g. lipid encapsulation)
  - Use of 'soaker' catheters to deposit the local over a nerve or tissue. Can be attached to a pump to provide a continuous infusion.

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## Management of Pain

- Novel Pharmacologic techniques
  - Tricyclic antidepressants
  - Minocycline (prevents activation of microglia)
  - Ziconotide (N-type calcium channel antagonist)
  - Capsaicin (desensitizes nociceptors via TRPV1)
  - Resiniferatoxin (TRPV1 agonist)
  - Etanercept (TNF antagonist)
  - Substance P-Saporin (destroys neurons with substance P receptors - NK1)
  - Prostaglandin receptor antagonists
  - Serotonergic (5HT<sub>1A</sub>) agonists

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## Management of Pain

- Pharmacologic manipulations
  - Apply the drugs more locally
    - Epidural/spinal application
    - Intra-articular opioids
  - Transdermal application
    - Fentanyl, buprenorphine, lidocaine
    - Electrophoresis
  - Transmucosal application
    - Fentanyl oralets (poppy lolly-pops)
    - Buprenorphine in cats
  - Prolong the duration of action
    - Lipid encapsulation
    - Nanotechnology

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## Pain Management



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## Acupuncture

### Analgesia

- Stimulation of acupuncture points produces analgesia in animals and in people
- Stimulation of non-acupuncture points does not produce analgesia although it may provide pain relief (stimulus induced analgesia and/or placebo effect)
- The analgesia produced by acupuncture is mediated via endogenous opioids (endorphins)

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## Acupuncture

### Analgesia

- Stimulation of Large Intestine 4 in people causes analgesia at a point on the "meridian" but little change on points off the meridian
- Genetic variation found in mice in the effectiveness of acupuncture analgesia

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Test analgesia with a pressure dolorimeter

Stimulate

Farber PL et al. Acupunct & Electro-Ther Res Int J 22:109-117, 1997

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## Complementary and Alternative Therapies for Pain

- Acupuncture - Clinical Analgesia
- Gold bead implantation in dogs with hip dysplasia
  - Two studies showed no effect
  - Most recent study showed improvement in 33/36 dogs at 6 months and a positive effect continued for two years.

*Yaeger et al. Acta Vet Scand 2007*

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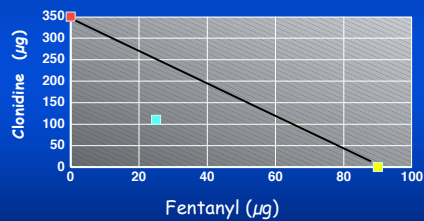
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## Synergism vs Addition



*Eisenach et al. 1994*

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## Perioperative Pain

- Conclusions
  - Manage pain using astute observation and empathy
  - Prevention is better than a cure?
  - Try to use "continuous" techniques
  - Use balanced techniques where needed
  - Response to therapy should be monitored and individualized

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## Chronic Pain

- "Pain is a more terrible lord of mankind than even death itself"

Albert  
Schwietzer



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