Acute Pain Management: From Clinical Evidence to Clinical Practice

BERNARD LEE MK
DIRECTOR, CHRONIC AND INTERVENTIONAL PAIN MANAGEMENT SERVICE
CONSULTANT PAIN SPECIALIST
FPM ANZCA (Australia)
CONSULTANT ANAESTHESIOLOGIST
M MED (ANAESTHESIOLOGY) (Singapore)
MEDICAL ACUPUNCTURIST
AMAC (Australia)
TYPES OF PAIN

Nociceptive Pain
- Noxious stimulus
- Pinch/pinprick
- Intense heat/cold
- Acute trauma
- Protective

Neuropathic Pain
- Post-operative pain
- Post-trauma
- Arthritis
- Inflammatory
- Healing/repair or pathological
- PNS and CNS lesions
- PHN/PDN/SCI
- Pathological

Functional Pain
- Fibromyalgia
- Pathological

CNS=Central nervous system; IBS=Irritable bowel syndrome; PDN=Painful diabetic neuropathy; PHN=Post-herpetic neuralgia; PNS=Peripheral nervous system; SCI=Spinal cord injury.

Multiple Types of Pain

Nociceptive pain
- Noxious stimuli
- Inflammation

Neuropathic pain
- Peripheral nerve damage
- Multiple mechanisms

Functional pain (non-inflammatory non-neuropathic)
- No known tissue or nerve damage
- Abnormal central processing

References:
Pain and Inflammation

Overview

- Osteoarthritis (OA)
- Rheumatoid Arthritis (RA)
- Ankylosing spondylitis (AS)
- Acute pain
  - Postoperative pain
  - Acute ankle sprain
  - Acute shoulder tendonitis/bursitis
  - Acute low back pain
Epidemiology of osteoarthritis (OA) and rheumatoid arthritis (RA)

• OA and RA are leading causes of severe long-term pain and physical disability\textsuperscript{1}

• Approximately 1 in 4 Europeans has some form of arthritis/rheumatism; 1 in 5 is under long-term treatment\textsuperscript{1,2}

• OA is the most common joint disorder and accounts for more disability among elderly patients than any other condition\textsuperscript{1}

• In developed countries, 1 in 10 of the population >60 y has significant clinical problems attributed to OA\textsuperscript{1}

• RA is the most common form of inflammatory joint disease and affects 0.3% to 1.0% of the general population in Europe\textsuperscript{1}

peripheral sensitization

External Stimulus

Sensitizing Stimulus

$PGE_2$

Bradykinin

$PKC_\varepsilon$

$PKA$

$SNS/PN3$

TTx resistant sodium channel

adapted from Woolf and Salter  Science 2000;288:1765
PGE2 increases excitability of neurones

No PGE₂

30 seconds after application of 1 mM PGE₂

COX-2 and Peripheral Sensitisation

Tissue Injury

COX-2 expressed

Increased neuronal membrane excitability

PGE$_2$

PKA

PKC$_\varepsilon$

Neurone firing threshold decreases

SNS/PN3
TTx resistant sodium channel
Interleukin-1β-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity

TAREK A. SAMAD*, KIMBERLY A. MOORE*, ADAM SAPIRSTEIN†, SARA BILLET* ANDREW ALLCHORNE‡, STEPHEN POOLE§, JOSEPH V. BONVENTRE & CLIFFORD J. WOOLF*‡

Neural Plasticity Research Group, Department of Anesthesia & Critical Care, Department of Anesthesia & Critical Care and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA
‡ Department of Anatomy, University College London, London WC1E 6BT, UK
§ National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Hertfordshire EN6 3QG, UK

Nature 2001;410:471 – 475
Convergence at WDR Neurone
Central Sensitisation

- tissue or nerve injury
- release of EAAs and neuropeptides
- increased depolarization at the NMDA receptor
- expanded receptive fields and hyperexcitability
- excitotoxicity
- loss of inhibition

Increased Pain

adapted from Dubner
**Central Sensitization May Have Contributed to OA Pain and Neuropathic Pain Symptoms**

- Focus group transcripts from participants with knee OA (N=80) were analyzed to determine the use of unprompted NP descriptors to characterize their pain (including burning, tingling, pins and needles, and numbness) to determine whether people with chronic, symptomatic knee OA use pain descriptors suggestive of underlying NP.

- The proportion of participants who used **NP descriptors** to characterize their pain was 34% (95% CI, 24% to 45%).

- Participants using NP descriptors were younger than those who did not (mean age ± SD: age: 64.8 ± 9.7 years vs 72.0 ± 10.0 years, respectively; $P=0.003$).

- Characteristics that did not statistically distinguish participants who used NP descriptors from those who did included duration of OA, pain intensity, OA severity, and gender.

OA = osteoarthritis; NP = neuropathic pain; CI = confidence interval; SD = standard deviation.

Central Sensitization in OA: Expansion of Symptoms Beyond the Joint

- Quantitative sensory testing of PPTs in patients with knee OA pain (n=48) and matched controls without knee pain (n=24) revealed that subjects with OA pain exhibited sensitization in both OA-affected and unaffected areas
  - Increasing pain intensity in the OA-affected (knee) joint was associated with lower PPT in OA-unaffected areas (eg, arm)^1

Central Sensitization in OA: Increased Pain Severity and Worse Pain-Associated Outcomes


<table>
<thead>
<tr>
<th>Measure</th>
<th>Spearman's rank correlation coefficient r</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patellar tendon</td>
<td>-0.545</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sacral 2 subcutaneous dermatome level</td>
<td>-0.546</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adductor longus muscle</td>
<td>-0.561</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WOMAC pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patellar tendon</td>
<td>-0.589</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sacral 2 subcutaneous dermatome level</td>
<td>-0.601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adductor longus muscle</td>
<td>-0.540</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WOMAC physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar 2 subcutaneous dermatome level</td>
<td>-0.550</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sacral 2 subcutaneous dermatome level</td>
<td>-0.509</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peroneus longus muscle</td>
<td>-0.571</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36 bodily pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar 1–Lumbar 2 supraspinous ligament</td>
<td>0.534</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar 2 subcutaneous dermatome level</td>
<td>0.606</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adductor longus muscle</td>
<td>0.569</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OA = osteoarthritis; PPT = pressure pain threshold; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities; SF-36 = short form-36 health survey.

A cross-sectional study that assessed hyperalgesia in patients with refractory OA-associated pain (n=62) reported significant correlations between PPT values at each listed site and VAS, WOMAC pain and physical activity subscales, and SF-36 bodily pain score.
SKIN

PRIMARY AFFERENT NERVE

Dorsal root ganglion

Dorsal horn

SPINAL CORD
central sensitization

adapted from Woolf and Salter Science 2000;288:1765
POSTSYNAPTIC PROCESS

Glutamate release

PRESYNAPTIC PROCESS

NMDA receptor

Second messengers:
- kinases (eg PKC),
- diacylglycerol,
- cAMP

Long term changes
(receptor function,
transmitter production)

CELL NUCLEUS

Gene transcription

C-fos oncogene
Cortical Reorganisation

1a Patients without phantom pain

1b Patients with phantom pain

D1 and D5

mouth

mirrored mouth of amputation side
I will show that my client is well tolerated and effective.
For chronic pain, most measures of treatment response involve patient-reported outcomes, for which the patient is the most important judge of whether changes are important or meaningful\textsuperscript{1,2}

- Determinations of statistical significance must be supplemented by consideration of the clinical importance of changes in outcome measures\textsuperscript{1}

The IMMPACT consensus meeting proposed provisional benchmarks for identifying clinically important changes in the specific outcome measures for chronic pain clinical trials\textsuperscript{1}

\begin{itemize}
  \item Minimally Important Improvement
  \[10\%-20\% \text{ Reduction in pain intensity}\]
  \item Moderately Important Improvement
  \[\geq 30\% \text{ Reduction in pain intensity}\]
  \item Substantial Improvement
  \[\geq 50\% \text{ Reduction in pain intensity}\]
\end{itemize}

NNT = number needed to treat; IMMPACT = Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

Patients with 50% reduction in pain vs. placebo

McQuay H, *BMJ* 1997
How effective was paracetamol compared with NSAIDs?

2007 League table of NNT for at least 50% pain relief over 4-6 hrs in patients with moderate to severe pain, (all oral analgesics except IM morphine)

[http://www.medicine.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/leagtab.html]
ETORICOXIB IN ACUTE PAIN

- Etoricoxib 120 mg has been approved for treating acute pain, which includes post-operative pain and other acute pain such as primary dysmenorrhea, and acute gouty arthritis.
- Efficacy of etoricoxib in the post-operative setting, as evaluated by NNT.
- COCHRANE REVIEW: Five randomized, placebo-controlled studies with a total number of 880 patients were included:
  -- Four studies on patients with dental pain following extraction of at least one impacted third molar
  -- One study on patients with pain following uncomplicated orthopaedic surgery
- NNT were calculated to measure at least 50% pain relief over 4-6 hrs (substantial pain relief) based on TOPAR scores.
Results: 120 mg etoricoxib with a NNT of 1.9 for acute post-operative pain

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Studies</th>
<th>Participants</th>
<th>Etoricoxib (%)</th>
<th>Placebo (%)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1</td>
<td>124</td>
<td>59</td>
<td>12</td>
<td>2.2 (1.6 to 3.1)</td>
</tr>
<tr>
<td>120</td>
<td>5</td>
<td>655</td>
<td>64</td>
<td>10</td>
<td>1.9 (1.7 to 2.1)</td>
</tr>
<tr>
<td>180 and 240</td>
<td>2</td>
<td>248</td>
<td>79</td>
<td>12</td>
<td>1.5 (1.3 to 1.7)</td>
</tr>
</tbody>
</table>

Etoricoxib in acute pain

- Indirect comparisons of NNTs for at least 50% pain relief over 4 to 6 hours in reviews of other analgesics using identical methods indicate that etoricoxib 120 mg:
  - has slightly better efficacy than rofecoxib 50 mg (2.2 (1.9 to 2.4); Barden 2005);
  - is significantly better than lumiracoxib 400mg (2.7 (2.2 to 3.5); Roy 2007) or
  - celecoxib 400 mg (2.5 (2.2 to 2.9); Derry 2008).
  - better than the non-selective NSAIDs ibuprofen 400 mg (2.7 (2.5 to 3.0); Collins 1999), naproxen 500 mg (2.7 (2.3 to 3.2; Derry 2009a) and diclofenac 50mg (2.4 (1.8 to 3.3;Derry 2009b).
The weighted median time to re-medication with ARCOXIA 120mg is about 24hrs vs. placebo at 1.8hrs.
Osteoarthritis
Etoricoxib 60 mg vs Naproxen

Results

Etoricoxib relieved pain and improved mobility and disease status

WOMAC Pain Subscale

WOMAC Physical Function Subscale

PGADS

Placebo (n=56)  Etoricoxib 60 mg (n=224)  Naproxen 1000 mg (n=221)

*0- to 100-mm VAS (0 = none to 100 = extreme); **0- to 100-mm VAS (0 = very well to 100 = very poor); †500 mg twice daily.

P<0.001 vs placebo for both etoricoxib and naproxen; P = NS etoricoxib vs naproxen.

Adverse effects of NSAIDs

Upper-GI
- Dose-dependent toxicity
  - Intolerability, dyspepsia
  - GI bleeding
  - Ulcers – bleeds / perforations

Renal
- Fluid retention, oedema, hypertension
- Renal dysfunction / failure
  - – acute / chronic
- Heart failure

Anti-platelet effects
- Contributes to blood loss

Hypersensitivity
- Angioedema, bronchospasm

BNF, March 2002
No Short-Term Adverse GI Effects - The Big Mistake!

• Study designed to evaluate short-term GI effects in elderly
• Study planned to enrol 160 patients
• Study terminated by investigator at 17 subjects:
  – 8 patients had ulcers!
  – 4 of 4 in ketorolac group!

‘… because of the unexpectedly high incidence of gastroduodenal ulcers observed…’

Harris et al. ClinTher 2001;23:1422
FDA Memorandum on NSAIDs & CV Risk 6 April 2005

Class Effect of All NSAIDs

- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

Cardiovascular Safety

- Arthritis patients often have concomitant CV disease\(^1\)
- Pain is an important predictor of CV risk\(^2,3\)
- Randomized controlled trials and observational data demonstrate that CV risk of etoricoxib appears similar to that of traditional NSAIDs\(^4-6\)
- Recent data suggest that differential CV effects of NSAIDs (selective and nonselective) may be independent of COX-2 inhibition\(^7,8\)

References:
### APTC endpoint (cardiovascular, haemorrhagic, and unknown death, and nonfatal myocardial infarction and stroke)

<table>
<thead>
<tr>
<th></th>
<th>Events per 100 patient years</th>
<th></th>
<th></th>
<th></th>
<th>Percent naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coxib</td>
<td>Coxib</td>
<td>Placebo</td>
<td>Coxib</td>
<td>NSAID</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.7</td>
<td>1.9</td>
<td>1.1</td>
<td>0.8</td>
<td>73</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.3</td>
<td>1.5</td>
<td>1.1</td>
<td>1.1</td>
<td>20</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
<td>2.0</td>
<td>about 50</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
<td>0.8</td>
<td>67</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td></td>
<td>0.9</td>
<td>0.8</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

5. ME Farkouh et al. Comparison of lumiracoxib with naproxen and ibuprofen in the therapeutic arthritis research and gastrointestinal event trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004 364: 675-684
RECOMMENDATIONS

NSAIDs / COXIBs

• Use lowest effective dose, shortest duration

• Not for patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures;

• Coxibs should not be prescribed for patients with established ischaemic heart disease, stroke or congestive heart failure;

• Caution for Coxibs for patients who have: hypertension, hyperlipidaemia, diabetes and smoking as well as peripheral arterial disease;

• Etoricoxib should not be prescribed for patients with hypertension whose blood pressure has not been adequately controlled.
"The antidepressiva works great for improving your mood. But maybe it's time to cut back the dosage."
Tricyclic Agents

- best documented analgesics here (NNT 2.2)
  - amitriptyline best investigated!
  - desipramine/nortriptyline less AEs
- start on low doses increases compliance!
- Often adverse effects (NNH 2.8)
- effect needs time!
- SSRIs not as effective (NNT 6.7)
  - noradrenergic effect necessary?
- venlafaxine another option?
## Antidepressants Compared with Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of trials</th>
<th>Antidepressant improved/total</th>
<th>Placebo improved/total</th>
<th>Relative benefit (95%CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td>13</td>
<td>180/260</td>
<td>73/205</td>
<td>1.9 (1.6 to 2.4)</td>
<td>3.0 (2.4 to 4.0)</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>3</td>
<td>43/77</td>
<td>8/68</td>
<td>4.8 (2.4 to 9.4)</td>
<td>2.3 (1.7 to 3.3)</td>
</tr>
<tr>
<td>Atypical facial pain</td>
<td>2</td>
<td>62/88</td>
<td>30/85</td>
<td>2.0 (1.5 to 2.8)</td>
<td>2.8 (2.0 to 4.7)</td>
</tr>
<tr>
<td>Central pain</td>
<td>1</td>
<td>10/15</td>
<td>1/15</td>
<td>10 (1.5 to 69)</td>
<td>1.7 (1.1 to 3.0)</td>
</tr>
</tbody>
</table>
Anticonvulsants as Membrane Stabilisers

- pregabalin
- gabapentin
- carbamazepine
- clonazepam
- valproate
- lamotrigine
- baclofen

pooled NNT 2.7
## Anticonvulsants Compared with Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of trials</th>
<th>Anticonvulsant improved/total</th>
<th>Placebo improved/total</th>
<th>Relative benefit (95%CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td>3</td>
<td>56/68</td>
<td>26/68</td>
<td>1.9 (1.4 to 2.7)</td>
<td>2.5 (1.8 to 4.0)</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>3</td>
<td>178/315</td>
<td>41/224</td>
<td>3.1 (2.3 to 4.1)</td>
<td>2.6 (2.2 to 3.3)</td>
</tr>
<tr>
<td>Migraine prophylaxis</td>
<td>2</td>
<td>63/74</td>
<td>17/77</td>
<td>3.7 (2.4 to 5.9)</td>
<td>1.6 (1.3 to 2.0)</td>
</tr>
<tr>
<td>Other pain syndromes</td>
<td>1</td>
<td>5/14</td>
<td>1/15</td>
<td>5.4 (0.7 to 40)</td>
<td>not calculated</td>
</tr>
</tbody>
</table>
Relative Activity on Serotonin and Norepinephrine Reuptake Among Antidepressants

<table>
<thead>
<tr>
<th>Serotonin</th>
<th>Mixed</th>
<th>Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Venlafaxine</td>
<td>Maprotiline</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Duloxetine</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Amiriptyline</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Milnacipran</td>
<td>Reboxetine</td>
</tr>
</tbody>
</table>

Opioids

• In principle, opioids are effective in nociceptive and some neuropathic pain; however, not always and not necessarily completely for dynamic pain!

• Possibly preferable opioids here are:
  – tramadol
    • noradrenergic and serotoninergic effect
  – morphine
    • Mu receptor antagonist/monaminergic effect
  – oxycodone
    • kappa receptor effect
**Opioids**

- ‘Lack of analgesic effect of opioids on neuropathic … pain’ Pain 1988;33:11
- ‘… intravenous … morphine reduce the pain of Osteoarthritis’ Neurology 1991;41:1024
- ‘A call for more science, not more rhetoric, regarding opioids and arthritic pain’ Pain 2001;47:1
- ‘Efficacy of oxycodone in neuropathic pain…’ Neurology 1998;50:1837
OPIOIDS FOR OA PAIN

- Osteoarthritis guidelines provide limited guidance on opioid use.
- The 1995 ACR guidelines for hip OA suggest opioids be avoided for long term use, but short term use may be helpful, without reference to primary data.\(^{15}\)
- The 1995 ACR knee OA guidelines do not discuss opioids directly.\(^{16}\)
- The 1998 UK guidelines on degenerative arthritis suggest that if relief is inadequate with 2.4 grams of ibuprofen and 4.0 grams of paracetamol a day, other antiinflammatories or opioids may be considered.\(^{18}\)
- The 2000 update of the ACR OA guidelines suggests that opioids might be used as a medication of last resort.\(^{17}\)
- Opioids are effective in OA hip and knee pain, and have predictable side effects.
- It would be unwise were physicians to discount an entire class of medications over unfounded fears and incomplete knowledge of their benefits.
USE OF ULTRACET IN OA KNEES

• The efficacy of tramadol/acetaminophen combination tablets (Ultracet®) as add-on and maintenance therapy in knee osteoarthritis pain inadequately controlled by nonsteroidal anti-inflammatory drug (NSAID).
  Park KS, Choi JJ, Kim WU, Min JK, Park SH, Cho CS

• Tramadol/APAP add-on significantly improved knee OA pain which had been inadequately controlled by NSAIDs. In those subjects who showed favorable response to tramadol/APAP and NSAID combination therapy, both tramadol/APAP and NSAIDs were effective at maintaining the pain-reduced state and there was no significant difference in efficacy between tramadol/APAP and NSAIDs.
Opioid Sparing Regimes

- Multimodal analgesia (Kehlet et al 1999)
- NSAIDs and COX-2 (Romsing, Moiniche 2004)
- Paracetamol (Romsing 2002)
- Ketamine (Elia, Tramer 2005)
- Gabapentin and Pregabalin (Dahl et al 2004)
- Gabapentin and Rofecoxib (Gilron et al 2005)

Opioid reduction 20 – 40%, Reduction of PONV 30%

Clinical effects?
Single-modality treatment of a Multi-modality problem is futile
“There’s no pain that’s so easy to bear than that of someone else.”

–Leriche

Van Gogh
“Old Man in Sorrow”
Dr Bernard Lee Mun Kam
FFPM, ANZCA (AUSTRALIA), M.MED (ANAESTHESIOLOGY) SINGAPORE,
FAMS (SINGAPORE), MBBS (SINGAPORE)
Director, Interventional Pain Management Service
Consultant Pain Specialist
Consultant Anaesthesiologist
Medical Acupuncturist

Singapore Paincare Center
290 Orchard Road #18-03 Paragon
Singapore 238859
Tel: +65 6235 6697  Fax: +65 6235 6846
Mobile: +65 9800 0499
enquiries@paincarecenter.com.sg
www.paincarecenter.com.sg