Learning objectives

- Know definitions of *pain* and *nociception*.
- Understand the difference between them.
- Appreciate that pain is a complex, multi-dimensional, whole-person experience not a sensation.
- Know that you can experience pain without tissue damage.
- Understand terms: acute, chronic, cancer, nociceptive & neuropathic pain.
- Understand basic anatomy, physiology & clinical pharmacology of nociceptive ('pain') pathways from periphery to spinal cord to brain.
- Understand where 'pain' receptors, ion channels & enzymes act along this pathway.
Learning objectives

- Understand that *central sensitization* (CS) (amplifier) and...
  conditioned pain modulation (damper)...
  modulate nociceptive ('pain signal') traffic in the CNS.

- Know that *allodynia* (touch pain) is the clinical sign for CS.

- Understand where analgesic drugs act along the ‘pain pathway’.

- Have a basic understanding of clinical pharmacology of analgesic drugs presented in this lecture & slide presentation.

- Understand basic principles of acute, chronic & neuropathic pain management.

- Pain is managed using *bio-medical-psycho-social-environmental* approach.
What is pain?

- Pain is ‘an unpleasant sensory & emotional experience…’
- …associated with actual or potential tissue damage’ (IASP 1979)
- Pain is an output of the conscious brain & not an input
- Pain is a subjective, multidimensional, whole-person experience
- Pain always occurs in a bio-medical-psycho-social-environmental context
What is nociception?

- 'Processing & encoding of noxious stimuli (tissue damage) in the nervous system' (IASP 2011)

- Transduces the 'energy' released by tissue damage...
  ...chemical, mechanical & thermal energy...
  ...into electrical signals for processing in nervous system

- Nociception is a neuro-physiological process

- Nociception is the main (but not the only) trigger for pain

- Nociception is NOT the same as pain
The difference between pain & nociception explained in a movie!

John Connor: “Does it hurt when you get shot”?

The Terminator: “I sense injuries (a great definition of nociception)...

The data could be called ‘pain’.”
Nociception
Transduction, transmission, modulation

transduction
Energy of tissue damage
TRPV channels
Inflammatory soup

transmission
voltage gated Na ion channels

modulation
Dorsal horn

Descending inhibition
‘signal inhibition’

Central sensitization
‘signal amplification’
Nociceptive (inflammatory) ‘soup’
Immune modulation of nociception in the nervous system

Interleukin 1, 6, TNF

Toll-like receptor 4
Nociceptors

Convert the energy released by tissue damage into neuro-electrical signals

- Heat
  - Acid (H+)
  - TRPV1

- Cold
  - TRPV8

- Mechanical

- Capsaicin cream 0.025%
- Menthol gel 2-4%
- Bandage, cast, splint
Nociceptive (inflammatory) soup
Prostaglandins

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Representative receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>TrkA</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>BK$_2$</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT$_3$</td>
</tr>
<tr>
<td>ATP</td>
<td>P2X$_3$</td>
</tr>
<tr>
<td>H$^+$</td>
<td>ASIC3/VR1</td>
</tr>
<tr>
<td>Lipids</td>
<td>PGE$_2$/CB1/VR1</td>
</tr>
<tr>
<td>Heat</td>
<td>VR1/VRL-1</td>
</tr>
<tr>
<td>Pressure</td>
<td>DEG/ENaC (?)</td>
</tr>
</tbody>
</table>
Cyclooxygenase (COX)
Produces prostaglandins

vasodilation  mucous  platelet plug  tissue growth
renal  stomach  bone, gut

NSAIDs
Cyclooxygenase COX-1
constitutive ('housekeeping') enzyme
COX-2 (coxibs)
Inducible (‘spring cleaning’) enzyme
(at times of tissue or organ stress)

- Boosts inflammation in disease eg arthritis
- COX-2 found in CNS (↑ central sensitization)
- Stomach mucous production is COX-1 (↓ peptic ulcer)
- COX ↑ tissue growth, cancer cells (↓ colon cancer?)
- Platelets do not have COX-2 (↓ bleeding risk)
- Renal arterioles (have COX-2) (still renal risk)
- Vascular (still hypertension & CVS risk)
- Celecoxib, parecoxib
Antidepressants
Effective for neuropathic (nerve) pain

- **Tricyclic antidepressants** (are best, NNT 3)
- **SNRIs (eg duloxetine)** (quite effective, NNT 6)
- **SSRIs** (not effective)
- **(Nor) adrenaline** is the body’s main pain-killing neurotransmitter
- ‘Adrenaline is an analgesic’
- TCAs also block Na channels & NMDA

Amitriptyline is a ‘dirty drug’ that works at multiple sites
Anticonvulsants

Extinguish "sparking wires" in neuropathic pain

- 'Membrane stabilizers' ↓ spontaneous electrical activity (ectopics)
  - neuropathic pain
  - migraine

- Block voltage gated Na ion channels
  - carbamazepine (NNT 2)
  - valproate
  - lignocaine

- Block specialized calcium channels (the α2δ subunit)
  - pregabalin, gabapentin (NNT 4)
Dorsal horn
This is where pain signal processing (modulation) goes on
Site of the 'pain gate'

PAIN MECHANISMS: A NEW THEORY

R. Melzack and P. D. Wall

Department of Psychology, McGill University and Department of Biology, Massachusetts Institute of Technology, Montreal, Canada and Boston, Massachusetts

Science, 150: 971–979, November 19, 1965
Central Sensitization

‘Pain’ signal (nociceptive) amplification

Increased nociceptive output for a given nociceptive input

A true amplifier effect
‘Wind-up’

Capacitance effect
pain signal ‘memory’

It makes sense for an ‘alarm’ to ‘ring’ louder so we don’t ignore it
Allodynia (touch pain)
Is the clinical sign for central sensitization
Greek for ‘the other pain’

If any of these non-painful stimuli feels painful,
you have detected allodynia...
...and therefore central sensitization
NMDA receptor ion channel
N-methyl-D-Aspartate
The nervous system’s signal amplifier (chemical ‘transistor’)

- Glutamate is an NMDA agonist
- Main excitatory amino acid (MSG)
- NMDA is amplifier channel in dorsal horn & brain
- Mediates central sensitization
  - ‘wind-up’
  - memory (hippocampus)
- Blocked by...
  - ketamine
  - dextromethorphan
  - TCAs
  - methadone
**Conditioned Pain Modulation (CPM)**

Descending ‘pain’ (nociceptive) inhibitory system

- Inhibits ‘pain signals’ ascending from dorsal horn
- Damping (pain brake)
- Inhibitory neurotransmitters
  - noradrenaline (the most important)
  - serotonin
  - endorphins
- CPM allows us to sit on our bottoms
  - there’s 45 kg/cm² pressure on our ischium when we sit
- CPM allows us to escape danger…
Pain Modulation in Balance

- Pain signal
- Sensitization
  - "Amplifier"
- CPM
  - "Damper"
Opioids
Slow everything down

- mu, delta, kappa, nociceptin receptors
- MOP DOP KOP NOP (IUPHAR)
- Neuro + endocrine + immune inhibitors
- ‘Opioids slow everything down’
- Analgesia
- Side effects
  - brain (sedation)
  - breathing, coughing
  - gut (constipation, gastric stasis, ileus)
  - bladder (retention)
  - person (lethargy)
Opioids

- Opioids are plant **alkaloids**
- Alkaloids have a similar structure to endogenous opioids (nature is amazing)
- eg endorphins, leu-enkephalin
Opioid receptors
7-membrane-spanning array-type receptors

Ca++  K+

Cell membrane

Resting
G-protein

Receptor occupied

GTP

Activated effector

Effector activated

Effector

GDP

Cellular responses

Australian Prescriber 1996: 19 (3)
Codeine (3-methyl-morphine)

Example of a pro-drug

- Prodrug is converted by the liver to its active form

- **Codeine** cytochrome P4502D6 (de-methylated) **morphine** (active)

- Di-acetyl-morphine (heroin) & tramadol are also pro drugs
Codeine (3-methyl-morphine)

- Genetic polymorphism of cytochrome P450 2D6
- Pharmacogenomics (isoenzymes)
- 10% slow metabolisers (it doesn’t work)
- 10% fast metabolisers (one tablet & I’m out)
  -30% of Africans & Middle East (risk of toxicity)
- Paediatric breast feeding & tonsillectomy deaths
- Social impacts of pharmacogenomics...
- Refugees from Middle East & Africa
- Change to S4 drug next year
Summary
Pain Pharmacotherapy Targets
Follow the pain pathway

- Na⁺
- Ca²⁺
- TRPV1
- Heat
- Capsaicin
- Agonists
- Neuronal Membrane
- Na⁺, Ca²⁺
- TRPV1
- Capsaicin
- Menthol
- Capsaicin
- TRPV1
- Neuronal Membrane
- Na⁺, Ca²⁺
- TRPV1
- Capsaicin
- Menthol
- NSAIDs, coxibs, steroids
- Lignocaine
- Anticonvulsants (carbamazepine)
- Gabapentin
- Pregabalin
- Ca²⁺ (α2δ)
- NMDA
- Ketamine
- Antidepressants
- Tramadol
- Tapentadol
- NA
- 5HT
- OR

VISSE MED 200 UNDA PAIN PHARMACOLOGY 2016 30
We’ve run out of time

Please read the following slides for self study
Don’t get too worried
There’s a fair bit there but take your time
Clinical pain management

Key principles

- Always believe the person-in-pain
- Try to make a pain diagnosis (can you identify a pain ‘generator’?)
  - NB may not always be possible (eg chronic low back pain)
- Make a pain assessment: QRST
  - Quality, Radiation/Relieving, Site/Severity, Timing
- Is the pain nociceptive or neuropathic?
- Is the pain acute, chronic, cancer, visceral?
- Always apply a bio-medical-psycho-social approach
- Always manage the whole person-in-pain (often a lot happening in their life)
Types of pain

- Acute pain
- Chronic pain
- Cancer pain
- Nociceptive pain (tissue injury or ‘inflammatory’ pain)
- Neuropathic pain (nerve pain)
- Visceral pain (pain from internal organs)
Acute Pain

- ‘Alarm’ system pain
- Nociceptive pain
- Inflammatory pain
- Pain \(\approx\) amount of tissue damage
- Pain gets better as tissues heal
- Protective & adaptive
- Highly preserved in evolution & animal kingdom
- From crustaceans (?) to humans
Acute pain is nature’s tissue-damage ‘alarm’
Acute pain

- Emergency (retrieval)
- Post operative pain (recovery room)
- Acute Pain Service rounds
- Labour ward
- Work or sports injury
- Renal colic
- Migraine
- Dysmenorrhea
- Acute coronary syndrome
Treat acute pain fast by...

Establishing a therapeutic steady-state plasma [ ] of the analgesic...

Remember, it takes 5 drug half-lives to reach steady-state

- IV loading for acute pain is fastest!
  - bolus every 2 mins to effect

- Oral loading is a bit slower
  - Rx...1/24 prn for opioids or tramadol

- A bit of applied pharmacokinetics...
- Most opioids have a $t_{1/2}$ of 3 hrs, so it would take 15 hrs (5 x 3 hrs) to reach a therapeutic SS plasma [ ] if we prescribed ‘3/24 prn’
Treat an acute pain emergency by...
Getting an adequate brain concentration of analgesic

- It’s a gas treating severe pain fast
- Gas gets from lungs-to-brain fast
- That’s how anaesthesia works!
- Nitrous oxide (Entonox®)
- Methoxyflurane (Penthrane®)
- eg labour pain
- renal colic
- painful dressings
## Analgesia league table for acute pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 400 mg</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen 400 mg</td>
<td>3</td>
</tr>
<tr>
<td>Pethidine 100 mg, morphine 10 mg inj.</td>
<td>3</td>
</tr>
<tr>
<td>Panadeine forte 60/1000 mg</td>
<td>3</td>
</tr>
<tr>
<td>Paracetamol 1000mg</td>
<td>4</td>
</tr>
<tr>
<td>Tramadol 100 mg</td>
<td>5</td>
</tr>
<tr>
<td>Codeine 60 mg</td>
<td>17</td>
</tr>
</tbody>
</table>
Chronic pain
Pain alarm malfunction

- Pain lasting beyond the time of normal tissue healing
- Pain lasting $\geq 3$ months
- No protective function (mal-adaptive)
- Alarm keeps ringing when there’s no emergency
- Pain $\neq$ amount of tissue damage
- Key message (remember this)... 
- You **CAN** experience pain without any tissue damage
  
  eg pressing your thumb nail, phantom limb pain, or back pain with a normal looking MRI (insurance companies can’t understand this?)
Cancer pain

- Acute or chronic
- Nociceptive pain (eg metastatic, pathological #)
- Neuropathic pain (eg lumbar plexus infiltration)
- Visceral pain (eg bowel obstruction)
- Due to treatment effects (chemo, radiotherapy, surgery)
- Psycho-social, spiritual, existential dimensions
- Palliative care
- Opioid analgesia is the mainstay of Rx
- WHO analgesia ladder
Neuropathic (nerve) pain

- Pain due to a lesion or disease of the nervous system (IASP 2011)
- PNS - Nerve injury
  - Radicular (nerve root)
  - PDN (diabetes), PHN (zoster)
  - trigeminal neuralgia
- CNS (central pain)
  - spinal cord injury
  - post-stroke pain
  - multiple sclerosis
Neuropathic pain

- No physiological function (maladaptive)
- Damage to pain ‘wires’
- Sparks from a fallen power line (‘ectopics’)
- Pain has ‘electrical’ qualities
- Shooting, zapping, shocks, lightning
- Stabbing, burning, aching
- Allodynia (touch pain)
- Numbness, weakness?
- Nerve damage leads to over-production of Na & Ca ion channels
- Pathological increase in nerve function
Visceral pain
Primitive, emotional & autonomic pain

- Pain from internal organs eg renal colic, AMI, labour pain, dysmenorrhea, IBS
- Transmitted via C pain fibres (slow, burning, aching pain)
- Transmitted via the old (paleo) spinal cord pathways
  - medial cord tracts (spino-parabrachial-limbic) & dorsal columns
- Signals project to limbic system (emotional & autonomic part of the brain)
  - ↑ emotions (distress), ↑ pain behaviors (grimacing, groaning, rolling around)
  - ↑ autonomic response (nausea, sweating, vasovagal)
- Poorly-localized pain, deep, dull, burning, gripping, ‘colicky’
Do opioids work for chronic pain?
This is a big question in health care at the moment

- **No, not that well:** NNT = 8 (NNH = 4) (Level I)
- More effective in over 60s (but more side effects)
- Avoid in LBP, headache, fibromyalgia, abdominal pain
- Ceiling dose is ≤ 90 mg oral morphine equivalents/day
- Don’t prescribe more than this for chronic pain
- Use tramadol SR, tapentadol SR or transdermal buprenorphine
- Opioid prescribing is always a therapeutic trial
What are the adverse effects of long-term opioids?

- Respiratory, sedation, dizziness, nausea, constipation
- Overuse (chemical-coping, addiction) (+ reward centre)
- Opioid-induced hyperalgesia & tolerance (pain gets *worse*)
- Endocrine changes (testosterone, osteoporosis)
- Immune suppression; *activates* glia via Toll-like receptors
- Cortical changes on fMRI (cognitive, anxiety, mood, motivation)
- Increased all cause mortality
WHO analgesia ladder (1986)
A major breakthrough in pain management
Paracetamol

- No one really knows how it works
- COX inhibition?
- Cannabinoid & serotonin receptor agonist?
- 30% ↓ in pain, 30% opioid sparing
- IV > oral > PR (satisfaction & dose reliability)
- Toxicity (liver)
- Reduce the dose in old, frail, < 45 kg, alcoholism
- May not be effective for chronic musculoskeletal pain (meta analysis)?
NSAIDs & coxibs

- Best analgesics for acute pain (level I) (see league table)
- 30% ↓ in pain & 30% opioid sparing
- Kidneys at risk (↓ renal blood flow)
- Hypertension/acute coronary syndrome/stroke (long term)
- Coxibs ↓ gastric irritation & no bleeding risk
- Celecoxib has best overall safety profile (gut, CVS, bleeding)
- Naproxen has best long term CVS risk
- Use NSAIDs & coxibs for acute pain, avoid long term use
Tramadol

- 1/3\textsuperscript{rd} opioid, 1/3\textsuperscript{rd} nor-adrenaline, 1/3\textsuperscript{rd} serotonin analgesia effect
- Metabolised by cytochrome P450 2D6 (same pharmacogenomics as codeine)
- 11 active metabolites (so it’s a pro drug, the metabolites provide the analgesia)
- Accumulates in renal impairment (reduce the dose)
- Good for neuropathic pain (NNT = 4)
- Less addiction (S4), tolerance & hyperalgesia
- Less respiratory depression (better in COPD, sleep apnoea)
- Less constipation
- Can mix carefully with antidepressants (serotonin syndrome, 1/7000)
- Avoid if risk of seizures
Tapentadol SR
Like tramadol without the serotonin

- *Mu opioid receptor agonist (MOR) (S8 drug) & nor adrenaline reuptake inhibitor (NOR)* in the same molecule
- Noradrenaline is main pain inhibitory neurotransmitter
- Works via CPM pathway in the spinal cord
- Effective in nociceptive & neuropathic pain (NNT 4)
- Less, constipation, less side effects than tramadol
- Minimal accumulation in renal impairment
- OK to combine with TCAs, SSRIs or SNRIs in sensible doses
- Tapentadol SR 50 mg ~ 10 mg oral oxycodone ~ 20 mg oral morphine
- Consider first line if prescribing opioids for chronic non cancer pain
"Particles of heat activate a spot of skin attached by a fine thread to a valve in the brain... this opens the valve allowing animal spirits to flow from a cavity into the muscles causing them to flinch, and turn the head and eyes toward the affected body part, also moving the hand and turn the body protectively."
Cyclooxygenase COX-1
Adverse effects of blocking COX-1

↑ vasoconstriction  ↓ renal, gut BF  ↓ BP, CVS risk
↑ mucous  ↓ platelet plug  ↓ tissue growth
↑ peptic ulcer  ↑ bleeding  ↓ bone healing

NSAIDs
All codeine-containing medications could be prescription-only from next year

October 2, 2015

Craig Butt, Aisha Dow