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

- Pain pathways involve the brain neuromatrix, medulla, spinal cord: dorsal horn, and nociceptive neurons.

- Nociception is the perception of pain and involves thermal, mechanical, and chemical inputs.

- Central sensitisation and peripheral sensitisation play crucial roles in pain processing.

- Neuroplasticity and learning are fundamental in the adaptation of pain responses.
Nociception: Transduction

Nociceptors
- Mechanoreceptors
- Polymodal Receptors
  - Distortion
  - Mechanical Injury
  - Thermal Irritation
  - Chemical Stimulation

Sensitisation – development of allodynia

- Brief noxious stimuli (Millisecond)
- Short term (Hours)
- Pathological inflammation (Days)
- CNS changes (Weeks)
  - Transient Pain
  - Hyperalgesia
  - Alloodynia

- Peripheral sensitisation (Minutes)
- Central sensitisation (Seconds)
- Transient Pain
  - Hyperalgesia
  - Alloodynia

- Cell loss (Minutes)
- New receptors (Seconds)
- Chronic Pain
  - Pathological
**Nociception Transduction**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
<th>Effect on Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Platelets, mast cells</td>
<td>Activates</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma</td>
<td>Activates</td>
</tr>
<tr>
<td>Substance P</td>
<td>Nerve terminals</td>
<td>Sensitises</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Damaged Cells</td>
<td>Sensitises</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Mast cells</td>
<td>Activates, sensitises</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Damaged cells</td>
<td>Sensitises</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Macrophages</td>
<td>Activates, sensitises</td>
</tr>
<tr>
<td>Protons</td>
<td>Tissue damage</td>
<td>Activates</td>
</tr>
</tbody>
</table>

**Nociception Transmission**

![Diagram of nociception transmission](image)
Spinal cord  Dorsal horn

Termination Areas in Spinal Cord

- C fibers
  - nociceptor
  - thermoreceptor
  - mechanoreceptor
- A fibers
  - nociceptor
  - mechanoreceptor
- A fibers
  - mechanoreceptor
  - not normally nociceptor

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
Acute pain neuromatrix

[Diagram]

Acute pain neuromatrix

[Diagram]
Acute pain neuromatrix

Recap

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

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

---

Chronic pain has systemic consequences

<table>
<thead>
<tr>
<th>Functional Domain</th>
<th>Stress Responses to Pain</th>
<th>Examples of Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/metabolic</td>
<td>Altered release of multiple hormones (e.g., ACTH, cortisol, catecholamines, insulin) with associated metabolic disturbances</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
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<tr>
<td></td>
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<td>Increased respiratory and heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased blood sugar</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased heart rate</td>
<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>Increased vascular resistance</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Increased blood pressure</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Increased myocardial oxygen demand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypercoagulation</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Decreased air flow due to involuntary (reflex muscle spasm) and voluntary (&quot;splinting&quot;) mechanisms that limit respiratory effort</td>
<td>Atelectasis</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased rate of gastric emptying</td>
<td>Delayed gastric emptying, constipation, anorexia, fevers</td>
</tr>
<tr>
<td></td>
<td>Decreased intestinal mobility</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle spasm</td>
<td>Immobility</td>
</tr>
<tr>
<td></td>
<td>Impaired muscle mobility and function</td>
<td>Weakness</td>
</tr>
<tr>
<td>Immune</td>
<td>Impaired immune function</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>
<pre><code>                     |                                            |                                                     |
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Structured approach to the patient in chronic pain

Anatomy

- Brain neuromatrix
- Medulla
- Spinal cord: dorsal horn
- Nociceptive neurons
- Nociception
  - Thermal
  - Mechanical
  - Chemical

Structured approach to the patient in chronic pain

Physiology

- Learning
- Neuroplasticity
- Central sensitisation
- Peripheral sensitisation
- Injury

Anatomy

- Brain neuromatrix
- Medulla
- Spinal cord: dorsal horn
- Nociceptive neurons
- Nociception
  - Thermal
  - Mechanical
  - Chemical

Hague, Shenker, BERH, 20
Structured approach to the patient in chronic pain

**Physiology**
- Learning
- Neuroplasticity
- Central sensitisation
- Peripheral sensitisation
- Injury

**Anatomy**
- Brain neuromatrix
- Medulla
- Spinal cord: dorsal horn
- Nociceptive neurons
- Nociception

**Clinical Assessment**
- Sleep, Depression, Anxiety
- Alterations in body scheme, functional status
- Allodynia, hyperalgesia, neuropathic pain descriptions
- Signs of inflammation, altered structure

- Age <40
- Depression
- High anxiety trait
- Less perceived Social Support
- “Anger style” of emotional regulation
- >1 year duration
- Pain report >4/10
- Altered body scheme (dysychiria)
- >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

**Clinical Assessment**

- Central nervous dysfunction (e.g. fibromyalgia, CRPS, chronic low back pain, phantom limb pain)
- Sleep, Depression, Anxiety
- Alterations in body scheme, functional status
- Allodynia, hyperalgesia, neuropathic pain descriptions
- Signs of inflammation, altered structure

- Central nervous lesions (e.g. stroke, Parkinson’s, MS)
- Endocrine dysfunction (e.g. Low vit D, thyroid abnormalities)
- Compression neuropathy (e.g. sciatica, CTS)
- Peripheral neuropathy (e.g. diabetes)
- Degenerative and MSK disease including Immune mediated inflammatory disease (e.g. RA, AS etc)
- Post-traumatic, Post-surgical, Chronic infection
Structured approach to the patient in chronic pain

**Physiology**

- Learning
- Neuroplasticity
- Central sensitisation
- Central sensitisation
- Peripheral sensitisation

**History**

- Psychosocial contributors

**Questionnaires**

- HAD
- NLSQ (depersonalisation)

**Medications**

- Previously tried
- Dosages
- Side Effects

**Fracture history**
**Structured approach to the patient in chronic pain**

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

**Structured approach to the patient in chronic pain**

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning Neuroplasticity</td>
<td>Mood assessment</td>
</tr>
<tr>
<td>Central sensitisation</td>
<td>Guarding / Distraction</td>
</tr>
<tr>
<td>Central sensitisation</td>
<td>Body scheme</td>
</tr>
<tr>
<td>Central sensitisation</td>
<td>Allodynia</td>
</tr>
<tr>
<td>Peripheral sensitisation</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td></td>
<td>Limb Movement</td>
</tr>
<tr>
<td></td>
<td>Active/passive</td>
</tr>
<tr>
<td></td>
<td>Site assessment</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
</tbody>
</table>
Structured approach to the patient in chronic pain

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

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 \(^6\)

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\(^5\) Management of Chronic pain in Adults, NHS Quality Improvement Scotland 2006.  
Biopsychosocial model

- Biological
- Psychological
- Social

Biopsychosocial model

- Biological
- Psychological
- Social
Why is a biopsychosocial perspective important?


4 pillars of care

- Physical and vocational rehabilitation
- Pain relief (medication and procedures)
- Psychological interventions
- Patient information and education to support self-management

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 life¹
  • Take into account the patient's desire for information, share decision making, and respond appropriately²


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. amitriptyline, duloxetine)
- Anticonvulsants (e.g. gabapentin, pregabalin)
- Topical analgesics (e.g. capsaicin, lidocaine 5% plaster)

Non-opioid analgesics: NSAIDS

- E.g. aspirin, ibuprofen

Efficacy

- Mainly act on nociceptive pain

Mode of action

- Inhibition of cyclooxygenase
- Prostaglandin synthesis decreases

Side effects

- GI irritation/bleeding
- Renal toxicity
- Potential drug-drug interactions
- Cardiovascular side-effects (Cox-2)

Other non-opioid analgesics: paracetamol

- Aniline derivative e.g. Panadol

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Mode of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic and antipyretic effects</td>
<td>Inhibition of central prostaglandin synthesis</td>
<td>Risk of toxic liver damage</td>
</tr>
<tr>
<td>No anti-inflammatory action</td>
<td>Not been fully explained</td>
<td></td>
</tr>
</tbody>
</table>

Other non-opioid analgesics:

- Paracetamol

Opioid analgesics

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

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Mode of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly effective in nociceptive pain</td>
<td>Activate the endogenous analgesic system</td>
<td>Nausea</td>
</tr>
<tr>
<td>Less effective in chronic states</td>
<td>Stimulate receptors in the limbic system to eliminate the subjective feeling pain</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Only partially effective in neuropathic pain</td>
<td>Affect descending pathways that modulate pain perception</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Reduce ascending pain signal transmission in the spinal cord</td>
<td>Dizziness or vertigo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry skin, pruritus</td>
</tr>
</tbody>
</table>


Endogenous pain modulation
### Antidepressants: TCAs

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Mode of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain¹</td>
<td>Inhibition of neuronal reuptake of noradrenaline and serotonin (5-HT)</td>
<td>Constipation¹</td>
</tr>
<tr>
<td>Complex regional pain syndrome¹</td>
<td></td>
<td>Dry mouth¹</td>
</tr>
<tr>
<td>Tension headache</td>
<td></td>
<td>Somnolence¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormalities in heart rate or rhythm¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased appetite</td>
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</tbody>
</table>


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

- E.g. duloxetine, venlafaxine

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Mode of action</th>
<th>Side effects (duloxetine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain¹²</td>
<td>Selectively inhibit reuptake of noradrenaline or serotonin or both</td>
<td>Nausea &amp; Vomiting²</td>
</tr>
<tr>
<td>SNRIs are better analgesics than SSRIs</td>
<td></td>
<td>Constipation²</td>
</tr>
<tr>
<td></td>
<td>Provide analgesia by intensifying descending inhibition</td>
<td>Somnolence¹²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mouth¹²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased sweating²</td>
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<tr>
<td></td>
<td></td>
<td>Loss of appetite²</td>
</tr>
</tbody>
</table>

Anticonvulsants

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Mode of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>Different modes of action: Gabapentin: binds to presynaptic voltage-dependent calcium channels</td>
<td>Sedation¹,²</td>
</tr>
<tr>
<td></td>
<td>Pregabalin: interacts with special N-type calcium channels</td>
<td>Dizziness¹,²</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine: blocks Na⁺ and Ca²⁺ channels</td>
<td>Ataxia¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral oedema¹,²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea¹,²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain³</td>
</tr>
</tbody>
</table>


Gabapentin

Pregabalin

Carbamazepine

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 benzylamine, 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:¹⁴
  - Rash
  - Pruritus
  - Erythema

Main side effects of pharmacological treatments

<table>
<thead>
<tr>
<th>Opioids</th>
<th>NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Gastrointestinal irritation/bleeding</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Constipation</td>
<td>Potential drug-drug interactions</td>
</tr>
<tr>
<td>Dizziness or vertigo</td>
<td>Cardiovascular side effects (e.g. myocardial infarction, stroke and hypertension) with some selective Cox-2 inhibitors</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
</tr>
<tr>
<td>Dry skin, pruritus</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>SNRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Constipation</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Nausea</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Increased sweating</td>
</tr>
</tbody>
</table>

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, Ayurvedic
  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

Dr Nick Shenker PhD FRCP

Addenbrooke’s Hospital