# Chronic Pain – Mechanisms and Management principles

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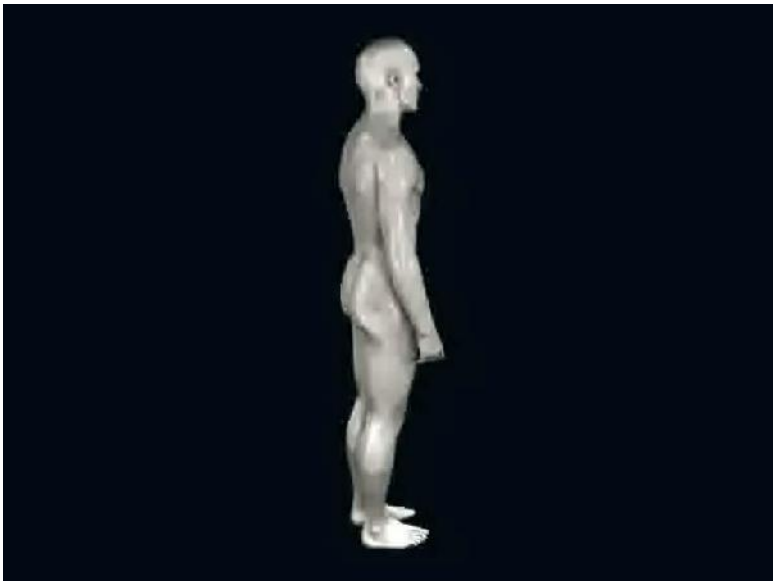
# What is pain?

International Association for the Study of Pain (IASP)

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'



# Pain pathways

Learning
Neuroplasticity

Central
sensitisation

Brain neuromatrix

Medulla

Central
sensitisation

Spinal cord: dorsal horn

Peripheral
sensitisation

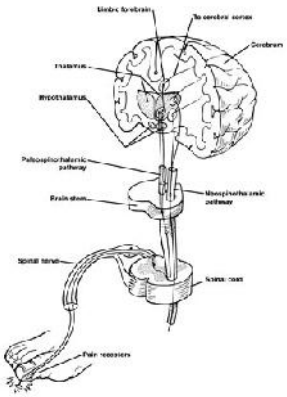
Nociceptive neurons

Nociception

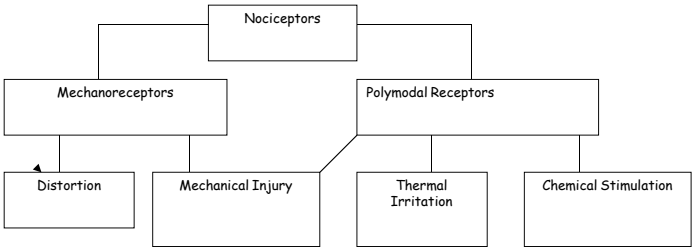
Thermal

Mechanical

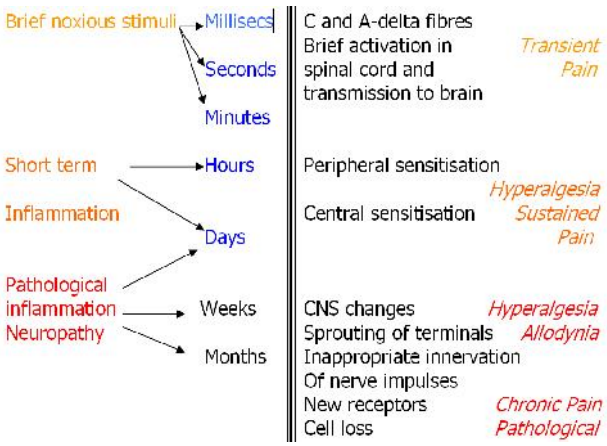
Chemical



# Nociception: Transduction



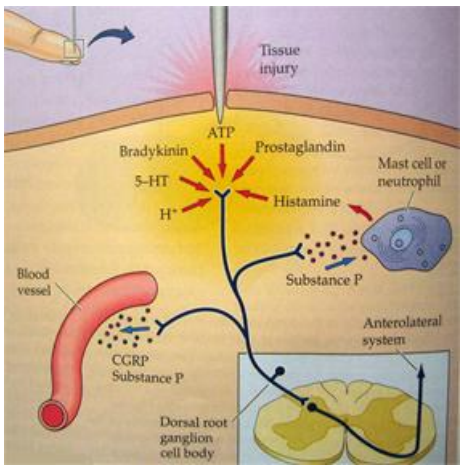

# Sensitisation – development of allodynia



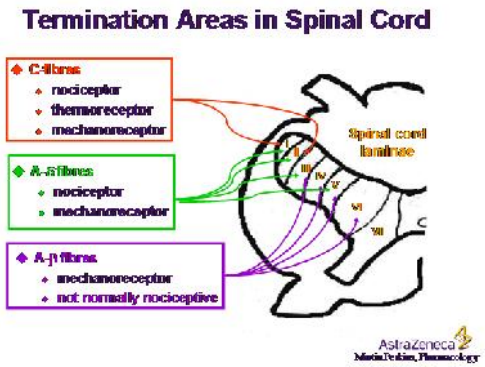
# Nociception Transduction

| Substance | Source | Effect on Nerve |
|---|---|---|
| Histamine | Platelets, mast cells | Activates |
| Bradykinin | Plasma | Activates |
| Substance P | Nerve terminals | Sensitises |
| Prostaglandins | Damaged Cells | Sensitises |
| Interleukins | Mast cells | Activates, sensitises |
| Leukotrienes | Damaged cells | Sensitises |
| TNF-α | Macrophages | Activates, sensitises |
| Protons | Tissue damage | Activates |

# Nociception Transmission



## Spinal cord Dorsal horn




## Spinal cord Cartesian model

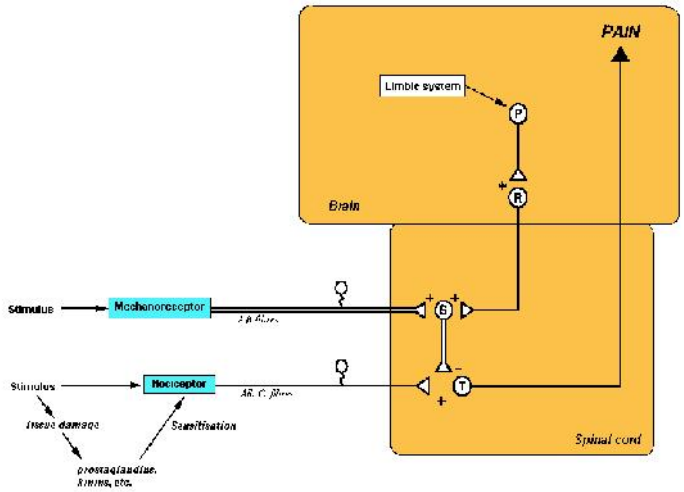
- Pain can be relieved by *counter-irritation*
- Gross tissue damage not be accompanied by pain
- Minor damage results in exquisite ‘burning’ pain
- Phantom limb pain

## Spinal cord Gate control

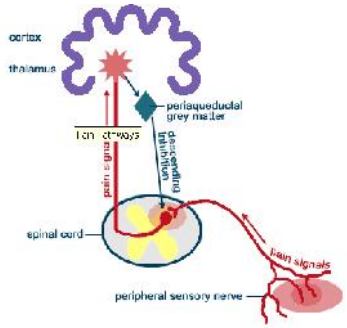
Ronald Melzack

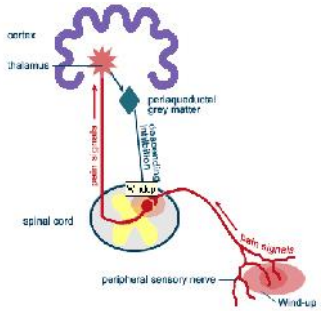
Patrick Wall

## Gating at the spinal cord

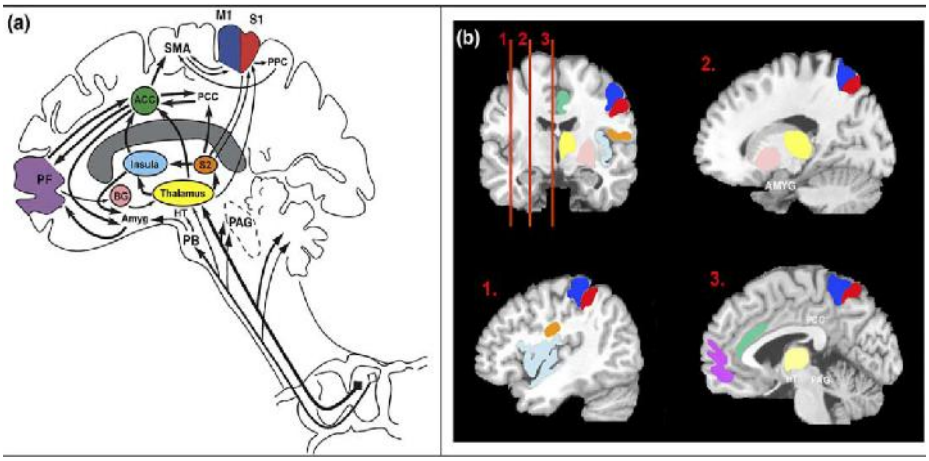


## Spinal cord. Wind-up.

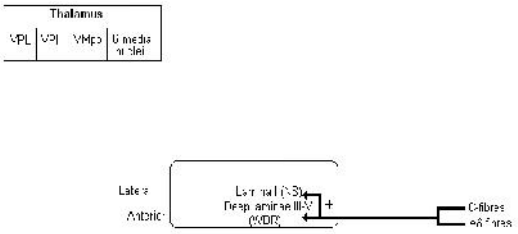



## Neuroanatomy of Pain



# Acute pain neuromatrix

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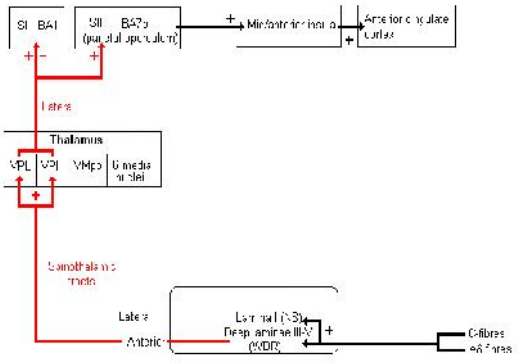

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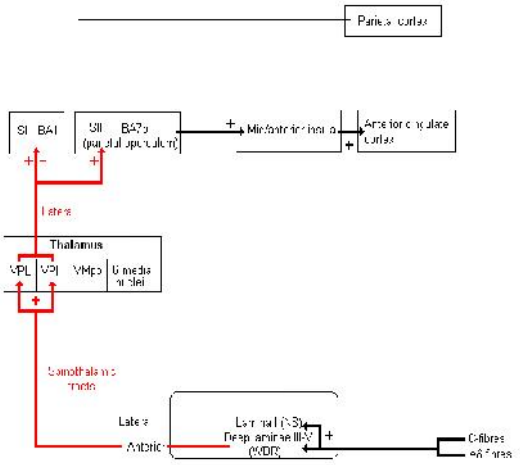


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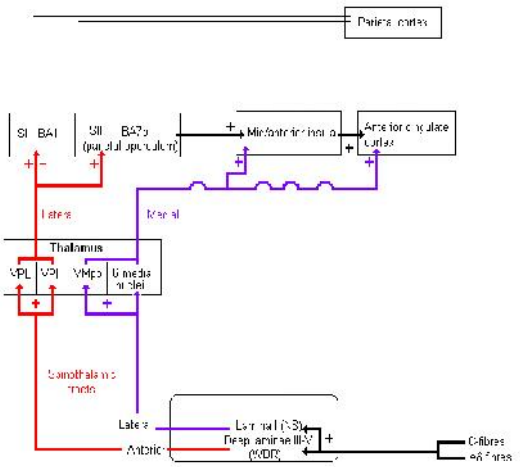

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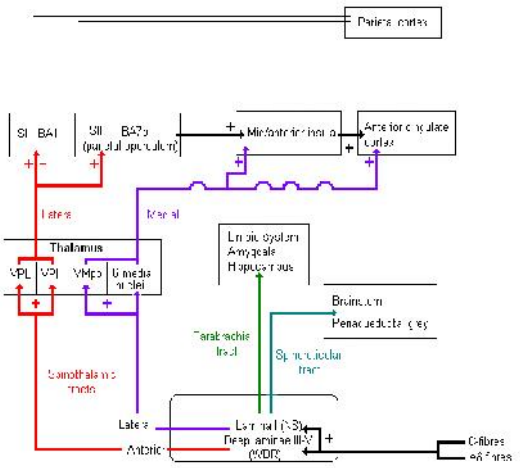


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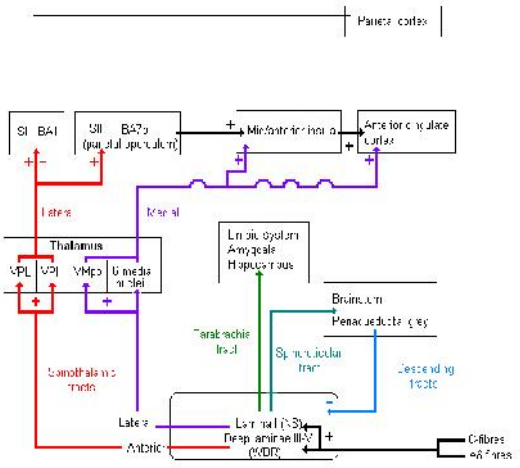

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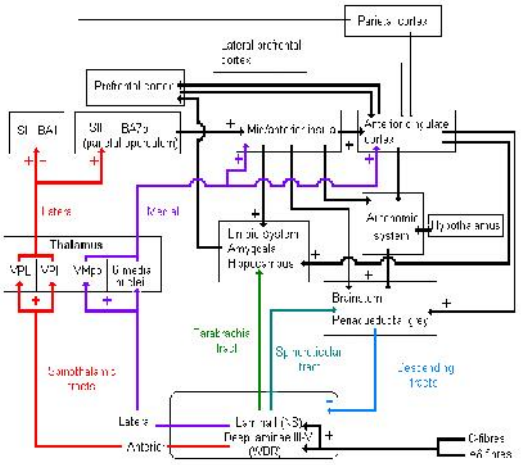
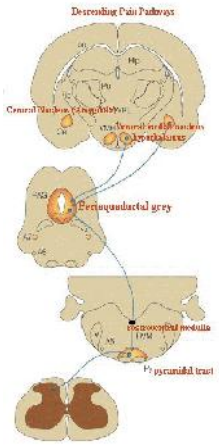



# Recap

- Nociception
- Peripheral Sensitisation
- Spinal gate
- Brain pathways
- Descending systems

# Spinal cord Descending systems

- Serotonergic
- Adrenergic
- Opioid
  - Diffuse Noxious Inhibitory Control (DNIC)

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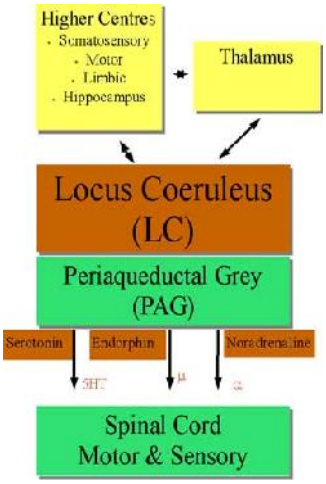
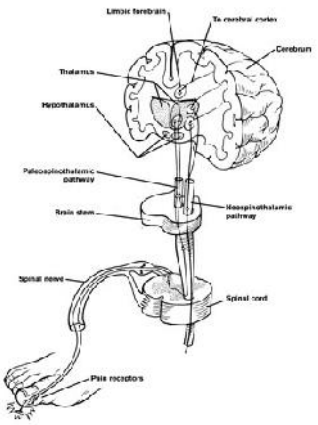


# Development of chronic pain


- Acute pain
  - Usually obvious tissue damage
  - Protective function
  - Increased nervous system activity[1]
  - Pain resolves upon healing

- Chronic pain
  - Pain beyond expected period of healing
  - Pain no longer serves a useful purpose
  - Changes in pain signalling and detection[2]
  - Degrades health and function

1. Woolf CJ, Costigan M. Proc Natl Acad Sci U S A. 1999;96:7723-30. 2. Woolf CJ, Max MB. Anesthesiology. 2001;95:241-9.

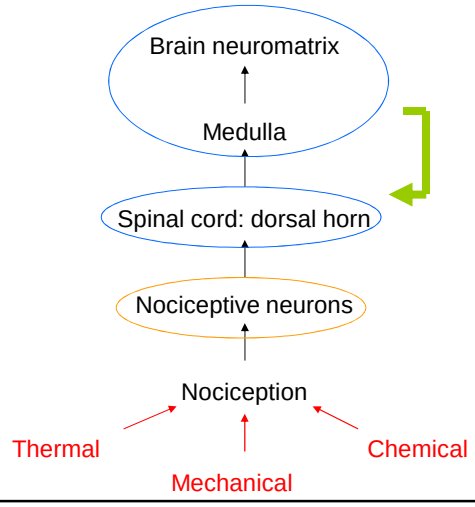
# Chronic pain has systemic consequences

| Functional Domain | Stress Responses to Pain | Examples of Clinical Manifestations |
|---|---|---|
| Endocrine/metabolic | Altered release of multiple hormones (e.g., ACTH, cortisol, catecholamines, insulin) with associated metabolic disturbances | Weight loss<br>Fever<br>Increased respiratory and heart rate<br>Shock<br>Increased blood sugar |
| Cardiovascular | Increased heart rate<br>Increased vascular resistance<br>Increased blood pressure<br>Increased myocardial oxygen demand<br>Hypercoagulation | Unstable angina<br>Myocardial infarction<br>Deep vein thrombosis |
| Respiratory | Decreased air flow due to involuntary (reflex muscle spasm) and voluntary ("splinting") mechanisms that limit respiratory effort | Atelectasis<br>Pneumonia |
| Gastrointestinal | Decreased rate of gastric emptying<br>Decreased intestinal motility | Delayed gastric emptying, constipation, anorexia, ileus |
| Musculoskeletal | Muscle spasm<br>Impaired muscle mobility and function | Immobility<br>Weakness<br>Fatigue |
| Immune | Impaired immune function | Infection |
| Genitourinary | Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance | Decreased urine output<br>Hypertension (fluid retention)<br>Electrolyte disturbances |

## Structured approach to the patient in chronic pain

Hague, Shenker, BERH, 20

***Anatomy***

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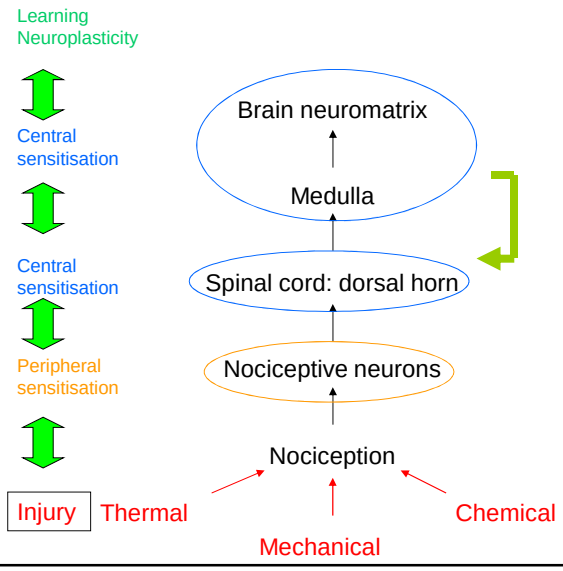
Hague, Shenker, BERH, 20

***Physiology*** ***Anatomy***



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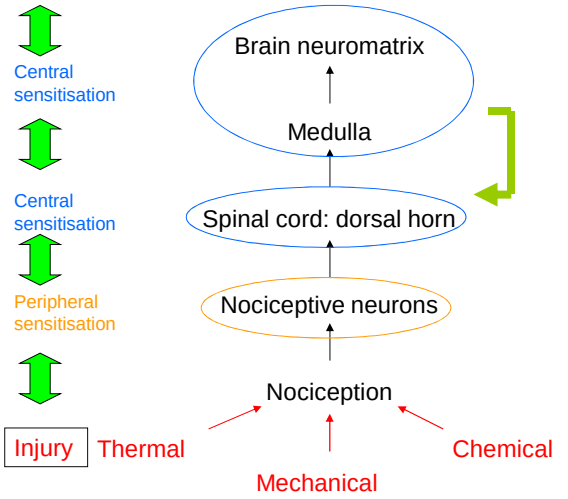
Hague, Shenker, BERH, 20




Age <40

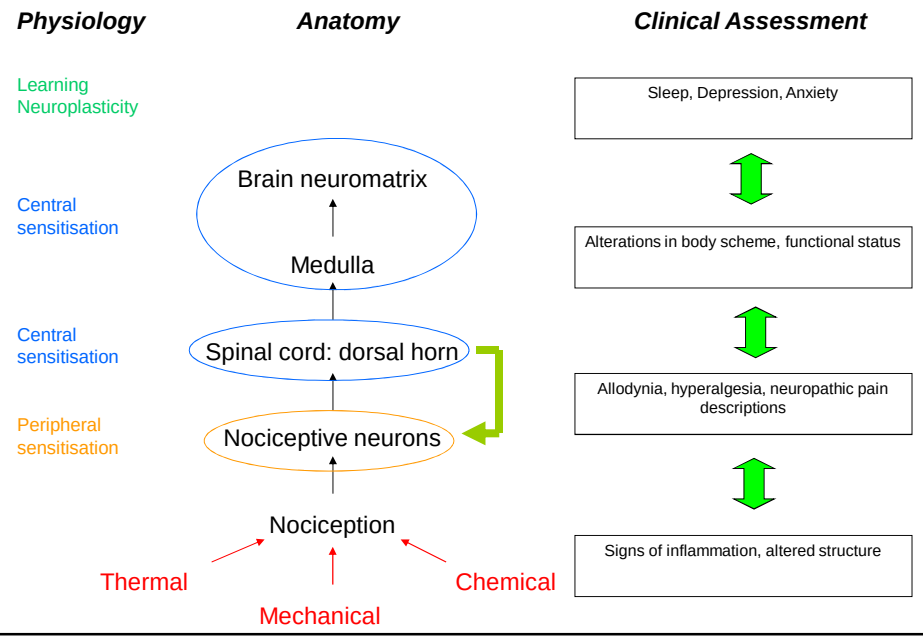
Depression
High anxiety trait
Less perceived Social Support
"Anger style" of emotional regulatio
>1 year duration

Pain report >4/10
Altered body scheme (dysynchiria)
>1 limb affected

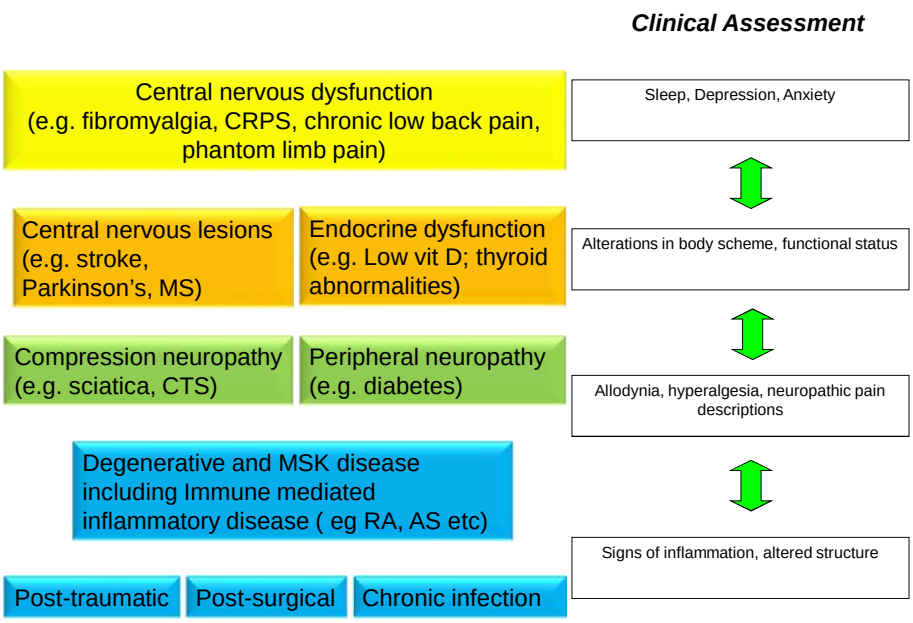
Post-operative complications
Cold limb presentation

Leg affected (vs arm)
Severity of injury

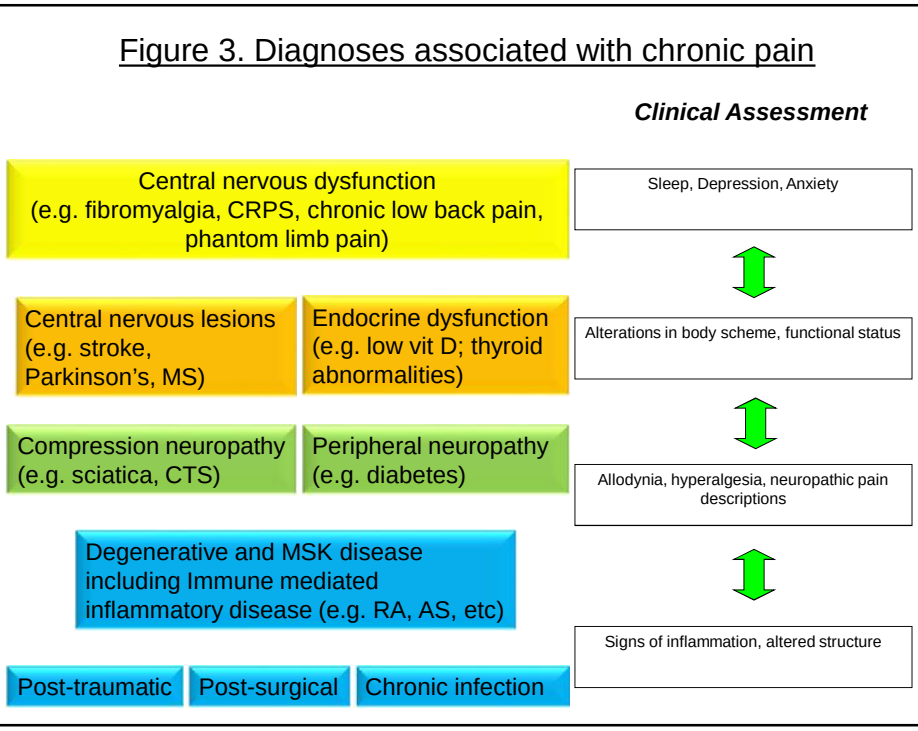
## Figure 2. Structured approach to the patient in chronic pain



## Figure 3. Diagnoses associated with chronic pain




## Figure 3. Diagnoses associated with chronic pain



## Structured approach to the patient in chronic pain

***Physiology***

Learning
Neuroplasticity

Central
sensitisation

Central
sensitisation

Peripheral
sensitisation

Injury

## Structured approach to the patient in chronic pain

***Physiology***

Learning
Neuroplasticity

Central
sensitisation

Central
sensitisation

Peripheral
sensitisation

Injury

***History***

Psychosocial contributors

***Questionnaires***
*HAD*
*NLSQ (depersonalisation)*

*BPI*

*Functional questionnaires*
- *UEFI/LEFI*
- *HAP*
- *TSS*

Medications –
- Previously tried
- Dosages
- Side Effects

Fracture history

## Structured approach to the patient in chronic pain

| ***Physiology*** | ***History*** | ***58 year old lady*** |
|---|---|---|
| Learning Neuroplasticity | Psychosocial contributors | Normal relationships, money. No litigation/insurance work |
| ↕ | ***Questionnaires*** | Sleep disturbed |
| Central sensitisation | *HAD* | *11/21 Anx ; 4 / 21 Dep* |
| ↕ | *NLSQ (depersonalisation)* | *3.4/6* |
| Central sensitisation | *BPI* | *3-7/10, average of 5/10* |
| ↕ | *Functional questionnaires* | |
| Peripheral sensitisation | *UEFI/LEFI* | *38/80 Upper & 25 /80 Lower* |
| ↕ | *HAP* | *57/94 Max; 34/94 adjusted* |
| Injury | Therapies | Physiotherapy |
| | Medications – Previously tried | NSAID; Codeine; Paracetamol |
| | Dosages | Amitriptyline 10mg |
| | Side Effects | |
| | Fracture history | |

## Structured approach to the patient in chronic pain

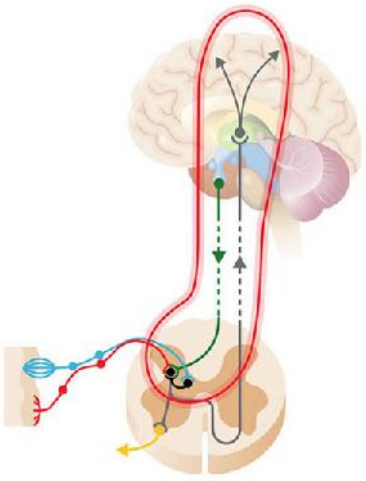
| ***Physiology*** | ***Examination*** |
|---|---|
| Learning Neuroplasticity | Mood assessment |
| ↕ | Guarding / Distraction |
| Central sensitisation | Body scheme |
| ↕ | Allodynia |
| Central sensitisation | Hyperalgesia |
| ↕ | Limb Movement |
| Peripheral sensitisation | Active/passive |
| ↕ | Site assessment |
| Injury | Skin |
| | Inflammation |

## Structured approach to the patient in chronic pain

| ***Physiology*** | ***Examination*** | ***58 year old lady*** |
|---|---|---|
| Learning Neuroplasticity | Mood assessment<br>Guarding / Distraction | Anxious, two crutches<br>Present |
| ↕ Central sensitisation | Body scheme | Abnormal |
| ↕ Central sensitisation | Allodynia<br>Hyperalgesia | Allodynia ++<br>Hyperalgesia ++ |
| ↕ Peripheral sensitisation | Limb Movement<br>Active/passive | Hip, knee, ankle OK<br>Toes much reduced |
| ↕ Injury | Site assessment<br>Skin<br>Inflammation | Colour and temp asymmetry<br>Swelling<br>Normal sweating, skin, nails |

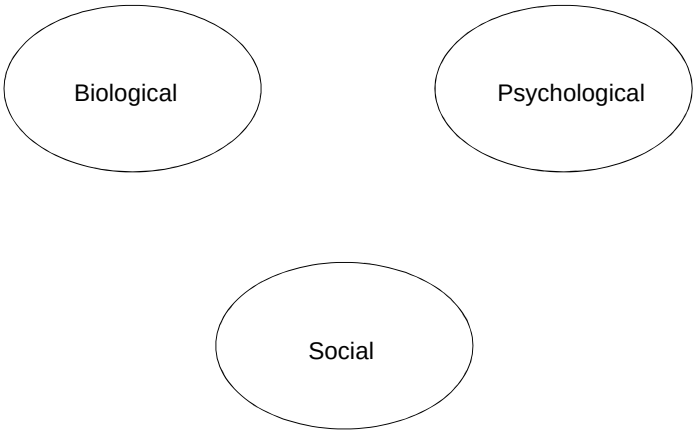
# Importance of early and effective treatment of pain

- A lower degree of chronicity relates to a better therapy result[1]
- Chronic pain is associated with morphological changes in the CNS [2,3]
- Once present, it is often persistent and seldom totally resolves even with treatment [4]
- Chronic pain causes tremendous personal suffering [5] and marked negative effects on wellbeing and quality of life [6]

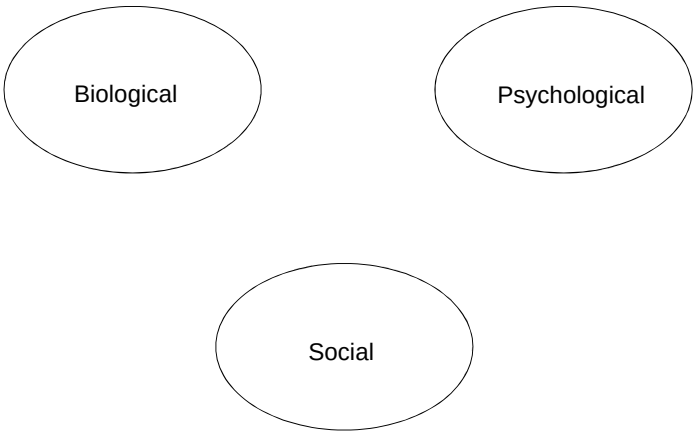


1 Schulte E *et al.* Eur J Pain 2010;14:308.e1-308.e10. 2 Tracey I, Bushnell MC. J Pain 2009;10:1113-20.
3 Apkarian AV *et al.* J Neurosci 2004;24:10410-5. 4. Elliott AM *et al.* Lancet 1999;354:1248–1252. 5. Management of Chronic pain in Adults, NHS Quality Improvement Scotland 2006. 6. Breivik H *et al.* Eur J Pain 2006;10:287-333.

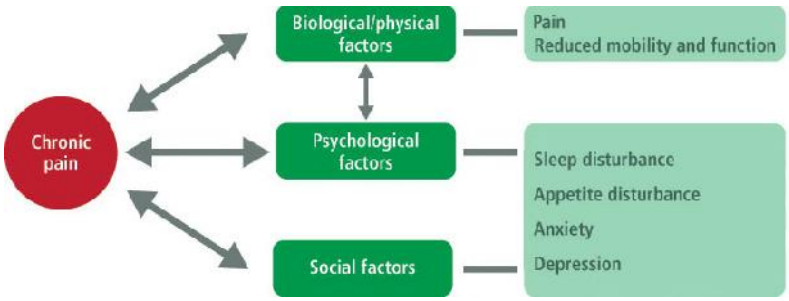
# Biopsychosocial model




# Biopsychosocial model



# Why is a biopsychosocial perspective important?




Edwards D *et al.* Pain Pract 2006;6:242-53.

# 4 pillars of care

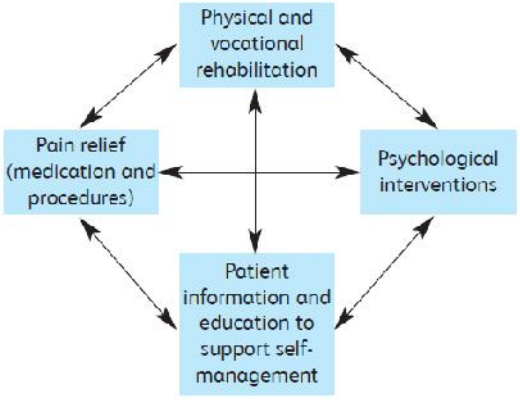



Fig 2 Four pillars of treatment for CRPS – an integrated interdisciplinary approach

# What is patient-centred care?

- The term patient-centred care means
  that healthcare professionals:
  - Engage with patients at a deep level, which includes understanding both their illness and how it will affect their life[1]
  - Take into account the patient's desire for information, share decision making, and respond appropriately[2]

1. Davies PG. J Epidemiol Community Health 2007;61:39. 2. Stewart M. BMJ 2001;322:444-5.

# Education of the patient and their relatives

- Biopsychosocial pain model
- Basic pharmacology
- Basic anatomy
- Weight management
- Information on relevant pain syndromes

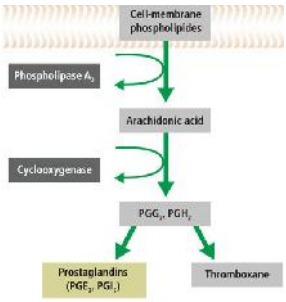
# Pharmacological approaches to chronic pain management

- Non-opioid analgesics (e.g. NSAIDs, paracetamol)
- Opioid analgesics (e.g. tramadol, codeine, morphine, oxycodone)
- Antidepressants (e.g. amytriptyline, duloxetine)
- Anticonvulsants (e.g. gabapentin, pregabalin)
- Topical analgesics (e.g. capsaicin, lidocaine 5% plaster)

# Non-opioid analgesics: NSAIDS

- E.g. aspirin, ibuprofen

| Efficacy | Mode of action | Side effects |
|---|---|---|
| Mainly act on nociceptive pain[1] | Inhibition of cyclooxygenase[1]<br>Prostaglandin synthesis decreases[1] | GI irritation/ bleeding[1]<br>Renal toxicity[1]<br>Potential drug-drug interactions<br>Cardiovascular side-effects (Cox-2)[1] |

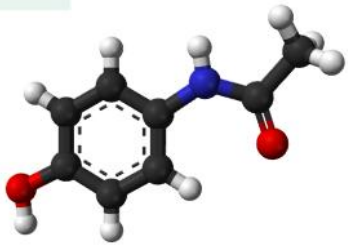



1. Warner TD, Mitchell JA. FASEB J 2004;18:790-804.

# Other non-opioid analgesics: paracetamol

- Aniline derivative e.g. Panadol

| Efficacy | Mode of action | Side effects |
|---|---|---|
| Analgesic and antipyretic effects<br>No anti-inflammatory action | Inhibition of central prostaglandin synthesis<br>Not been fully explained | Risk of toxic liver damage |



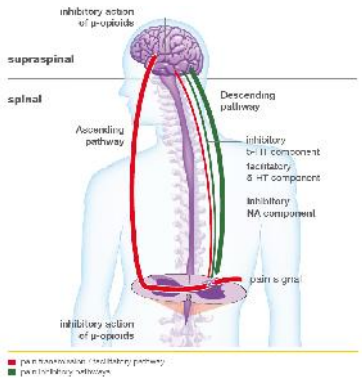
Mattia A, Coluzzi F. Minerva Anestesiol. 2009;75:644-53.

# Opioid analgesics

- Weak opioids: e.g. tramadol and codeine, strong opioids: e.g morphine and

| Efficacy | Mode of action[1] | Side effects[2,3] |
|---|---|---|
| Mainly effective in nociceptive pain<br>Less effective in chronic states<br>Only partially effective in neuropathic pain | Activate the endogenous analgesic system<br>- Stimulate receptors in the limbic system to eliminate the subjective feeling pain<br>- Affect descending pathways that modulate pain perception<br>- Reduce ascending pain signal transmission in the spinal cord | Nausea<br>Vomiting<br>Constipation<br>Dizziness or vertigo<br>Somnolence<br>Dry skin, pruritus |

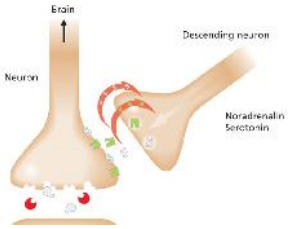
**Endogenous pain modulation**




1. Hawthorn J & Redmond K (1998) Pain causes and management. Blackwell Science Ltd. 2. Furlan AD *et al.* CMAJ 2006;174:1589-94.
3. Jacobsen R *et al.* J Opioid Manag 2007;3:207-14.

# Antidepressants: TCAs

| Efficacy | Mode of action | Side effects |
|---|---|---|
| Neuropathic pain[1]<br>Complex regional pain syndrome[1]<br>Tension headache | Inhibition of neuronal reuptake of noradrenaline and serotonin (5-HT) | Constipation[1]<br>Dry mouth[1]<br>Somnolence[1]<br>Abnormalities in heart rate or rhythm[1]<br>Insomnia<br>Increased appetite |

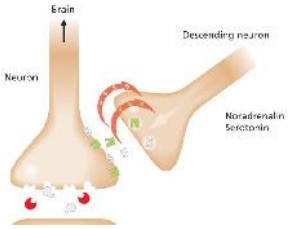



1. Dworkin RH *et al.* Arch Neurol. 2003;60:1524-34.

## Antidepressants: Selective serotonin and noradrenalin reuptake inhibitors (SSRIs & SNRIs)

- E.g. duloxetine, venlafaxine

| Efficacy | Mode of action | Side effects (duloxetine) |
|---|---|---|
| Neuropathic pain[1,2]<br>SNRIs are better analgesics than SSRIs | Selectively inhibit reuptake of noradrenaline or serotonin or both<br>Provide analgesia by intensifying descending inhibition | Nausea & Vomiting[2]<br>Constipation[2]<br>Somnolence[1,2]<br>Dry mouth[2]<br>Increased sweating[2]<br>Loss of appetite[2] |

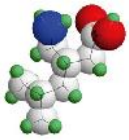



1. Quilici S *et al.* BMC Neurol. 2009;9:6. 2. Attal N *et al.* Eur J Neurol. 2006;13:1153-69.

# Anticonvulsants

| Efficacy | Mode of action | Side effects |
|---|---|---|
| Neuropathic pain[1,2] | Different modes of action:<br>**Gabapentin:** binds to presynaptic voltage-dependent calcium channels[1]<br>**Pregabalin:** interacts with special N-type calcium channels[1]<br>**Carbamazepine:** blocks $Na^{+1}$ and $Ca^{2+}$ channels | Sedation[1,2]<br>Dizziness[1,2]<br>Ataxia[1]<br>Peripheral oedema[1,2]<br>Nausea[1,2]<br>Weight gain[3] |

**Gabapentin**



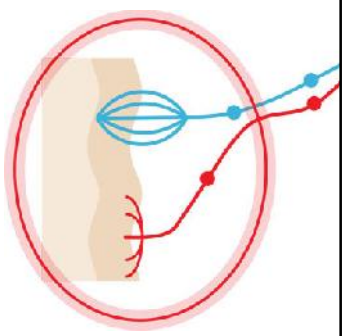
**Pregabalin**

**Carbamazepine**

1. Attal N *et al.* Eur J Neurol. 2006;13:1153-69. 2.Dworkin RH *et al.* Arch Neurol. 2003;60:1524-34.
3. Ettinger AB, Argoff CE. Neurotherapeutics. 2007;4:75-83.

# Topical analgesics

- Main categories of topical analgesics include:
  - Rubefacients: traditional formulations based on salicylate and nicotinate esters, capsaicin and capsicum extracts and derivatives
  - NSAIDs: diclofenac, felbinac, ibuprofen, ketoprofen, piroxicam, naproxen, flurbiprofen and other NSAIDs
  - A miscellaneous group: including benzydamine, mucopolysaccharide polysulphate, salicylamide and cooling sprays
  - Lidocaine 5% medicated plaster
- Topical analgesics reduce pain impulses transmitted by:
  - A-delta-fibres
  - C-fibres
- Main side effects are localised application site reactions, including:[1-4]
  - Rash
  - Pruritus
  - Erythema



1. Boots Company PLC. Boots Pain Relief Heat Rub SmPC. January 2008. 2. Diomed Developments Limited. Ibuleve Gel SmPC. January 2009. 3. Meda Pharmaceuticals. Difflam Cream SmPC. March 2010.
4. Grünenthal Ltd. Versatis 5% Medicated Plaster SmPC. September 2009.

# Main side effects of pharmacological treatments

| Opioids[1,2] | NSAIDs[3] |
|---|---|
| Nausea | Gastrointestinal irritation/bleeding |
| Vomiting | Renal toxicity |
| Constipation | Potential drug-drug interactions |
| Dizziness or vertigo | Cardiovascular side effects (e.g. myocardial infarction, stroke and hypertension) with some selective Cox-2 inhibitors |
| Somnolence | |
| Dry skin, pruritus | |
| **Anticonvulsants[4,5,6]** | **SNRIs[5,7]** |
| Sedation | Nausea |
| Dizziness | Vomiting |
| Ataxia | Constipation |
| Peripheral oedema | Somnolence |
| Nausea | Dry mouth |
| Weight gain | Increased sweating |
| | Loss of appetite |

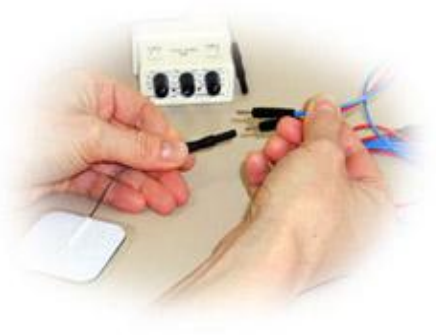
1. Furlan AD *et al.* CMAJ 2006;174:1589-94. 2. Jacobsen R *et al.* J Opioid Manag 2007;3:207-14. 3. Warner TD, Mitchell JA. FASEB J 2004;18:790-804. 4. Ettinger AB, Argoff CE. Neurotherapeutics 2007;4:75-83. 5. Attal N *et al.* Eur J Neurol 2006;13:1153-69. 6. Dworkin RH *et al.* Arch Neurol 2003;60:1524-34. 7. Quicili S *et al.* BMC Neurol 2009;9:6.

# Physiotherapy and strength training

- Physiotherapy and strength training aim to relieve pain and improve mobility
- Various methods are used, including:
  - –Massage
  - –Joint mobilisations
  - –Manipulation
  - –Electrotherapy / US

# Peripheral stimulation and interventional therapy

- Peripheral stimulation, e.g.
  - Transcutaneous electrical nerve stimulation (TENS)
  - Acupuncture
- Interventional therapy, e.g.
  - Nerve blocks
  - Spinal stimulation
  - Surgical pain management



# Complementary / alternative medicine


- Some more established than others

eg. Chiropracter, Osteopath, Acupuncture, Homeopathy, Herbal, Aryuvedic

Vs

Beauty therapy, Colonic hydrotherapy, Colour Breathing, Hopi Ear Candles, ReHarmonising

# Clinical assessment

- Peripheral (tissue) driver
  - OA, soft tissue, nerve damage, inflammation
- Peripheral sensitisation
  - Allodynia, hyperalgesia
- Central sensitisation
  - Sleep, systemic features, depersonalisation, body scheme
- Psychosocial
  - Mood, family, community, housing, benefits, litigation

# Conclusions

- Pain is complex
- Treat tissue damage and pain will go but…
  - Some damage is irreversible
  - Possible that pain exists with no damage
- Chronic pain approach helpful in parallel:
  - WHO Pain ladder
  - Adjuncts are useful
  - Biopsychosocial approach required
  - Palliate and counsel

# Chronic Pain – Mechanisms and Management principles

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