Declaration

- Pharma
  - Research, education, advisory
    - Mundipharma
    - Pfizer
    - bioCSL

- Education
  - University of Melbourne
  - NPS

- Memberships
  - Australian Pain Society
  - EFC
“The pain of the mind is worse than the pain of the body”
Publilius Syrus (Roman author, 1st century B.C.)

Summary

• Pain assessments should consider person and pathology
  – recognise psycho-social factors (which may have a neurological basis)

• Pain is a multidimensional experience
  – more than just sensory, with multiple areas of the brain activated
    • sensation, mood, meaning

• Person with MS may have a normal or abnormal sensory system
  – may have prolonged pain experience, slower to recover from acute pain
  – may develop central neuropathic pain from MS
  – may develop secondary pains
    • musculoskeletal
    • internal organs
Pain pathways

- Nociception
  - respond to thermal, chemical and mechanical stimuli
  - somatic
    - deep, superficial
  - visceral
    - include vagal afferents

- Multiple brain centres activated
  - sensory-discriminative: SS1, SS2,
  - affective-motivational: ACC, Insular
  - cognitive-evaluative: PFC
    - prominent in chronic pain

- Pain is a multidimensional experience
  

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Pain physiology: clinical

- Animal and human pain models demonstrate nervous system sensitisation
  - primary hyper-algesia
  - secondary hyper-algesia
  - ? “tertiary” hyper-algesia

- Response
  - recovery
    - 25-95%
  - neuro-plasticity
    - central sensitisation
    - immune activation
  - brain changes

- “Neuropathic”
  - Injury to nervous system
  - 3% acute pain
  - higher in chronic pain
Persistent trauma pain

- Epidemiology suggest influence of
  - psychological
  - social factors

- Persistent pain following trauma
  - acute pain severity OR 2.4
  - compensation OR 2.1
  - pre-injury disability OR 1.8
  - failure to finish high school OR 1.5
  
  » Williamson O J Orthop Trauma 2009; 23: 139
  
  - other studies discuss pain control attitudes, catastrophising
  
  » Holmes A Pain Medicine 2010; 11: 1599

Sensitisation in pain

- Peripheral
  - tissue inflammation leads to sensitised nerves
    - primary hyperalgesia

- Central
  - spinal cord up-regulation
    - secondary hyperalgesia
  - ? brain: “memory”

- Area of wound sensitivity predicts pain at 6 mths
  - can be reduced by NSAIDS, ketamine
    
    » Eisenach RAPM 2006; 31: 1

- Temporal summation
  - measures sensitisation potential
  - anxiety, catastrophising associated with ↑TS
    
Conditioned Pain Modulation

- Pain activates descending inhibitory control
  - opioid, nor-adrenergic systems
  - measurable
    • cold pressor test, heat pain test

- Implications
  - predictive of pain severity, persistence
    » Yarnitsky D. *Pain* 2008; 138: 22
  - reduced in catastrophising/anxiety
    » Goodin BR.
    » *J Pain* 2009; 10: 180
  - therapeutic target
    • SNRI in DPN
      » Yarnitsky D.
      » *Pain* 2012
      » 153: 1193

The Nociception Spectrum

Lower ← Supra-threshold → Higher
Lower ← Temporal Summation → Higher
More Efficient ← CPM → Less Efficient

Anti-nociceptive ← CPM → Pro-nociceptive

Figure 2. The Expression of Psychophysical Tests along the Pain Modulation Profile.

- Neurological basis for differences between individuals
  - pain experience
  - impact of pain on physical, psychological and social functioning
  - response to therapy/recovery
Catastrophizing: a predictive factor for postoperative pain

- High catastrophising levels associated with increased pain severity, increased risk of chronic pain and poorer QOL
  - unclear re analgesia consumption
    » Khan R. Am J Surgery 2011; 201: 122

Assessment of pain

- **Who is the person**: education, past pain experience, anxiety
  - yellow flags
    - *psycho-social factors associated with increased risk of disability, distress*
  - co-morbidities
    - nerve/brain changes, pre-existing chronic pain
      - 8+% aged hospital admissions on opioids

- **What are the potential mechanisms**: nociceptive, neuropathic
  - red flags
    - *clinical indicators of possible serious medical conditions*
  - superficial, deep somatic; visceral pain
    - *inflammatory component post-operatively*
  - assessment tools: 0-10, descriptors, Abbey pain scale

- **What is the impact**: physical, psychological, social
  - cardio-respiratory, bowels, metabolic, cognitive in acute
  - psycho-social more prominent over time
**Classifying pain**

- Duration, mechanism, etiology, site
- Nociceptive pain
  - somatic vs visceral; e.g. inflammatory, degenerative, ca
- Neuropathic pain
  - peripheral nerve and/or central nervous system lesion or dysfunction
- Mixed: neuropathic or neurogenic component in many chronic pain states

**Management of persistent pain**

- **Manage from a bio-psycho-social perspective**
  - Education, preparation, standardise treatment
    - Morrison S. *J Am Geriatrics Society* 2009; 57
  - CBT for catastrophisers pre ortho surgery of benefit in pilot study
    - Riddle D. *Arch Phys Med Rehab* 2011; 92: 859
  - Pharmacological
    - opioids: efficacy in acute/subacute, concerns in chronic use
      - nociceptive pain
    - adjuvant medications/techniques ➔ preventative analgesia
      - regionals, ketamine, TCAD/SNRI, GBP-inoids, clonidine
  - Non-pharmacological
    - relaxation response, cognitive training
    - exercise/physical strategies
      - PT, Tai Chi, weight loss
  - Social impact/interaction/engagement
    - discharge planning, communication
**Effects of persistent pain**

- Bio
  - Hyperalgesia (Increased sensitivity)
  - Concentration/cognitive
  - Sleep disturbance
  - Physical de-conditioning
- Psychological
  - Mood disturbance
  - Anxiety
  - Health worries
- Social
  - Decreased socialisation
  - Carer stress
  - Financial

![Diagram of pain formulation](image1)

Fig. 1. Formulation of a patient’s pain problems. Presenting problem: the patient is not performing his or her usual activities, and reports pain. Adapted from Looser (1982), with permission.

**CBT model includes:**

- Pain related fear leads to increasing disability (fear-avoidance model)
Non specific low back pain

- **Common**
  - natural history improve 3 mths
  - 20% some pain at 1 yr
- **Low % significant pathology**
  - Ca, fracture, infection
  - multiple nociceptive potential sources
- **Look for red, yellow flags on Hx**
  - little in examination
- **Poor correlation between imaging and pain**
  - “degenerative” changes common
  - Bone scan with SPECT views
  - Diagnostic/therapeutic blocks
  - Care with CT

Multiple Sclerosis

- **Inflammatory CNS disease with demyelination**
  - white matter plaques
    - periventricular, cervical cord, brain stem
  - grey matter gliosis
    - cortical (subpial, intra or leucocortical), cerebellum, thalamus
    » Zivadinov *BMC Neurol* 2012; 12: 9
  - ? cranial nerve inflammation
    - optic, trigeminal
- **Demographics**
  - women > men (2:1)
  - 2-150/100,000
  - genetic, geographics
Multiple Sclerosis

• Variable clinical course
  – relapsing remitting
    • 80%, may be benign, start with clinically isolated syndrome
  – secondary progressive
    • progressive decline between attacks (RR), yrs later
  – primary progressive
    • 10-15% initial cases
  – progressive relapsing
• ? variants
  – Devic’s disease, Maarburg MS, Schilder’s

Multiple Sclerosis

• Clinical
  – sensory
    • hypo-aesthesia, paraesthesia, pain
  – motor
    • weakness, spasms, clonus, co-ordination
  – autonomic
    • bladder, bowel
  – bulbar symptoms, visual
  – fatigue, emotional lability
  – cognitive impairment

• Secondary effects
  – falls/injury, treatment effects, energy
  – psycho-social implications
**MS: Treatment**

- iv steroids for acute attacks, +/- plasmapheresis
- disease modifying
  - Fingolimod
  - Interferon beta-1a, 1b
  - Mitoxantrone (monthly)
  - Natalizumab (monthly)
- symptom and disability management
  - Spasticity
  - continence
  - pain
  - multidisciplinary rehabilitation

**Pain in MS**

- Prevalence
  - 11-28% acute MS
  - 40-79% chronic
    - point prevalence 50%

- Continuous Central Neuropathic pain
  - subcortical plaques (sensory)
    - lower > upper limb "dysaesthetic" (unpleasant) pains
  - spinal cord lesions, ? Thalamus
    - chest wall

- Intermittent Central Neuropathic pain
  - trigeminal "neuropathy"
    - entry zone lesion
  - Lhemitte's phenomenon: shooting sensation with neck bend
Pain in MS

- Musculoskeletal
  - spasticity, spasms
  - joint fibrosis
- Visceral
  - bladder
  - bowel: constipation
- Mixed syndromes
  - headache in 11-23%

  » MS practice 2009, MSaustralia
  » Oconnor A. Pain 2008; 137: 96

MS and pain

- cross sectional study in 94 community MS pts
  - 64% chronic pain
    - 60% of these with dyseaesthetic pain, mean 5/10
  - higher pain grade ass with greater disability, HCU
  - worse AsQOL psych subscale

  » Khan F. J Pain 2007; 8: 614

- questionnaire survey of 4,600 veterans with MS
  - 62% response rate, >90% male
  - 92% some pain, 69% moderate or greater severity
  - associations between pain, physical interference, and mental health

  » Hirsh A. Arch Phsy Med Rehab 2009; 90: 646
MS and pain

- CBT cluster analysis (Turk and Rudy) in 62 MS pts
  - Pain Impact Rating Questionnaire
  - General Health Questionnaire - 28
  - MS Impact Scale – 29

- 3 clusters
  - “adaptive copers” 40%
    - low pain, high support, low distress
  - “dysfunctional” 36%
    - high pain, disability, distress, moderate support
  - “interpersonally distressed” 23%
    - lower pain, moderate disability, distress, low support

  » Khan F. Int J Rehab Res 2011; 34: 235

NSLBP and you

- 70% lifetime incidence, high recurrence rate
- Posture, work set up, duration, genetics, smoking, WCA factors
- Core stability poor in persistent pain
  - diaphragm, pelvic floor, multifidis
  - transversus abdominus
Clinical issues

- Care models
  - neurologist/care team
  - treatment trials/research
  - cognitive impairment

- central neuropathic pain
  - resistant to treatment
  - TCAD, GBP toxicity compounds MS effects

- difficult engagement into multidisciplinary care
  - transport, time, ?benefit

Allied Health

- Principles
  - assess and engage client in self-management approach
  - target unhelpful thinking and behaviours
  - optimise physical-psycho-social function

- Pain Management Programs
  - education on neurophysiology and impact of pain
  - individual sessions targeting specific issues
  - CBT: cognitive restructuring, ↑ self efficacy, relaxation, anxiety management
  - PT: posture, gait/movement, fitness
  - OT: domestic and social ADL, occupational

- Combination: yoga (mindfullness), Tai Chi, pilates
**Rehab in MS**

- RCT of rehab care in MS
  - wait list/usual care control
  - individual +/- 5 day inpatient rehab
    - neuro-psych
    - OT, PT, SP, medications
  - treatment and follow-up over 12 mths
  - improvements in FIM- motor and psych
    - but minimal or no improvement in MSIS and GHQ
  - deterioration in control group
    - improved: 71 vs 13%; deterioration 17 vs 59%
      » Khan F J Neurol Neurosurg Psychiatry 2008; 79: 1230

**NSAIDS and Paracetamol**

- Peripheral and central COX activation in inflammation
  - IL-1β activates peripheral and central COX 2
  - regional anaesthesia fails to prevent central effects
- Meta-analysis
  - opioid sparing 15-55%, reduced N/V, sedation 30%
    » Elia Anesthesiology 2005; 103; 1296
    » Marrett Anesthesiology 2005; 102: 1249
- Dosing important
  - need CNS concentration: not ketorolac, ibuprofen
  - appears 5-14 days recommended, pre-emptive best
- Pre-operative paracetamol > post incisional in meta-analysis
  - mild reduced pain score, opioid consumption, N/V
    - po loading preferred to iv post incision
Ketamine

• Pre-emptive NMDA antag prevents receptor up-regulation with nerve injury and hyperalgesia in animals
  » Wilson Pain 2005; 117: 421

• RCT ketamine intra-op spine surgery pts on opioids
  – 30% less opioid pca use
  – less pain at 6 weeks
    • mean VAS 3.1 vs 4.2
    • 70% less opioid use
  » Loftus Anesthesiology 2010; 113: 639

• Cochrane review
  – modest but statistically significant reduction in chronic pain after surgery
  – GBP, PreGabalin not significant
  » Chaparro L. Cochrane Database Syst Rev 2013; 7: CD008307

• Case series in chronic neuropathic pain, opioid tolerance

Anti-neuropathics

• Gabapentin/Pregabalin
  – evidence in neuropathic pain
  – anti-hyperalgesia
  – sedative, easy dose titration

• Valproate, Carbamazepine

• TCAD/SNRI
  – anticholinergic effects
  – effective in PHN, including preventative
  – NNT 2.2-2.6

• topical therapies
  – Lignocaine: 2-5%
  – amitriptyline/clonidine
Multimodal therapy

- Combining drugs of different classes to improve efficacy and reduce adverse effects
  - Opioids and paracetamol/NSAIDS
  - Local Anaesthetics and opioids

- Nortriptyline, Gabapentin, or combined in neuropathic pain
  - dosing 20-100, 1200-3600 mg
    - lower when combined
    - dry mouth, sedation issue

  *Gilron I et al Lancet 2009; 374: 1252*

Opioids

- Effective in acute (nociceptive) pain
  - up to 70% pain severity reduction
  - dose response relationship
    - potential toxicity

- Less effective in chronic pain
  - 30% pain reduction (nociceptive)
    - varied tolerance to side effects
      - *CMAJ 2006; 174: 1189*
  - ? role in neuropathic pain
    - ? mixed opioids

- Higher doses associated with
  - anxiety/psychological distress
  - substance use disorder
    - *Clinical J Pain 2010; 26: 1*
  - cancer/palliative treatment
Opioids

- Large range strong opioids, patient variability
  - Morphine
    - longer t1/2 in older, accumulation risk
    - more potent, equal efficacy via PCA in aged
  - Fentanyl
    - potent, no metabolites, patch
  - Oxycodone
    - abuse deterrent formulations
  - Hydromorphone
  - Methadone
    - long t1/2, potent, cardiac concerns

- Tapentadol
  - nor-adrenaline re-uptake inhibition, SR only
  - ? role in neuropathic pain, ? less constipation
    - 50 mg equivalent to 10 mg oxycodone
      » Vadivelu N. J Pain Research 2011; 4: 211

Buprenorphine

- Effective in cancer and neuropathic pain
  - broader pain phenotypes
- Less tolerance and dependence
  - can be combined other opioids; anti-hyperalgesic
- Less adverse effects
  - cognitive, constipation, respiratory depression
- Safe in aged, renal disease
  » Davis M. J Support Oncol 2012; 10: 209
  » Vadivelu N. Clin Interv Aging 2008; 3: 421

- Low intrinsic efficacy means higher receptor occupancy required
  - no apparent ceiling for analgesia, but limited respiratory depression
    - 0.3 mg comparable to 10 mg morphine in acute studies
      » Raffa RB. J Clin Pharm Therapeutics 2014; 39: 577
Other issues with opioids: persistent pain

- Improved understanding/experience of long term use
  - tolerance, pain sensitivity may increase
  - hormonal
  - immune dysfunction
    - ?? increased cancer recurrence
      » Lennon FE Anesthesiology 2012; 116: 940
  - sleep disordered breathing, dental, cardiovascular risks

- Addiction: low rates if risk stratified in chronic non malignant pain
  - no history of abuse: estimated 0.19% addiction, 0.59% aberrant use
  - increases to 3.3 and 11% if risk factors
    » Fishbain D. Pain Medicine 2008; 9: 444
  - Long term use oxycodone
    - majority dose stable after 3 months, side effects less
      - 2.6% misuse rate

Reviewing and maintaining opioid therapy

- Regular review initially
  - define nociception
  - reassess/reaffirm messages, education, permit
  - engage non-pharmacological management

- Adjuvant medications
  - regular paracetamol +/- NSAIDs
  - anti-hyperalgesic medication
    - Gabapentin/Pregabalin
      - 100-300 mg tds GBP
    - TCAD/SNRI
      - Nortiptylne 10-25 mg nocte
      - Duloxetine 30-60 mg daily
    » Myers J. BMC Musculoskeletal Disorders 2014; 15: 76
  - Clonidine (50-100 mcgm tds)

- ? Role for rotation or opioid withdrawal/reduction with ketamine
Bone Scan with SPECT

Figure 3 SPECT/CT images (axial, sagittal, coronal) localizing intense focal tracer uptake to the right L3/L4 facet joint (continuous arrow) consistent with facet joint arthritis.

Carstensen M. Chiro Man Therap 2011; 19: 2

Anti-oxidants

- Vitamin c
  - prevention of CRPS in limb injury
  » Zollinger J Bone Joint Surg Am 2007; 89: 1424

- Pollen extract + vitamins in bladder inflammation
  » Cai T. Urologia 2013; 16: epub

- Combination antioxidants in pancreatitis
  - Selenium, betacarotene, L-methionine, Vit C, E
  - less pain, improved function, QOL
  » Kirk J Gastroenterol Surg 2006; 10: 499

- “turmeric”
  - oral extract acts as anti-TNF
  - ? role in rheumatoid
Cannabinoids

- Animal studies suggest reduces adverse memories and pain conditioning in fear-conditioned rodents
  - ? role in reducing anxiety, distress in development of pain chronicity

- Multiple Sclerosis: mild benefit
  - Different pain types
    - Central neuropathic pain
    - Spasticity related pain
  - Moderate reduction in pain
    - Associated reduced spasticity, improved function
      » Wade D. Multiple Sclerosis 2010; 16: 707
  - Add-on therapy in resistant spasticity: 30-40% respond
    - Adverse effects common but mild, less with slow titration
      » Saste-Garriga J. Expert Rev Neurother 2011; 11: 627
      » Novotna A. Eur J Neurol 2011; 18: 1122

Cannabinoids

- Chronic non-cancer pain
  - Systematic review noted varied trial designs, short duration
    - 15/18 trials showed modest analgesic benefit cf placebo
      - secondary benefit for sleep
      - few adverse effects
        » Lynch M. Br J Pharmacology 2011; 72: 735
  - Neuropathic pain states
    - HIV neuropathy, nerve injury, brachial plexus
      - 30% average pain relief
  - Chronic nociceptive pain e.g. arthritis
    - equivalent to weak opioid, 30% pain reduction
    - improved mood, sleep, coping
      - ? less opioid tolerance
Medicinal cannabis and the older person

- USA/European experience
  - 50% for chronic pain
  - common in older persons
    - 1/3 >60yrs in dutch program
    - high CBD, low THC preferred: less anxiety
      » Brunt T. J Clin Psychopharmacol 2014; 34: 34
- P-kinetic, p-dynamic considerations
  - cognitive adverse effects
- 5 trials report older persons
  - no effects on dyskinesia, CINV, SOB
  - may reduce behavioural, anorexia with dementia
  - adverse effects >placebo
  - lack of data in older persons
    - pain in particular
      » Van der Elsen G. Ageing Research Reviews 2014; 14: 56

Basic Retraining – Posture
Posture correction

- Start from the pelvis and let it “flow” up your spine – correct pelvic tilt pre-activates multifidus throughout spine

- 3 components:
  - neutral pelvis
  - shoulders retracted
  - chin tucked

- Tr Abdominus exercises

Thank You

- A/Prof Fary Khan
- Dr Kevin Young

The Royal Melbourne Hospital