

# Analgesia



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# Analgesia

*derives from Greek an- ("without") and -algia ("pain")*

- Analgesia is an alteration in the sense of pain without loss of consciousness.
- Analgesia may occur in the CNS or in peripheral nerves and nociceptors
- Perception of pain can be modified by the body according to the Gate Control theory of pain

*Melzack & Wall*

to understand

**ANALGESIA,**

one needs to understand

**PAIN**

*"an unpleasant sensory and emotional experience  
associated with actual or potential tissue damage..."*

*International Association for the Study of Pain*

# Pain is subjective



*Pain is whatever the experiencing person says it is, existing whenever he says it does*

*Margo McCaffery, 1968*

**Pain** is part of the body's **defense system** - triggering mental and physical behavior to end the painful experience.

**Pain** is a conscious experience.

**Nociception** - the unconscious activity induced by a harmful stimulus in sense receptors, peripheral nerves, spinal column and brain.

## **Adaptive mechanisms:**

Noxious stimulus → unpleasant sensation (PAIN) → AVOID

Acute inflammation → HYPERALGESIA → minimisation of contact with or movement of affected structure → healing

*Ann Intern Med 2004; 140:441-51*

## **Nociceptive pain** - 3 types:

- 1. Superficial** somatic - caused by injury to the skin or superficial tissues  
→ sharp, well-defined, localized pain of short duration e.g. burn
- 2. Deep** somatic - originates from ligaments, tendons, bones, muscles, fasciae or blood vessels  
→ a dull, aching, poorly-localized pain of longer duration e.g. sprain
- 3. Visceral** pain - these nociceptors are located within body organs and internal cavities  
→ aching or cramping, of a longer duration than somatic pain.  
It may be well-localized, but often it is difficult to localize and exhibits "referred" pain

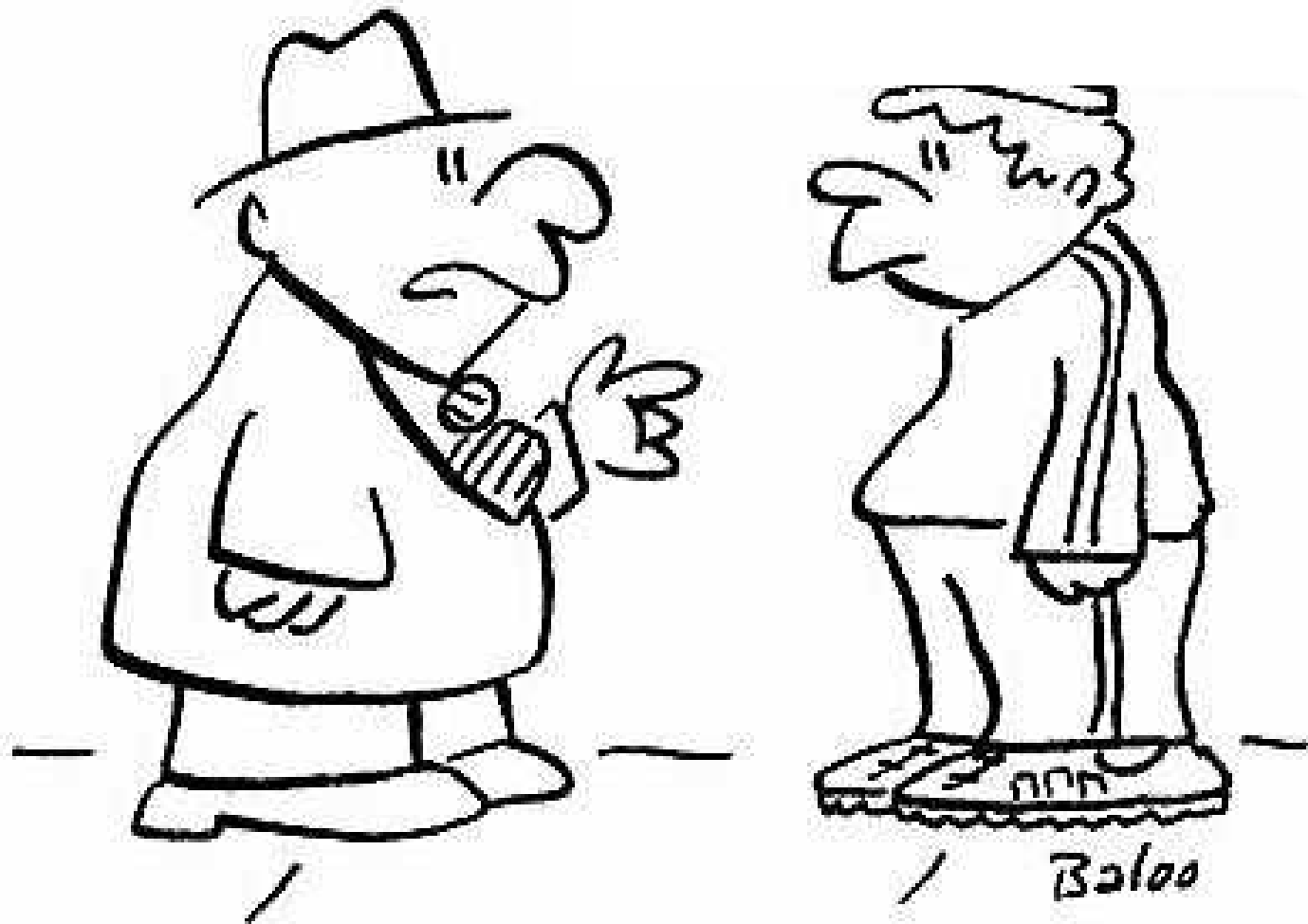
Nociception, even in the absence of pain, may trigger withdrawal reflexes and a variety of **autonomic responses** e.g.



Pallor,  
bradycardia,  
hypotension,  
light-headedness,  
nausea  
and fainting

**Pain threshold** - the least experience of pain which a subject can recognize.

**Pain tolerance**, - the greatest level of pain which a subject is prepared to tolerate.



"I don't need that exercise stuff  
— I cross the pain threshold just  
getting out of bed in the morning."

The subjective nature of pain challenges the patient-clinician relationship



**Pain experience (and expression) is affected by:**

Social and cultural factors

Secondary gain (e.g. disability payments, litigation, family dynamics)

Mood

Pain often treated with drugs that have abuse potential

## Perception of chronic pain

- Relates to genetic variability (demonstrated in twin studies and candidate genes )

*Brain 2007; 130:3041-49*

- Pain “neuromatrix” (after Melzack) – pain originates in the brain and not peripheral nerves
- Pain perception is influenced by physiological stress response

## Objective Evaluation of chronic pain

- Cognitive factors (catastrophizing) and psychological factors (depression ) influence central representation of pain

*Brain 2004;127:835-843*

- Using fMRI, the subjective report of pain relates to brain regions known to receive afferent input from painful stimuli

*Arthritis Rheum 2002; 46:1333-43*

- Fibromyalgia patients differ from healthy controls with regard to central pain representation

*Arthritis Res Ther 2006; 8:224*

- 80% of female respondents in an RA study report PAIN as their major health impairment

*Rheumatology 2003; 42:995-1000*

- Strong link between PAIN and psyche symptoms

*Ann Rheum Dis 2007; 66:1195–1201*

of 238 patients: 13% have high depression scores  
20-30% have high anxiety scores

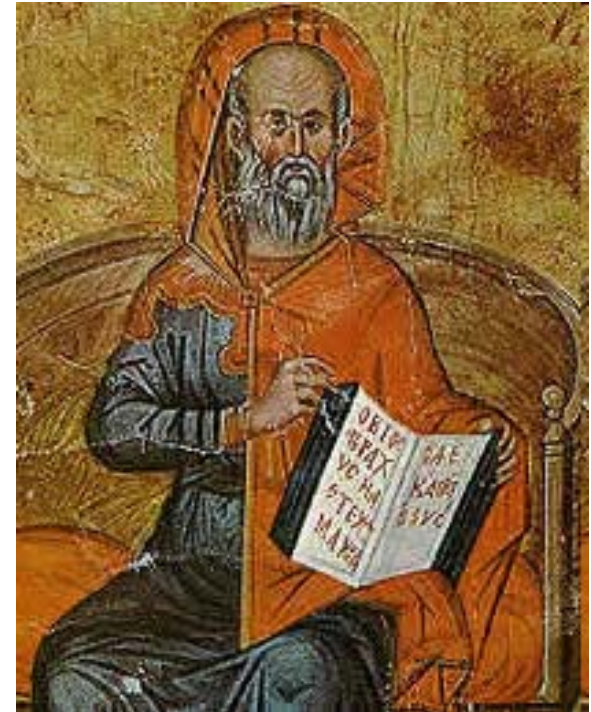
# **Classification of Analgesia**

- 1. Paracetamol**
- 2. NSAIDs**
- 3. COX-2 inhibitors**
- 4. Opiates and morphinomimetics**
- 5. Psychotropic agents**
- 6. Atypical and adjuvant analgesics**

**Hippocrates** recommended poplar tree juices for eye disease and willow bark to alleviate fever and the pain of childbirth.

Throughout Roman times willow bark was recommended for pain and inflammation.

The medicinal use of salicylate-containing plants also occurred in China and other parts of Asia.



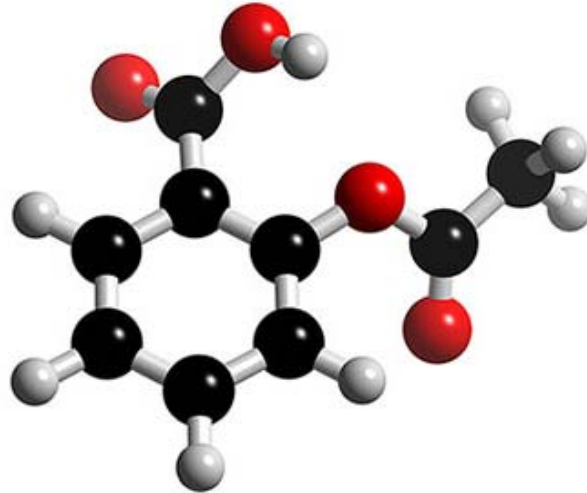


## Sir John Vane

"When a chemically diverse group of drugs all share the same therapeutic qualities and the same side effects, it is fairly certain that the actions of those drugs are based on a single biochemical intervention."

The discovery in 1971 that each of the chemically diverse members of this large group of drugs all act by inhibiting **prostaglandin biosynthesis** provided a unifying explanation of their therapeutic actions.

*Vane JR, Botting RM: The history of anti-inflammatory drugs and their mechanism of action. In Bazan N, Botting J, Vane J (eds): New Targets in Inflammation: Inhibitors of COX-2 or Adhesion Molecules. London, Kluwer Academic Publishers and William Harvey Press, 1996, p 1.*



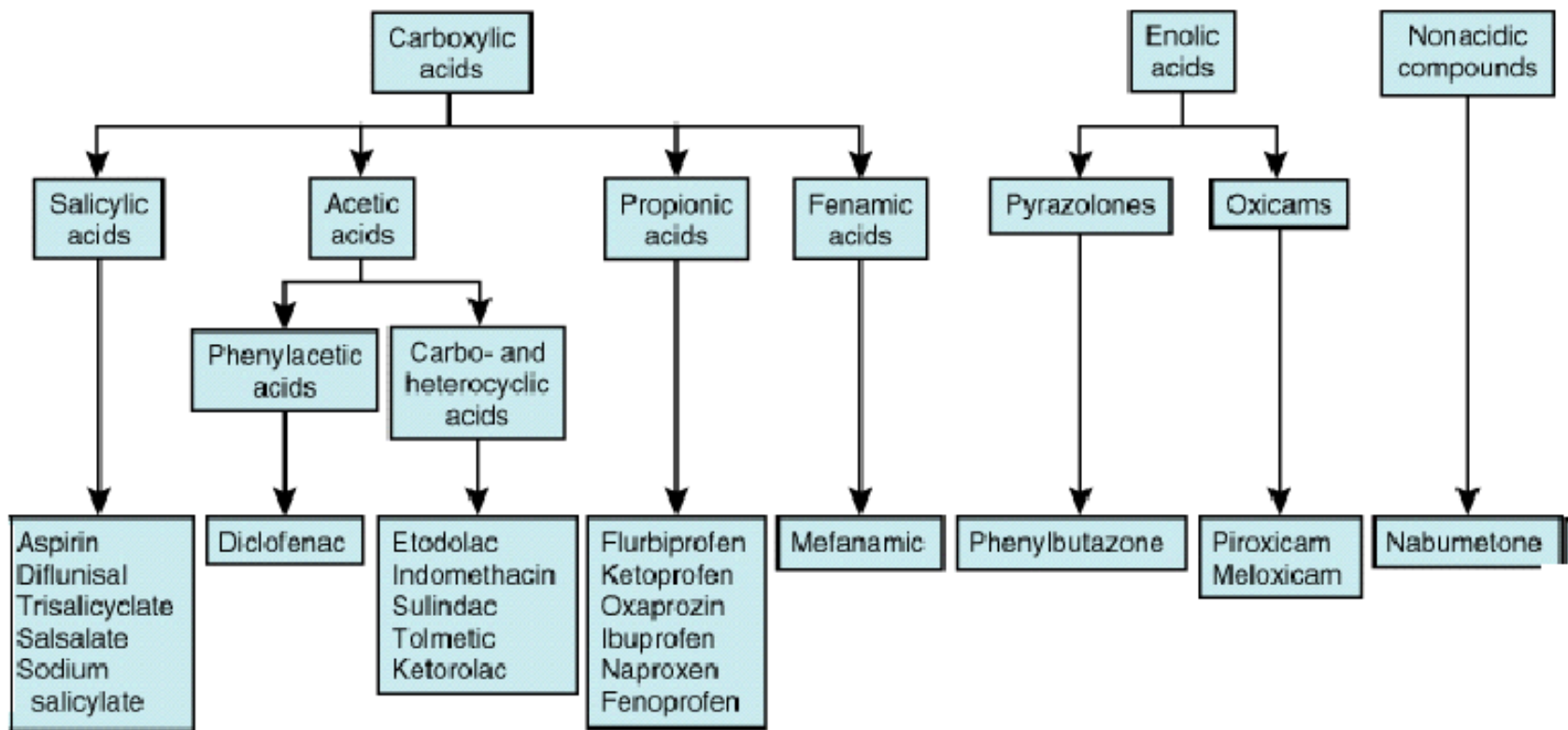
By 1999, 100 years after aspirin was introduced, two drugs that specifically inhibit COX-2, celecoxib and rofecoxib were approved for treatment of arthritis and pain

# COX-1

- Constitutively expressed in most cells
- Its expression is not altered by inflammatory stimuli.
- COX-1 is available to increase PG production acutely when an abrupt increase in arachidonic acid substrate occurs
- COX-1 is the only isoform expressed in mature platelets and is the dominant isoform in normal gastroduodenal mucosa

# COX-2

- Rapid increase in transcription in response to inflammatory signals
- COX-2 expression is highly induced by pro-inflammatory cytokines (e.g. TNF- $\alpha$  and IL-1 $\beta$ ), microbial products (e.g. lipopolysaccharide), and mitogens (e.g. phorbol ester and growth factors)
- COX-2 expression is inhibited by glucocorticoids.

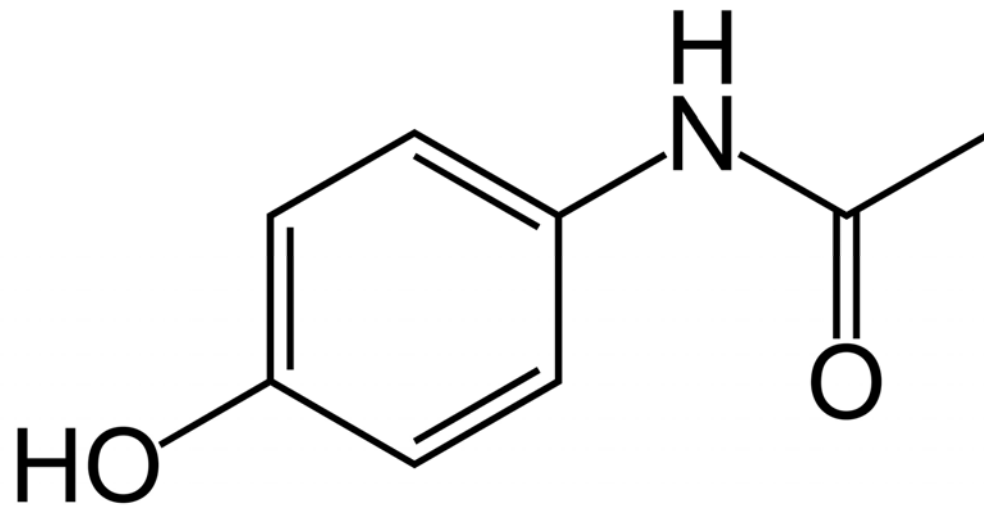


## **Analgesic effect of NSAIDs**

- NSAIDs relieve pain when used in doses lower than that required to demonstrate suppression of inflammation.
- The analgesic action of NSAIDs is likely to be due to inhibition of PG production both peripherally and centrally.
- PGs sensitize peripheral nociceptors to other chemical mediators of pain, such as bradykinin, histamine and nitric oxide
- PGs play a role in central sensitization at the spinal level.  
In the dorsal horn of the spinal cord, COX-2 is constitutively expressed and is up-regulated during inflammation.
- The analgesic activity of COX-2-specific NSAIDs is correlated with decreased csf PG levels. The analgesic effect of paracetamol occurs in the absence of significant anti-inflammatory activity, suggesting a central mechanism.



Paracetamol



- The mechanism of action of paracetamol is unclear
- The antipyretic and analgesic actions of paracetamol are due to inhibition of COX in the CNS
- At therapeutic doses, paracetamol does not inhibit COX in peripheral tissues, which could explain its very weak anti-inflammatory activity
- Paracetamol inhibits COX2 to a degree comparable with NSAIDs and COX2 inhibitors
- COX1 blockade (on platelet suppression), important for CV protection, is not achieved

# Paracetamol

Onset of action in 30min with short terminal elimination phase half-life (approx 2hrs after therapeutic dose)

Therefore needs to be taken as 1gm 4times a day

## Concerns about hepatotoxicity

- Patients with viral hepatitis given standard doses of paracetamol had increase in transaminases
- The hepatotoxic potential influenced by
  1. microsome-inducing drugs
  2. underlying disease
  3. acute or chronic alcohol use
  4. ethnicity
  5. age

Acetaminophen (paracetamol) is first-line analgesic recommended by ACR for OA

*Pain 2007; 129:279-286*



## **Paracetamol and Renal Function**

*Arch Intern Med 2004; 164:1519-1524*

The Nurses Health Study - those who took a 'lifetime intake' of at least 3000gm of paracetamol had a multivariate adjusted odds ratio of 2.19 ( $P < 0.001$ ) for reduction of 30 l/min or more of eGFR compared with those who took <100gm over the period.

## **Paracetamol and HT**

Nurses Health Study

*Hypertension 2005; 46:500-507*

>500gm/day associated with higher risk of HT  
(multivariate RR 1.99, P<0.001)

*Arch Int Med 2007; 167:394-399*

Men who used paracetamol 6-7times/week had a multivariable adjusted RR of HT of 1.34 (95% CI) compared with non-users (P=0.01 for trend)

## **Paracetamol and GI side effects**

From UK GP Research Database

*Basic Clin Pharmacol Toxicol 2006; 98:297-303*

Analysis of 1494 cases and 9532 controls:

- Paracetamol was associated with a small risk of upper GI S/E :

RR 1.3% [95% CI]

- RR is increased to 3.6 if >2gm paracetamol consumed/day
- RR is 13.2 if NSAIDs and paracetamol at >2gm/day was used

# **NSAIDs**

Cardiovascular risk

MI risk differs between NSAIDs and COX2s

Diclofenac RR of 1.4 (95%CI)

## Upper GI Risk

*Gut 2006; 55:1731-38*

Naproxen was associated with highest risk of GI bleeding (RR 7.3, 95% CI)

Combination with low-dose aspirin increased RR to 12.7

*Lancet 2007;369:1621-26*

Study of 273 pts with history of NSAID-induced GI ulceration

Randomised to Celecoxib + esomeprazole or Celecoxib + placebo

No patient on combination had a re-bleed vs. 12 who rec'd Celecoxib alone  
(P= 0.0004)

*Lancet 2007; 370:2138-2151*

Excellent review on evidence & controversies surrounding COX2s and NSAID prescription

Aspirin + COX2 co-prescribed reduce incidence of MI

*Clin. Gastroenterol. Hepatal. 2007; 5:1167-74*

Incidence of GI ulcers no different between patients on  
COX2 + aspirin vs. NSAID, aspirin + PPI

Low dose aspirin with COX2 is preferable to  
non-selective NSAIDs, given similar anti-inflammatory properties,  
superior GI tolerability and absence of interaction with aspirin

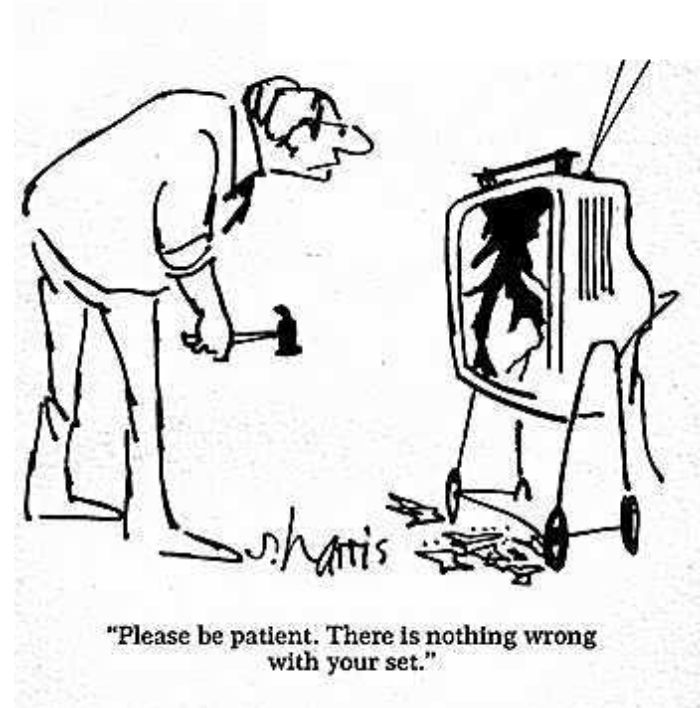
## **Hepatic Risk**

*Fundam Clin Pharmacol 2006; 20:391-395*

14% of all AE in NSAIDs were for hepatotoxicity

- **Aging** is accompanied by changes in physiology resulting in altered **pharmacokinetics and pharmacodynamics**

- Decreased drug clearance may be the consequence of reductions in hepatic mass, enzymatic activity, blood flow, renal plasma flow, GFR and tubular function
- The elderly are more likely to experience adverse GI and renal effects related to NSAIDs
- The elderly have more illnesses and take more medications, increasing the possibility of drug-drug interactions
- Older patients may also be more likely to self-medicate or make errors in drug dosing



# COX2-specific vs. non-specific NSAIDs

- *If cost were not a consideration ...*

there is no situation in which nonspecific NSAIDs, other than aspirin for cardiovascular prophylaxis, has an advantage over COX-2's

- Patients at high risk of ulcers that require aspirin for cardio-prophylaxis **require** ulcer prophylaxis (with misoprostil or PPI), regardless of NSAIDs.

# Opioids

Weak – codeine, dextropropoxyphene and tramadol

Strong – morphine & oxycodone

*CMAJ 2006;174: 1589-94*

Meta-analysis of effectiveness of opioids for non-cancer pain

- 33% abandon therapy because of SE



*Arthritis Rheum 2006:55:35-41*

- 4% RA patients use opioids in 1 year and 24% at some point in the 6yr period of review (esp. tramadol, and codeine)
- Association between chronic opiate use and psychiatric medication co-prescription

# Tramadol

Weak opiate with serotonin-releasing and nor-adrenaline reuptake inhibitory properties

Fewer SE on GI cf. codeine

No effect on renal system

but, can lower seizure threshold



*Cochrane review of tramadol for OA (2006)*

Tramadol patients had a 12% relative decrease in pain relative to baseline

SE were common, esp. nausea, dizziness, constipation, fatigue and headache

Number needed to harm for major AE was 8

Tramadol, if tolerated, provides helpful increment in the analgesia ladder



"I'M THE ONE WITH THE MEDICAL DEGREE, I'LL DETERMINE  
IF YOUR BACK IS BOTHERING YOU, OR NOT..."

*Ann Intern Med 2007; 147:505-14*

## **A review of evidence for medication in chronic low back pain**

Tramadol and stronger opioids show moderate benefit

– but only 2/11 studies are placebo controlled!!

### ***Recommendations -***

- paracetamol first for mild - moderate pain
- for more severe pain balance risks of improved analgesia from NSAID with the GI and CV risks
- trial of opioids recommended for severe pain in selected patients

## Alpha-2-delta ligands

**Gabapentin and pregabalin** can act as ligands for alpha-2-delta subunits of voltage-gated calcium channels



Reduces Ca flux



Reduces neurotransmitter release associated with activation of excitatory aa and substance P

*These drugs work in Fibromyalgia...*

*Arthritis Rheum 2005;52:1264-1273*

**Pregabalin** at 450mg/day produces 50% reduction in endpoint mean pain cf. placebo (P<0.001)

Also improvement in sleep, fatigue and QoL

But no improvement in tender point pain threshold

## **Norepinephrine and serotonin reuptake inhibitors (Tricyclics)**

- Norepinephrine and serotonin are important mediators of descending inhibition of noxious signalling and also NB in stress-response pathways
- Meta-analyses have demonstrated efficacy of tricyclics in Fibromyalgia  
*Arthritis Res Ther 2006;8:212-232*
- however there is mixed efficacy for selective SRIs

<b>Agent</b>	<b>Class</b>	<b>Mechanism</b>	<b>Comments</b>
<b>Gabapentin</b>	Anticonvulsant	$\alpha$ -2- $\delta$ ligand Affects Ca flux and release of excitatory aa	Divided doses 1200-2400mg/day
<b>Pregabalin</b>	Anticonvulsant	$\alpha$ -2- $\delta$ ligand Affects Ca flux and release of excitatory aa	Divided doses 2x/day 300-450mg /day
<b>Amitryptaline</b>	Antidepressant	Noradren. & serotonin reuptake inhibitors with anticholinergic, antiadrenergic, antihistaminergic and quinidine-like effects	Pleotropic actions increase side-effects Avoid in elderly
<b>Fluoxetine</b>	Antidepressant	SRI	More effect on mood than pain
<b>Duloxetine</b>	Antidepressant	Balanced Norepineph & SRI	For neuropathic pain GI side-effects + insomnia
<b>Tramadol</b>	Analgesic	M-opioid-receptor agonist Noradren + serotonin reuptake inhibition	Can get withdrawal: also abuse & dependence

***Other strategies for relief of pain related to Rheumatic disorders for which there is some evidence:***

Weight loss if appropriate

Footwear

Walking aides

Education

Self-management schemes

Exercise

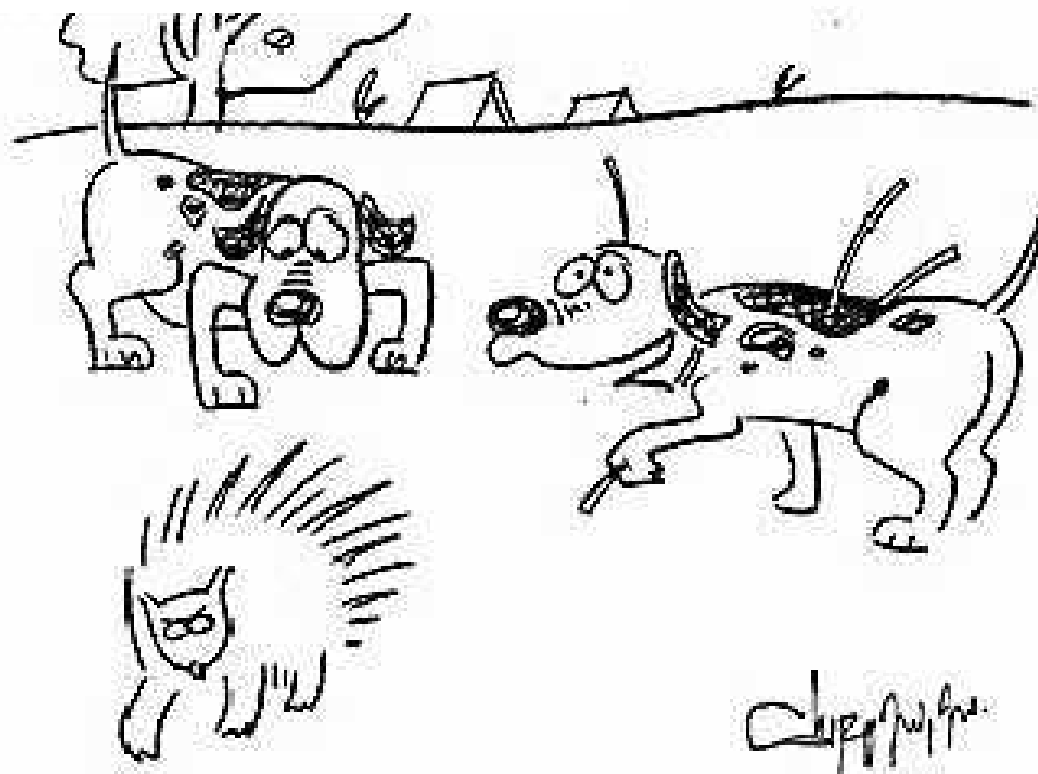
Physiotherapy

Acupuncture

Local treatment with IA steroids

TENS

Surgery



Hey! my lower back pain! It's gone!"

## Summary

Pain is highly subjective

Chronic pain occurs when there is an uncoupling of Nociceptive processes from noxious stimulation

The analgesic action of NSAIDs is likely to be due to inhibition of PG production both peripherally and centrally

The mechanism of action of paracetamol is unclear

Trial of opioids is recommended for severe pain in selected patients

Many patients with primary rheumatic disease have co-morbid Fibromyalgia

WANNA PAY EXTRA FOR  
THE PAINKILLER OR  
GET THE FREE ONE ?

