Treatment of Pain: New Developments and Research Findings
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EAPC, Prague
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The analgesic ladder today:

- NSAID/paracetamol
- Neuropathic pain: nortriptyline, gabapentin
- Treatment of constipation and nausea: tramadol, codeine, tapentadol, buprenorphine (SL, TD)
- Slow:
  - CR oxycodone/SR morphine
  - TD fentanyl/methadone
- Fast:
  - IR oxycodone/morphine
  - TM fentanyl
- Special techniques:
  - radiotherapy
  - SC infusions/PCA
  - spinal analgesia, neurolytic blocks
  - neurosurgical procedures

Psychosocial support

- buprenorphine (SL, TD)
- tramadol, codeine, tapentadol
- NSAID/paracetamol
- Neuropathic pain: nortriptyline, gabapentin
- Treatment of constipation and nausea
Analgesics in the future?

- New opioids
- COX-2 inhibitors
- Inhibitors of microglia
- MAP kinase inhibitors
- antiNGFs
- TRP-channel modulators
μ-opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer
Bortsov AV & al., Anesthesiology 2012
COX-2-expression and PGE2 concentration in breast tumours of mice after 13 days of treatment with morphine ± celecoxib

Farooqui M & al., Br J Cancer 2007
Effect of morphine ± celecoxib on tumour angiogenesis and tumour growth after 13 days of treatment

Farooqui M & al., Br J Cancer 2007
Effect of morphine ± celecoxib on survival and pain behaviour in SCK tumour bearing mice
Farooqui M & al., Br J Cancer 2007
Microglia

- Microglia are resident macrophages of the brain and spinal cord
- Microglia act as the first active immune defense in the CNS
- Microglia and astrocytes are distributed in large (non-overlapping) regions throughout the CNS
- Microglia scavenge the CNS from
  - damaged neurones
  - plaques
  - infectious agents
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Opioids can activate glia via different mechanisms

- Through opioid receptors
- Non-stereoselective effect via TLR4
  - All structural classes of opioids activate TLR4
  - Opioid antagonists non-stereoselectively block TLR4 signaling
Glial activation: possible new therapeutic options

• Ibudilast (AV411)
• Propentofylline
• Minocycline
• Naloxone/Naltrexone
  – (+)naloxone
Coadministration of minocycline (50 μg) with morphine (15 μg) reduces morphine induced activation of microglia and astrocytes (Cui Y & al., Brain, Behavior, and Immunity 2008)
Reversal of morphine tolerance with ibudilast

Lilius T & al., Anesthesiology 2009
Cetuximab alleviates neuropathic pain despite tumour progression (Kersten C & Cameron MG, BMJ Case Rep 2012)

- 68-year old male patient
- rectal ca + pelvic recurrence
- radiating pain down his left leg
- pain was debilitating and resistant to standard treatments for 3 years
- dramatic relief of pain 3-4 h after an infusion of the antiEGF receptor antibody Cetuximab
- the effect lasted for 12 days
- repeated every 12 days for 3.5 years
- no effect with placebo (20% of the dose of Cetuximab)
- pain relief even when his cancer was in radiological progression
- AEs: mild acne
- mechanism? inhibition of MAPK signalling in glial cells?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatments given in an attempt to relieve the patient’s pain</th>
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<tbody>
<tr>
<td>Type of intervention</td>
<td>Specific treatment</td>
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<tr>
<td>Analgesic medication</td>
<td>Paracetamol, Morphine</td>
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<tr>
<td>Antiepileptic medication</td>
<td>Gabapentin, Carbamazepine, Pregabalin</td>
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<td>Antidepressant medication</td>
<td>Amitriptyline, Prenisolone</td>
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<tr>
<td>Anti-inflammatory medication</td>
<td>Non-steroidal anti-inflammatories, 5-Fluorouracil/leucovorin</td>
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<tr>
<td>Chemotherapy</td>
<td>Capcitabine, Irinotecan, Oxaliplatin</td>
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<tr>
<td>Other</td>
<td>Hyperbaric oxygen, Acupuncture, Palliative radiation</td>
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</tbody>
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p38 MAP kinase inhibitor dilmapimod in neuropathic pain following nerve injury
Anand P & al., EJP 2011

- exploratory, multi-centre, double-blind, placebo-controlled, 2-period, cross-over trial
- 43 patients completed the study
- dilmapimod (15 mg/d) provided significantly (p<0.0034) better pain relief compared with placebo
- dilmapimod was well tolerated
NGF regulates multiple receptors / ion channels expressed by sensory nerve fibers that innervate bone

- P2X3
- EP
- ET$_A$R
- B2
- TRPV1
- ASIC3
- Na$^+$ Channel
Nerve sprouting, neuroma formation and late stage cancer pain (Mantyh WG & al., Neuroscience 2010)
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Anti-NGF therapy attenuates tumour-induced nerve sprouting and cancer pain

Jimenez-Andrade JM & al., Pain 2011
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