Neuropathic Pain in Palliative Care
Neuropathic Pain in Advanced Cancer

- Affects 40% of patients
- Multiple concurrent pains are common
- Often complex pathophysiology with mixed components
  - Nocioceptive
  - Neuropathic
  - Referred
Neuropathic Pain

‘Pain caused by a lesion or disease of the somatosensory nervous system'.

- Central neuropathic pain is caused by a lesion or disease of the central somatosensory nervous system
- Peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system

IASP 2011
### Aetiological Classification

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
<th>Incidence per 100 000 (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma</strong></td>
<td><em>Post surgery</em></td>
<td>? 50%</td>
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<tr>
<td></td>
<td><em>Phantom limb</em></td>
<td>20</td>
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<td></td>
<td><em>Spinal cord injury</em></td>
<td>50</td>
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<td><em>Complex regional pain syndrome</em></td>
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<td><strong>Infection/inflammation</strong></td>
<td><em>Post herpetic neuralgia</em></td>
<td>180</td>
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<td></td>
<td><em>HIV</em></td>
<td>5</td>
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<tr>
<td><strong>Cancer</strong></td>
<td><em>Invasion/compression</em></td>
<td>75</td>
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<tr>
<td><strong>Ischaemia</strong></td>
<td><em>Painful diabetic neuropathy</em></td>
<td>220</td>
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<td></td>
<td><em>Central post stroke pain</em></td>
<td>10</td>
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<tr>
<td><strong>Compression</strong></td>
<td><em>Sciatica</em></td>
<td>775</td>
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<td></td>
<td><em>Trigeminal neuralgia (Cancer)</em></td>
<td>5</td>
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<tr>
<td><strong>Drugs</strong></td>
<td><em>Chemotherapy e.g. paclitaxel</em></td>
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<td><em>Reverse transcriptase inhibitors</em></td>
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Pathophysiology

• Peripheral
  • Ion channels
  • Neuropeptides
  • Nociceptor sensitisation
  • Abnormal axonal responses

• Central
  • Central sensitisation
  • Cortical re-organisation
  • Spinal re-organisation
Characteristics

• Positive phenomena
  • Characteristics
    • Burning
    • Electric shock
    • Lancinating
  • Sensory disturbance
    • Hyperalgesia
    • Allodynia
    • Hyperpathia
Characteristics

• Negative phenomena
  • Impaired sensation e.g. pin-prick
• Autonomic features
  • Vasomotor (blood flow)
  • Sudomotor (sweat glands)
• Greater pain intensity than nociceptive pain
Principles of pain control

- Determine cause of pain
- Treat cause of pain
- Good analgesia
  - By the clock
  - By the mouth
  - By the ladder
- With this approach around 80% pain can be controlled
Opioids for moderate to severe pain
When morphine doesn’t work

- The clinical response to morphine is highly variable
- Less pain relief with single doses of opioids
- More likely to escalate opioid doses
  - Inadequate analgesia
  - Intolerable side effects
- Need to consider
  - Alternative opioids
  - Co-analgesics
Co-analgesic (adjuvant drugs)

- Drugs that have a primary indication other than pain
- Used to enhance the analgesic efficacy of opioids
- Can treat symptoms that exacerbate pain
- Can help patients balance dose related adverse effects of opioids
- Fewer patients experience pain relief from co-analgesics than from opioid analgesics
Co-analgesics
NICE Guidance – First line therapies

- **Antidepressant**
  - Amitriptyline or Duloxetine
- **Anticonvulsant**
  - Gabapentin or Pregabalin
- **NB** - Duloxetine and pregabalin are only included as first line as they are licenced for this indication and amitriptyline and gabapentin are not
NICE - Guidance

- Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment
- If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.
- Consider tramadol only if acute rescue therapy is needed *(different issues for patients with mixed nociceptive and neuropathic pain)*
- Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.
Recommendations are based on

• Efficacy and side effect data
  • No significant difference between gabapentin and pregabalin

• Economic data
  • NICE draft guidance reports that both amitriptyline and gabapentin represent good value for money.
  • For duloxetine and pregabalin, mean cost-per-QALY estimates suggest poor value for money in comparison with less expensive treatments, particularly gabapentin and amitriptyline.
Antidepressants

- TCA e.g. amitriptyline
  - SSRI and NARI
  - Possible NMDA receptor antagonist
- Main analgesic action by potentiation of descending inhibitory pathways
- NNT 2.0
- Analgesic action at lower doses than for depression
- Limited by side effects
Antidepressants

- SNRIs e.g. duloxetine
- Main analgesic action by potentiation of descending inhibitory pathways
- NNT 4-5
- Acts within days
- Analgesia at lower doses than for depression
- Good side effect profile
Anticonvulsants

• Gabapentinoids e.g. gabapentin, pregabalin
• Main action
  • Interacts at the αδ site of calcium channels
  • Inhibits glutamate, NA and substance P release
  • Decreased neurotransmitter release prevents the spread of neuronal excitability
• Maximum action by 2 weeks
• NNT 3.5
• Moderate side effects
NMDA Antagonists

• Ketamine
  • Anaesthetic
  • Opioid sparing effects
  • Clinically useful in nocioceptive and neuropathic pain
  • No NNT data
  • Analgesia at sub-anaesthetic doses
  • Psychomimetic side effects
NMDA Antagonists

• Methadone
  • Varied receptor properties
    • Primarily a mu agonist with some δ agonist action
    • NMDA antagonist
    • SSRI
  • Lack of known metabolites
  • Long unpredictable half-life can result in accumulation
  • Different titration and initiation process to other opioids
  • Can be used as a co-analgesic as well as an alternative opioid
TENS

• Originally developed as a way of controlling pain through the 'gate' theory.
• When set on low pulse rate may also stimulate endorphin release
• Varying evidence for efficacy (Cochrane review inconclusive)
• Gives patient control
• Usually well tolerated
Interventional techniques

- Interventional techniques
  - Modulative
    - Neuraxial procedures
    - Nerve stimulation
      - TENS
  - Ablative
    - Neurolytic blocks
Spinal cord stimulation

• Direct stimulation of the spinal cord
• Blocks pain signals reaching brain
• Concept first utilised in 1967
Summary

• Pain is common in advanced cancer
• The nature of this pain is complex
• Neuropathic pain is more severe and more difficult to control than nocioceptive pain
• Opioids are still the first line drug
• Co-analgesics include numerous drugs and diverse classes
• Sequential trials of adjuvants is needed
• But – always treat the whole patient and not just the pain
Who Ya Gonna Call?

Specialist Palliative Care Advice Line
(North Herts – 01462679540)
PHARMACOLOGICAL MANAGEMENT OF NEUROPATHIC PAIN

STEP ONE - ASSESS & TREAT UNDERLYING CAUSE

STEP TWO - FOLLOW WHO ANALGESIC LADDER

STEP THREE - ADD A NEUROPATHIC ANALGESIC EITHER ANTIDEPRESSANT OR ANTICONVULSANT

ANTIDEPRESSANTS
- 1st line Amitriptyline
- 2nd line Duloxetine

ANTICONVULSANTS
- 1st line Gabapentin
- 2nd line Pregabalin

STEP 4 - IF PAIN NOT CONTROLLED AT THERAPEUTIC DOSE ADD A DRUG FROM THE ALTERNATIVE CLASS

STEP 5 - IF PAIN NOT CONTROLLED AT THERAPEUTIC DOSES CONSIDER THIRD LINE ANALGESICS

NMDA ANTAGONISTS
- Methadone
- Ketamine

MISCELLANEOUS
- Lidocaine plasters
- Dexamethasone

OTHER INTERVENTIONS, SUCH AS TENS AND NERVE BLOCKS, CAN BE CONSIDERED AT ANY STAGE