Pain Management

Current perspectives

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Stress – Depression – Chronic pain relationship

*Moldofsky in Arthr Rheum, 1979
Thiagarajah et al in Int J Clin Rheum, 2014*

**Serotonin Synthesis**

1. L-tryptophan
2. L-tryptophan hydroxylase
   - 5-hydroxytryptophan
3. 5-hydroxytryptophan decarboxylase
   - 5-hydroxytryptamine (serotonin)
4. Monoamine oxidase
   - 5-hydroxyindoleacetaldehyde
Fibromyalgia and Chronic Pain Syndromes
A White Paper Detailing Current Challenges in the Field

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- New knowledge – not reaching clinicians
- Less well understood than nociceptive / neuropathic pain
- Overlaps with OA  RA  SLE
- Overlaps with chronic low back pain and chronic headaches
Diclofenac use and cardiovascular risks: series of nationwide cohort studies

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1 370 832 diclofenac initiators
3 878 454 ibuprofen initiators
291 490 naproxen initiators
768 781 paracetamol initiators
1 303 209 non-initiators of NSAID’s

→ Major CVS events at 30 days
   (AF, stroke, MI, cardiac death)
   - 50% increase vs non-initiators
   - 30% increase vs naproxen
   - 20% increase vs ibuprofen / paracetamol

→ 4,5 fold increase in GI bleeding

“Time to acknowledge the potential health risk of diclofenac and reduce its use.”
“Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components.”
Acute pain

Holdcroft in Core topics in Pain, 2005

- Normal biological response
- Protects / promotes healing
- Unrelieved acute pain:
  - ↑ catecholamines
  - ↑ heart rate
  - Delayed healing
  - Nervous system effects
  - May evolve into chronic pain
- Must be treated and its cause be removed
Chronic pain

Holdcroft in Core topics in Pain, 2005

- Persists longer than the expected time for healing (>3 months)
- No “warning” function
- Pain becomes the “disease”
- Emotional / psychosocial factors important
- Complex to treat
  - Interdisciplinary approach
Acute non-specific pain

*Sachs in Am Fam Phys, 2005*

- **Paracetamol**
- Inadequate analgesia with 1 gr qid
- ? NSAIDs contra-indicated

**No**
- NSAID / COXIB
- Inadequate analgesia / side-effects

**Yes**
- Tramadol – paracetamol combination
- Inadequate analgesia
- Strong opioid
Centrally acting analgesics

Paracetamol
- **Nikles in Am J Ther, 2005**
- **Schug in Clin Rheum, 2006**
- **Nikles in Am J Ther, 2005**
- **Schug in Clin Rheum, 2006**

**Central effect**
- No specific binding sites
- Serotonergic anti-nociceptive pathway
- Endocannabinoid system
- Acute post-op pain vs chronic pain

**Proven synergy**
- NSAIDs
- Tramadol
- Opioids
Tramadol

- Central acting atypical opioid
- Both mono-aminergic and opioid effects
- Much less opioid receptor affinity than morphine

Very low abuse potential (< 1/100 000)
Tramadol (37.5mg) / Paracetamol (325mg)

- Rational combination therapy ($NNT=3$)
- Faster onset and longer duration
- 25% less tramadol - less nausea
- Triple (+) mechanism of action

Positive studies in:
- Post-op pain
- Low back pain
- Fibromyalgia
- Neuropathic pain
- OA flares

NB: Mixed nociceptive – neuropathic pain
Warning
Focussing only on pain intensity in the assessment of chronic pain patients
*Sullivan in Pain, 2016*

- Results in the strongest analgesics for the wrong patients.

‘Higher pain intensity in chronic musculo-skeletal pain mostly indicates more emotional and psychosocial factors.’
Assessment of patients in chronic pain

Meyer in SA Fam Pract, 2011

- Unique and personal experience
- DN-4 / PHQ-9
- Measure
The Patient Health Questionnaire (PHQ-9)

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling asleep, staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself – or that you’re a failure of have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or, the opposite – being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Treatment goals for chronic pain patients

Ashburn in Lancet, 1999
Meyer in SA Fam Pract, 2007

- Reduction of pain (*30% is clinically significant*)
- Improvement in co-morbidities (e.g. mood and sleep)
- Improve patient’s functioning

Return to work
Chronic pain – multimodal approach

- Assessment of patient
- Physical therapy
- Supervised exercise
- Pharmacotherapy
- Education
- Behavioural therapy
- Occupational therapy

MORE
Primary analgesics

- Paracetamol
- NSAID’s / COX-2 inhibitors
  - Ibuprofen
  - Diclofenac
  - Naproxen
  - Celecoxib
  - Etoricoxib, etc
- Opioids
  - Mild
    - Codeine
    - Tramadol
  - Strong:
    - Morphine
    - Hydromorphone
    - Buprenorphine
    - Oxycodone
    - Fentanyl
    - Tapentadol

Adjuvant analgesics

- Tricyclics
  - Amitriptyline, Cyclobenzaprine
- SNRI’s
  - Duloxetine, etc.
- Anticonvulsants:
  - Carbamazepine
  - Gabapentin
  - Pregabalin

Local anaesthetics

Diverse analgesics

- Ketamine
- Cannabinoids
- Muscle relaxants

Topical analgesics

- Lidocaine patch
- Capsaicin patch
Mechanism-based pain classification

Woolf in Ann Int Med, 2009

NOCICEPTIVE PAIN
Tissue damage activates nociceptors
  *e.g. osteo-arthritis*
  *surgery*

Mixed pain
Both types of pain co-exist

e.g. Low back pain
Cancer pain

NEUROPATHIC PAIN
Lesion or disease of nervous system

Symptoms:
- Numbness
- Paraesthesia
- Hyperalgesia
- Electric-shocks
- Burning, etc

IDIOPATHIC / FUNCTIONAL PAIN

Mechanism-based pain classification

Woolf in Ann Int Med, 2009
Neuropathic pain

Disease / lesion of the somato-sensory nervous system

- Diabetic polyneuropathy
- Post herpetic neuralgia
- HIV neuropathy
- Trigeminal neuralgia
- Low back pain
- Chronic post-surgery pain (CPSP)
- Mechanical compression
- Cancer
- Chemotherapy
- Amputation (“Phantom pain”)
Chronic post-surgery pain (CPSP)

Kehlet et al in Lancet, 2006

Common causes of chronic pain

- Thoracotomy – up to 20-30%
- Breast surgery – up to 10-15%
- Limb amputation – up to 40%
- Gallbladder surgery – up to 20%
- Failed back surgery syndrome – up to 30%, etc

NB: Analgesia in peri-operative period
Peri-operative pain management

*Brown et al in Best Prac Research Clin Anaest, 2003*

**Systemic analgesics**
- Paracetamol
- NSAIDS / COXIBS
- Central diverse analgesics
  - Tramadol
  - Ketamine
- Opioids

**Regional techniques**
- Epidural analgesia
  - Local anaesthetic
  - Opioids
  - Adjuvants
- Peripheral nerve blocks
- Intra-articular analgesics
- Wound infiltration

**MULTIMODAL APPROACH**
Low back pain with neuropathic components

- Often overlooked
- 15-59% of LBP patients
- Leg pain
- Higher pain / disability levels
Pharmacotherapy in chronic neuropathic pain

Dworkin et al in Pain, 2007

First line

- **Antidepressants**
  - Tricyclics (*amitriptyline*)
  - SNRIs (*duloxetine*)

- **α2-δ ligands**
  - Pregabalin
  - Gabapentin

Second line

- **Tramadol**
  - Severe pain
  - Acute flare-up

Third line

- **Strong opioids**
  - Very careful patient selection
  - Tapentadol

- **Cannabinoids**
Algorithm for osteoarthritis of knee
Briyere et al in Sem Arthr Rheum, 2014

Step 2: Background treatment

Paracetamol
or
Chronic SYSADOA
(Symptomatic Slow-acting Drugs for Osteo-arthritis)

Glucosamine-sulphate
Chondroitin-sulphate

Still symptomatic: Add
Topical NSAIDS
Topical capsaicin

Refer to physio for assessment (e.g. mal-alignment)
Algorithm for osteoarthritis of knee

Briyere et al in Sem Arthr Rheum, 2014

Step 3: Advanced pharmacological management

Oral NSAIDS / COXIBS (Intermittently)

- **Increased GI risk:**
  - Avoid non-selective NSAIDs
  - COX-2 selective NSAIDs (±PPI)

- **Increased CV risk:**
  - Prefer naproxen

- **Increased renal risk:**
  - Avoid NSAIDS

- **Intra-articular hyaluronate**
- **Intra-articular corticosteroid**
Algorithm for osteoarthritis of the knee

Briyere et al in Sem Arthr Rheum, 2014

- Short-term tramadol
- Duloxetine

End-stage disease

Joint replacement surgery

If contra-indicated

Strong opioid analgesics (NB: guidelines)
“Last resort”
High potency opioids in chronic pain

Evans in Best Practice, 2000
Russell in Pain Medicine, 2002
Niesch et al in Cochrane Rev, 2009
Noble et al in Cochrane Rev, 2010

Short term use for acute pain
End-of-life pain

Chronic non-cancer pain – controversial

- Morphine sulphate
- Fentanyl
- Oxycodone, etc
SA Guidelines for long term high potency opioid therapy in chronic non-cancer pain

Raff et al in SAMJ, 2014 (Suppl)

“... appropriate and very careful patient selection and follow-up is paramount ...”

- Opioid risk assessment
- Psycho-social assessment
Opioid-induced hyperalgesia

Chu et al in J Pain, 2006
Edit in Br J Anaesth, 2010
Lee et al in Pain Physician, 2011
Velayudhan et al in Cont Educ Anaesth, 2014

Paradoxical increase in pain

- Hyperalgesia
- Mostly more diffuse
- Worsens with ↑ dosage
- May occur within 1 month

NB: Poorly defined pain disorders e.g. low back pain, FMS.

NB: Codeine combination drugs
Chronic widespread pain

Gran in Res Clin Rheum, 2003
Yunus in Best Pract Rheum, 2007

- ±10-12% of general population
- Mostly a spectrum of disorders
  - Psychiatric disorders
  - Rheumatic disorders
  - Sleep disorders
- Fibromyalgia in 30-40% of patients with CWP
What triggers FMS?

*Clauw in Ann Int Med, 2008
Elliot in Spine, 2015*

- Psychological stressors
- Early life stressors
- Infections
- Peripheral pain syndromes (eg. RA, SLE)
- Physical trauma (involving the trunk)
1990 ACR classification criteria for FMS
Woolfe et al in Arthr Rheum, 1990

- Widespread musculoskeletal pain > 3 months in all 4 quadrants
- > 11/18 painful tender points with digital pressure of 4kg/cm²
2010 ACR diagnostic criteria for FMS

Wolfe et al in Arth Care Res, 2010

- Widespread Pain Index (WPI)
  - 19 body areas
- Symptom Severity Scale (SS)
  - Fatigue: 0-3
  - Sleep: 0-3
  - Cognitive: 0-3
  - Somatic symptoms: 0-3
Recognized as a valid pain syndrome based on recent neurophysiological evidence

- Paradigm shift in diagnosis:
  - Diagnosis and management “concentrated” in primary care
  - Do not “over-investigate” or “over-refer”
  - Not “all-or-nothing” phenomenon (“fibromyalgia-ness”)

Emphasis on non-pharmacological strategies
Treatment of FMS

Non-pharmacological

- Cardiovascular exercise
- Patient education
- Cognitive behavioral therapy
- Multimodal approach
- Treat peripheral pain generators

Pharmacological

Modest evidence

- Pregabalin
- Duloxetine
- Amitriptyline
- Cyclobenzaprine
- Tramadol ± paracetamol

Primary Care
A new clinical model for the management of low back pain

Gordon Waddell, 1987

“The last 3 decades has seen a radical shift in the understanding and management of chronic LBP, from the biomedical model of specific organic pathology / structural damage and physical “fixes”, to the comprehensive biopsychosocial model, with emphasis on restoration of function.”
## Warning signs of serious causes of back pain

*Maher et al in Aus Prescriber, 2011*

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<tr>
<th>Cancer</th>
<th>Vertebral infection</th>
<th>Cauda equina syndrome</th>
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<tbody>
<tr>
<td>History of cancer</td>
<td>Fever</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Unexplained weight loss</td>
<td>Intravenous drug use</td>
<td>Faecal incontinence</td>
</tr>
<tr>
<td>Failure to improve after 1 month</td>
<td>Recent infection</td>
<td>Saddle anaesthesia</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>Immuno-compromised state</td>
<td>Lower limb weakness</td>
</tr>
<tr>
<td>Night pain</td>
<td>Rest pain</td>
<td></td>
</tr>
</tbody>
</table>

- **Vertebral infection**: Fever, Intravenous drug use, Recent infection, Immuno-compromised state, Rest pain
- **Cauda equina syndrome**: Urinary retention, Faecal incontinence, Saddle anaesthesia, Lower limb weakness
Cauda equina syndrome

Do you have bilateral leg pain?

When last did you pass urine / open your bowls?

Can you feel your bladder when it is full?

Does your backside / genital area feel normal?

“Saddle anaesthesia”

Can you tighten your anus?

May develop gradually

Most frequent finding: urinary retention

Chou in Ann Int Med, 2007
Garner in MPS Casebook, 2009
Low back pain assessment
Focused clinical examination

- General observation
- Regional back examination (tenderness)
  - Ankle and knee reflexes
  - Ankle and big toe dorsiflexion strength
  - Hop on each leg
  - Walk on heels then toes

Remember
- Abdominal / pelvic screening
- Peripheral pulses
- Urine dipstix
Answer 3 questions

Waddell in Backpain Revolution, 1991
Maher et al in Austr Prescr, 2011

- Serious spinal disease?
- Nerve root involvement?
- Disease elsewhere?
  - Inflammatory e.g. AS
  - Abdominal / Pelvic

If negative: SIMPLE / NON-SPECIFIC BACK PAIN

Are there yellow flags?
Yellow Flags

- Belief that LBP is harmful / disabling
- Fear avoidance behaviour / reduced activity
- Reliance on passive treatment versus active participation
- Depressed mood / social withdrawal
- Job dissatisfaction
- Compensation claims
- “Threatening” diagnostic labels
- Impaired sleep
Etiology of low back pain

**Structural**
- Facet joint OA
- Prolapsed disc
- Spinal stenosis
- Spondylolisthesis

**Infection**
- Osteitis
- TB
- Paraspinal abscess

**Inflammatory**
- Ankylosing spondylitis
- RA
- Spondylo-arthritis

**Metabolic**
- Osteoporotic collapse
- Hyperparathyroidism

**Neoplasm**
- Primary and secondary

**Referred pain**
- Aorta
- Urogenital
- Hip

**Musculoskeletal / Neurological**
- Myofascial pain
- Fibromyalgia

Speed in BMJ, 2004
Airaksinen et al in Eur Spine J 2006
Balaque et al in Lancet, 2007
Savigny et al in BMJ 2009
Spine, 2009
Ann Intern Med, 2011
Exclude red flags

Reassure patient of good prognosis
- 90% recover within 4 weeks

Patient to stay active
- RTW

Short course analgesic / NSAID / Coxib / Muscle relaxant

Consider physical therapy / spinal manipulation

Be aware of yellow flags
Advice for acute non-specific LBP patient

Maher et al in Austr Prescr, 2011

- Reassure there is no serious disease
- Avoid labelling such as:
  - “disc trouble”
  - “degeneration”
- Reassure of good natural history
- Encourage staying active
- Use simple safe treatments for symptom control
Management of persistent non-specific low back pain: summary of NICE guidelines


Persistent LBP (6 – 12 weeks)

- Educational advice
  - Benign
- Exercise
  - Supervised
- Physical therapy / spinal manipulation (8-12 sessions over 12 weeks)
- Needling (8-10 sessions over 12 weeks)
- May add:
  - Amitriptyline
  - Pregabalin
- Combo → Physical / psychological
  - Cognitive behavioural

- Exercise
- Manual
- Needling
Guidelines for chronic non-specific LBP

*Speed in BMJ, 2004*
*Airaksinen et al in Eur Spine J 2006*
*Balaque et al in Lancet, 2007*
*Savigny P et al in BMJ 2009*
*Chouw in Spine, 2009*
*[www.uptodate.com], 2015*

**Inter-disciplinary**

- Education
- Supervised exercise

- Address psychosocial issues
- Cognitive behavioural therapy
- Short-term pharmacotherapy
  - Paracetamol
  - NSAIDs / COXIBS
  - Muscle relaxants
  - Opioids (intermittently)