Persistent post surgical pain

Myles Conroy
Why persistent?

- A better term
- Understood by patients
- No negative connotation (chronic = incurable?)
- No arbitrary time constraint (ie chronic = >1, 3, or 6 months?)
- All chronic pain was once acute....it just persisted!
Incidence varies with definition, severity

Estimates ... 15000-30000 new cases in Australia each year

22.5% patients attending UK chronic pain clinics cite surgery as cause for pain, 18.7% trauma (Crombie, Pain, 1998)

Nowegian population study
- 40% prevalence in surgical area 3M-3Y, 18% severe
- 10% if exclude same pain preop,
- 6% if exclude any pain preop (n=2043, Johanssen 2012)
## Incidence

### Table 1.2  Incidence of chronic pain after surgery

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Incidence of chronic pain (%)</th>
<th>Estimated incidence of chronic severe pain [&gt;5 out of 10/10] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30–85</td>
<td>5–10</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>5–65</td>
<td>10</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>11–57</td>
<td>5–10</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>5–63</td>
<td>2–4</td>
</tr>
<tr>
<td>Coronary bypass</td>
<td>30–50</td>
<td>5–10</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>6–55</td>
<td>4</td>
</tr>
<tr>
<td>Hip arthroplasty</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3–50</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0–37</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Dental surgery</td>
<td>5–13</td>
<td>Not estimated</td>
</tr>
</tbody>
</table>

*Sources: Adapted from Kehlet 2006, Macrae 2008, Wylde 2011.*

*(From Acute Pain Management: Scientific evidence 4th Ed)*
Scope of the problem...

Surgical procedure type
- Caesarian 6-55% at 12 months, 4% severe
- Inguinal hernia 5-35%, severe or limiting 2-11%
- Thoracotomy 60%, severe 3-5%
- Cardiac 30-50%, severe 5-10%
- Knee arthroplasty 44%, 15% severe
- Hip arthroplasty 28%, 12% severe
- Mastectomy 30%, 5-10% severe
- Amputation - stump pain 21-51% phantom pain 30-70%, 5-10% severe

(Kehlet 2006, Macrae 2008, Wylde 2011)
A surrogate for persistent pain?
Clarke, BMJ 2014 (n=39,140)
  3.1% >90d postop
  assoc younger age, lower income, comorbs
    benzos, SSRIs, ACEis
  gynae < open prostate < thoracic

Alam, JAMA Int Med 2012 (n=391,139)
  day stay surgery
  7.1% Rx opioids within 1 week, >10% still taking at 1 year
  0.3% Rx NSAIDs, 25% still taking at 1 year
Pathophysiological Mechanisms

- Neuropathic pain (incl. neuroma formation)
  - Approx. ½ cases positive on DN4 (Duale J Pain 2014)
- Peripheral sensitisation (ongoing inflammation)
- Central sensitisation (i.e. allodynia)
  - Repeated C fibre input – NMDA activation (Mg plug)
  - WDR neuron explains convergence
  - Loss of inhibitory interneurons
- Genetic susceptibility
  - COMT haplotypes in experimental & TMJ pain
  - Mu opioid genotype association with pain after abdominal Sx
- CRPS
“Wind up” – central sensitisation

- Repeated C fiber activation -> NMDA activation (removal Mg plug)
- Amplification in second order neurons
- may outlast painful stimulus...potentiation
- WDR (wide dynamic range) neuron explains convergence – lowering of pain threshold outside area of inflammation
- Nerve damage – spontaneous ectopic discharge contributes to sensitisation
- Loss of inhibitory interneurons – facilitation through loss of descending inhibition
Can we identify those at risk?
Can we do anything about it?
Yes.......and Yes (probably)!
Consider
- Surgery factors
- Patient factors
- Anaesthesia factors
TKR

- Pain in knee = indication for surgery
- Preop opioids common (OIH)
- Often associated with severe acute pain with movement (...fear avoidant)
- Nerve injury routine (infrapatellar et al)
Surgical predictors

- **Surgery type**
  - Open v. laparoscopic
    - Cholecystectomy – 9.7% v 3.4% (p<0.05) (Stiff BJ Surg 94)

- **Known nerve entrapment/section**
  - Breast – intercostobrachial nerve
  - Thoracotomy – intercostal nerve
  - Hernia/LUSCS – ilioinguinal/genitofemoral nerve
  - TKR – infrapatellar nerve
  - Outside wound – retraction, tourniquet, oedema, etc

- **Duration of surgery** - >3h (Peters Ann Surg 2007)

- **Surgical unit** (high v. low volume)
  - High volume breast surgeons – less chronic pain
  (Tasmuth, Eur J Surg Oncol, 1999)
Surgical technique?

- Sparing intercostobrachial nerve at mastectomy – reduces numbness but not pain - Level I (Warrier 2014, 3 RCTs)
- Sparing v. neurectomy of ilioinguinal nerve at hernia repair
  - International guidelines 2011 recommend preservation all nerves
  - One RCT supports neurectomy Malekpour 2008
    - n=100, 21% v. 6% - level II
Patient Predictors

- Severe acute postoperative pain
- Preoperative pain, past or concurrent. (within surgical field or not)
- Preoperative opioids
- Female gender
- Younger age (infant protected?)
- Radiotherapy or neurotoxic chemotherapy
- Genetic polymorphisms? ....can we predict a pain phenotype?
Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk

David Yarnitsky \textsuperscript{a,*}, Yonathan Crispel \textsuperscript{a}, Elon Eisenberg \textsuperscript{b}, Yelena Granovsky \textsuperscript{a},
Alon Ben-Nun \textsuperscript{c}, Elliot Sprecher \textsuperscript{a}, Lael-Anson Best \textsuperscript{c}, Michal Granot \textsuperscript{d}

“Diffuse Noxious Inhibitory Control”
DNIC measured by the decrease in reported pain due to a test stimulus (heat electrode on forearm) when a concomitant heat stimulus (contralateral hot water immersion) is applied \textbf{pre thoracotomy}

DNIC did not predict acute pain

Efficient DNIC reduces risk chronic pain OR 0.52

Severe acute pain increased risk of chronic pain OR 1.8
Psychosocial predictors

- Preoperative anxiety, depression
- Catastrophising
- PTSD
- Social supports v. Spousal solicitousness
- Compensation issues
- Late return to work

Hinrichs-Rocker Eur J Pain 2009
Surgery – a psychological crossroad

Fear-avoidance model

Vlaeyen Pain 2000
An example
Predicting postherniotomy pain

- Aasvang, Anesthesiol 2010
- Prospective study n=464
- Pain at 6 months (12.4% mod-severe)
  - Preop activity impairment score
  - Preop pain to tonic heat stimulation
  - Depression/Anxiety
  - Open v laparoscopic (16% v. 8.1%)
  - Strong association with groin numbness, pain at 30 days
  - All p<0.02
Not much!
New area of investigation
Few prospective trials
Outcomes difficult to assess
No standardised criteria

Some evidence to support
Regional analgesia
Ketamine
Gabapentin
Nitrous oxide
Acute hyperalgesia/tachyphylaxis well described (thoracic, abdominal surgery)

Some evidence for reversal with ketamine

Chronic pain 1 year after cardiac surgery

- Von Gulik et al. BJA 2012. n=90, retrospective
- Dose dependent effect of remifentanil
- OR 8.9 p=0.01
- Also younger age <69 (OR 7), BMI >28 (OR 9)
Regional analgesia

- Cochrane review 2013 (Andreae) “Level 1”
  - Pain at 6 months v. systemic analgesia

- Thoracotomy (3 RCTs n=250)
  - Epidural NNT=4 (OR 0.33, 0.2-0.56)

- Mastectomy (2 RCTs n=89)
  - Paravertebral NNT=5 (OR 0.37, 0.14-0.94)
Regional analgesia

- Epidural & open colonic resection
  - RCT Level II Lavand’homme 2005
    - Intraoperative v. postop v. systemic
  - Case control level III OR 0.19 (0.05-0.76) Bouman 2014
- Spinal anaesthesia for LUSCS and hysterectomy
  - Retrospective LUSCS spinal 17% v. GA 37% (Nikolajsen 2004)
  - Retrospective TAH spinal v. GA OR 0.42 (0.11-0.85) Brandsborg 2007
Epidurals & Phantom limb pain

- Meta-analysis supports epidural analgesia timing important preop/intraop/postop NNT 5.8 for severe phantom pain postop inconclusive
- No good evidence to support ketamine, gabapentin or peripheral nerve block (useful for acute pain Rx)

Gehling & Tryba, Shmerz 17(1)
Regional anaesthesia & orthopaedic surgery

- Overwhelming support for acute pain in multiple systematic reviews
- Disappointingly no evidence in chronic pain!
Wound Infiltration

- Iliac crest bone harvest site ropivacaine infusion – Level II Blumenthal 2005
- Craniotomy – Level II Batoz 2009
- EMLA & Mastectomy Fassoulaki
IV Lignocaine infusion

- Numerous studies of perioperative lignocaine infusions demonstrate reduced acute pain and morphine requirements esp abdominal surgery
- Demonstrated pre-emptive & preventive effects
- Good evidence for faster return of gut fn after bowel, prostate Sx
- Supportive evidence in mastectomy only
  - Level II Grigoras 2012 n=36, 2/17 v 9/19, p=0.03
Ketamine

- Excellent evidence in acute pain with pre-emptive and preventive effects
- Chronic pain
  - Cochrane (Chaparro 2013) Level I, 14 RCTs, n=1388
    - Mainly abdominal surgery
    - >24h – OR 0.63 (0.47-0.83)
    - <24h – OR 0.45 (0.26-0.78)
    - NNT ~14
Ketamine

- THR – ketamine with GA
  - Reduced rest pain at 6/12 – 21% v. 8% Remerand 2009
Pregabalin – controversy!

- Two conflicting meta-analysis by the same author...(Clarke 2012, 2013)
  - Re-analysed data with unpublished studies-refuted benefit for gabapentin and pregabalin
  - Strong positive studies in TKR & cardiac surgery

- Ongoing uncertainty – heterogenous studies, publication bias, study design & definitions
- Side effects significant
Pregabalin & TKR

- **Pregabalin** for 14 days reduces chronic neuropathic pain after TKR at 3, 6 months (0 v. 8.7, 5.2%, p<0.05). Also better ROM up to 30d.
  .....but at the cost of increased sedation & confusion, falls risk

Buvanendran Anesth Analg 2010 110 199-207

....author later reduces doses used in clinical practice
Evidence supports regional analgesia (epidural/femoral catheter) for early rehabilitation and ROM. ROM at 1, 3 months similar Capdevila (Anesthesiol 99;91).

No data for pain outcomes

48h Ketamine (+FNC) improves early rehab but ROM, pain same at 6, 12 weeks Adam (Anesth Analg 2005;100)
Pre-emptive analgesia (pre-incisional)
- shown for epidural analgesia in acute pain post thoracotomy, but not pain at 6 months (Bong et al J Cardiothorac vasc anesth 19(6) 786-93)
- Some evidence for epidural in chronic pain post laparotomy (L’avandhomme Anesthesiol 2005)
- Amputation studies – preop epidural of some benefit?

Preventive analgesia
- benefit extends beyond duration of drug action
- Delivered over time of increased pain to prevent central sensitisation– i.e into postop period
Pre-emptive Analgesia in Acute Pain

Animal studies convincing, controversy in human studies
same intervention pre v. post incision

Combined 3 outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Upper</th>
<th>Lower</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural analgesia (37)</td>
<td>.38</td>
<td>.47</td>
<td>.28</td>
<td>.00</td>
</tr>
<tr>
<td>Local anesthetics (26)</td>
<td>.29</td>
<td>.40</td>
<td>.17</td>
<td>.00</td>
</tr>
<tr>
<td>NMDA antagonists (18)</td>
<td>.10</td>
<td>.22</td>
<td>-.03</td>
<td>.12</td>
</tr>
<tr>
<td>NSAIDs (30)</td>
<td>.38</td>
<td>.48</td>
<td>.27</td>
<td>.00</td>
</tr>
<tr>
<td>Systemic opioids (13)</td>
<td>-.10</td>
<td>.07</td>
<td>-.26</td>
<td>.25</td>
</tr>
</tbody>
</table>

Note – supplemental analgesia reduced ~50% for epidural, NSAID, LA
Opioids – the good guys???

- Opioid-induced hyperalgesia (v. tolerance)
- Known to exist with intraoperative remifentanil and long term opioid use, at least partially reversed with ketamine
- What about opioids like morphine in postoperative pain?
- “metaflammation” - TLR and glial interleukin response, role for stereoselsctive naloxone?
- More questions than answers....
Abdominal surgery

- **LUSCS**
  Australian f/u study – n = 426.
  Wound pain at 2/12 14.6%, 12/12 4.2%
  Liu Anaesth Int Care 2013
  Rpt LUSCS - Preoperative scar hyperalgesia (41%)
  associated with acute postop pain
  Ortner Eur J Pain 2013
  retrospective – chronic pain at 10 months
  spinal 17% v. GA 37%
  Nikolajsen Acta Anaes Scand 2004

- **TAH**
  retrospective -1299 women at 12 months
  Incidence pain >2d/wk – 13.7%
  spinal v. GA OR 0.42 (0.21-0.85)
  Brandsborg Anesthesiol 106(5)
Sen, Anesthesiol 2009
N=60
placebo v. intraop ketamine v. gabapentin 1200mg
Standard GA - sevo/N20, fentanyl, morphine
PCA morphine reduction ketamine 35% gabapentin 42% (p<0.001)
Incisional pain 1,3,6 months lower in gabapentin v. ketamine, placebo
Epidurals & abdominal surgery

- Good evidence for improved acute pain outcomes and medical Cx after AAA repair
  (Nishimori Cochrane Rev 2012)
- Chronic pain after surgery?
  - Case control study n=101
  - pain 6 months 34% v 17.6%
  - OR 0.42 (0.16-1.05)
  - Adjusted for risk factors 0.19 (0.05-0.76)
  - (age, sex, gender, preop pain)
  (Bouman Pain Pract 2014)
Randomised, double blind trial of 85 patients having open colonic resection

- All had intraop ketamine
- 4 treatment groups, intra/postop
  iv = clonidine/lignocaine/morphine
  Epi = clonidine/bupivacaine/sufentanil
  G1 – iv intraop +postop
  G2 – iv intraop + epidural postop
  G3 – epi intraop + epi postop
  G4 – epi intraop + iv postop
G1 = iv-iv, G2 = iv-epi, G3 = epi-epi, G4 = epi-iv
Conclusions

- Epidural provides superior analgesia in the short and long term
- *Intraoperative* epidural use reduces residual pain at 1 year
- Preemptive effect of epidural – protective for sensitisation occurring intraoperatively
Incidence of chronic pain 57% @ 3M, 47% @ 6M (Bayman J Pain 2014)

**Epidural** reduces chronic pain at 6 months v. PCA morphine
- OR 0.33 (0.20-0.56) NNT 4
  - Andreae, Cochrane Review 2012 - 3 trials, n=250
- 48 v. 75% (p<0.05)
  - Senturk Anesth Analg 02 94(1)
- No comparison with paravertebral for chronic pain

**Ketamine**...conflicting evidence
- Duale Eur J Pain 09 13(5) – IV PCA, ketamine v. saline
- No difference at 4 months
Thoracotomy

- Gabapentin
  - Acute pain
    - 2 Negative single dose RCTs
    - 1 RCT showing reduced pain & morphine, improved lung function (Rx 3/7)
  - Persistent pain
    - RCT Gabapentin v Naproxen for 2/12 and reduced pain, neuropathic sx for established pain
      Solak Eur J Cardiohor Surg 2007
Evidence supports ketamine for reduced acute pain, morphine consumption AND pain at 6 weeks

Loftus Anesthesiol 2010;113

Gabapentin morphine-sparing for acute pain, less morphine SEs

Turan Anesthesiol 2004;100
Ketamine with GA reduced rest pain at 6 months: 21% v. 8%

Reimerand Anesth Analg 2009;109
Acute orthopaedic rehabilitation
“standard care” historical controls v. standing orders, access to breakthrough analgesia protocol and preememptive analgesia 1 hr before physiotherapy
Increased opioid use
faster to mobility and shorter LOS
Reduced chronic pain 15% v. 4% (p=0.02)
.......so good analgesia improves outcomes!

Morrison JAGS 2009
Orthopaedics – Outcomes of good simple analgesia?

A: Percent of Patients in Intervention and Control Groups Reporting Moderate to Very Severe Pain With Walking For the 6 Months Following Discharge

Weeks Following Discharge From Rehabilitation

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>12</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>18</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>24</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Morrison JAGS 2009
Dynamic view on early postop pain scores
Useful predictor of chronic neuropathic pain

N=128

Pain scores at 3 months (pain inventory & DN4) correlated with pain diary

58% had persistent pain at surgical site
11% had severe neuropathic pain
- correlated with pain trajectory

Flat pain trajectory worthy of early postop intervention?

Lavand’homme Clin Orthop Relat Res 2014
Mastectomy

- Major risks
  - Axillary dissection – intercostobrachial nerve
  - Radiotherapy
  - Strong association with catastrophising/psychological

  Belfer J Pain 2013

- Paravertebral blockade (+/- GA) associated with reduced chronic pain OR o.37, NNT 5
  - Cochrane Review, Adreae 2012. Note only 2 studies, N=89
  - No complications reported??
Mastectomy

- EMLA also protective 43 v 91%
  Fassoulaki RAPM 25(4) 350-5
- Gabapentin – chronic pain 5 v 25%
  Fassoulaki Eur J Anesth 24(6)521-8
- Venlafaxine- 10 days. Pain at 6 months 14% v. 40%
  (v placebo /gabapentin)
  Amr Clin J Pain 2010
- Lignocaine –periop - Pain at 3 months 12 v 47%
  Grigoras Clin J Pain 2012
Reviewed 40 RCTs – Ketamine (14) Gabapentin (10) Pregabalin (5) NSAIDs (3) Steroids (3) Lignocaine (1)

“modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin”
Varied surgeries
Positive studies used higher doses (1200gaba/300preg) and continued postop

Gabapentin OR 0.57 (0.27-0.98 p0.04)
Pregabalin OR 0.09 (0.02-0.79, p0.002)
Gabapentin & pregabalin

- Significant promise but...
- Publication bias?
- Varied dosing/surgeries/outcome measures
- Side effects (sedation) at higher doses
- More data needed
- Suitable for selected patients
  - Screening tool??
Nitrous oxide

- Post hoc analysis of ENIGMA I trial, 640 Asians major surgery >2hrs, 70% N₂O v. 70% O₂
- Phone interview, pain persisting >3/12
- Persistent pain 10.9%, severe 9.2%
- $N_2O \text{ OR } 0.43$ (0.23-0.83)
- No difference for acute pain
- NMDA antagonism? (ketamine-like)

Chan, Pain 2011
Effect studied prospectively in ENIGMA II
n=2924. Pain @ 1Y 12.2%, 3.8% severe
No effect for nitrous overall
Asian subset, n=674, RR 0.7 (0.5-0.98)
p=0.031
  Associated with genetic polymorphism in methylene tetrahydrofolate reductase gene

Chan, BJA 2016
Antidepressants

- 15 studies in postoperative pain Wong Anesthesiol 2014
- Generally heterogenous, undersized
- benefit v. placebo
- Acute pain – 8/15
- Persistent pain 1/3
  - Breast - Venlafaxine v. gabapentin, placebo Amr Clin j Pain 2010
  - Negative studies
    - duloxetine (TKR)
    - Escitalopram (CABG)
Can we prevent CRPS?

- CRPS post surgical est. >74000/yr in USA
- Up to 22% after UL trauma/Sx
- Evidence for Vitamin C
  - 2 prospective RCTs, upper limb fracture
dose-response relationship

\[ 500\text{mg/d for 50d} - 2.4\% \text{ v } 10.1\% \text{. NNT~12} \]

Zollinger (Lancet, 1999;354 and JBJS 2007;89)

1 prospective (historical controls) ankle/foot Sx n=420
1.7\% v. 9.6\%
Besse, Foot Ankle Surg 2009 15(4)
Persistent post surgical pain is common
We can identify those at increased risk
Some perioperative interventions may work
  ▪ Regional analgesia
  ▪ Ketamine
  ▪ Gabapentin/pregabalin
  ▪ Nitrous oxide
  ▪ Vitamin C
  ▪ Lignocaine
What can we do?

- Consider long term impairment a risk of surgery
- Consider periop interventions in those at risk
- Acute postop pain Mx – evidence based

“Perioperative Pain Planning Unit”
- Pre and post acute care in those at risk
- Role for pain risk assessment questions/testing?
- Opportunity for research
Research Questions

- Why do some patients with nerve injury develop persistent pain while others do not?
- What are the genetic factors that predispose patients to persistent post surgical pain?
- Can we identify patients preoperatively with psychological risk factors and modify their risk with education, psychological interventions?