Preventing chronic pain after surgery

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Professor
Depts. of Anesthesiology & Pharmacology,
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“... The wound healed in four weeks... Ever since the wound began to heal he has had great and increasing pain and numbness in the foot. These feelings seem to arise just above the wound, and to run down to the toes. The pain is darting, pricking, and in the foot burning... ...which are made worse by heat, dependence of foot, etc.”
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## Chronic pain after surgery

**Magnitude of the problem**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Chronic pain incidence (% of surgeries)</th>
<th>Severe pain (%)</th>
<th>U.S. surgical volume per year (‘94–’96)</th>
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<td>30-50</td>
<td>5-10</td>
<td>159K</td>
</tr>
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<td>Breast surgery</td>
<td>20-30</td>
<td>5-10</td>
<td>479K</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30-40</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Herniorraphy</td>
<td>10</td>
<td>2-4</td>
<td>609K</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>30-50</td>
<td>5-10</td>
<td>598K</td>
</tr>
<tr>
<td>C-section</td>
<td>10</td>
<td>4</td>
<td>220K</td>
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U.S.: ≥ **300,000** people/yr will develop chronic pain after surgery;

In at least **150,000**, this will be *severe, disabling pain*. 
### Surgery as a cause of chronic pain

Survey of 10 UK hospital-based pain clinics, 1989-92

<table>
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<th>Putative cause</th>
<th>% of patients&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>Degenerative</td>
<td>34.2</td>
</tr>
<tr>
<td>Surgery</td>
<td>22.5</td>
</tr>
<tr>
<td>No definite cause</td>
<td>20.2</td>
</tr>
<tr>
<td>Trauma</td>
<td>18.7</td>
</tr>
<tr>
<td>Infective</td>
<td>7.2</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>6.7</td>
</tr>
<tr>
<td>Tumour</td>
<td>3.5</td>
</tr>
<tr>
<td>Others</td>
<td>6.2</td>
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<sup>a</sup> Crombie et. al., Pain 1998
Preventing chronic pain after surgery

- Chronic pain syndromes following surgery are at least as difficult to treat as other neuropathic pains; Prevention may be more successful than palliation.
Preventing chronic pain after surgery

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- Predictability and discreteness of surgical tissue injury allows for:
  - observation of acute-to-chronic transition
  - appropriately timed preventive strategies
  - determination of predictors of susceptibility
  - rigorous evaluation of preventive interventions
Preventing chronic pain after surgery

Possible strategies

- avoid surgery

- modify surgical technique (e.g. nerve sparing, laparoscopic vs. open)

- ‘aggressive’ treatment of early inflammatory pain

- pharmacological (or otherwise) suppression of nerve injury sequelae (e.g. neuroma formation, trophic factor/ion channel proliferation, central plasticity)
Distinguishing between pain itself and “Induction” of a chronic pain state

- e.g. morphine may reduce ongoing pain but have no effect on the transition from early postoperative pain to chronic pain after surgery

- e.g. a NGF antagonist (nerve growth factor) may have no effect on ongoing pain but may suppress or prevent the induction of chronic pain after surgery
Studying chronic pain after surgery
‘Natural history’

evaluate patients with ‘surgical disease’
(e.g. biomedical, genetic, psychosocial predictors)

surgery
(routine perioperative pain treatment)

Evaluate sensory function and pain-related outcomes
from time of surgery out to timepoints of interest
(e.g. 3, 6 and 12 months)
Risk factors/predictors of chronic postsurgical pain

- surgical (e.g. invasiveness, nerve injury, duration of surgery)

- psychosocial (e.g. anxiety, catastrophizing, gender, fear of surgery)

- genetics (e.g. do specific gene polymorphisms predispose?)

Risk factors/predictors of chronic postsurgical pain

- surgical (e.g. invasiveness, nerve injury, duration of surgery)
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- genetics (e.g. do specific gene polymorphisms predispose?)

1. continued efforts to understand predictors will serve to guide future preventive efforts
2. understanding predictors could also help restrict risky and/or costly preventive therapies only to individuals at risk

Fillingim et. al., J Pain 2009.
Studying chronic pain after surgery

Effect of surgical stimulus

-evaluate- patients with ‘surgical disease’

- surgery
- modified surgical technique
- no surgery

Evaluate sensory function and pain-related outcomes from time of surgery out to timepoints of interest (e.g. 3, 6 and 12 months)
**Studying** chronic pain after surgery

*Effects of perioperative interventions*

- **evaluate** patients with ‘surgical disease’

  surgery

  pre-, intra- and postoperative interventions of interest (and appropriate controls)

  Evaluate sensory function and pain-related outcomes from time of surgery out to timepoints of interest (e.g. 3, 6 and 12 months)
Do current analgesic/anesthetic drugs prevent chronic pain after surgery?

- should consider evidence on a drug-specific and procedure-specific basis

- few studies have reported outcomes at timepoints of interest (e.g. 3, 6, 12 months)

- meta-analyses are currently underway, however, supportive EVIDENCE IS LIMITED! (re: pharmacological prevention)
Welcome to prospect
*Click the text in the blue boxes below for further Information

A new clinical tool for postoperative pain management in common surgical procedures

A set of procedure-specific, evidence-based recommendations

Managed and developed by anaesthesiologists and surgeons

Why prospect?

CLICK CIRCLES TO VIEW PROCEDURE-SPECIFIC RECOMMENDATIONS:

- Abdominal Hysterectomy
- Haemorrhoid Surgery
- Herniorrhaphy
- Laparoscopic Cholecystectomy Update
- Non-Cosmetic Breast Surgery
- Open Colonic Resection
- Thoracotomy
- Total Hip Arthroplasty
- Total Knee Arthroplasty

Kehlet et. al., Best Pract Res Clin Anaesthesiol, 2007
Phantom limb pain in amputees
during the first 12 months following limb amputation,
after preoperative lumbar epidural blockade

Søren Bach a, Morten F. Noreng b and Niels U. Tjellden b
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25 pts. with PREOPERATIVE pain in limb to be amputated

11 pts. lumbar epidural opioid+LA or either one

< - - - Tx of PREop pain - - - >

14 pts. systemic analgesia opioids, NSAIDs etc.

below-knee amputation
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below-knee amputation

phantom limb pain

3/11  7 days
0/11  6 months*
0/11  1 year

14 pts. systemic analgesia opioids, NSAIDs etc.

9/14
5/14
3/14
Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation

Lone Nikolajsen, Susanne Ilkjaer, Jørgen H Christensen, Karsten Krøner, Troels S Jensen
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- varying levels of preop pain but randomization stratified by pain level

- “blockade” group: 18 hours preop of epid bupiv/morph

- postop analgesia identical in both groups (epid bupiv/morph for 3-5 days + paracetamol)
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- phantom pain (block vs not):
  1 week - 14/27 vs 15/27
  3 months - 14/17 vs 10/20 (.09)
  6 months - 13/16 vs 11/20
  12 months - 9/12 vs 11/16
Does neuraxial anesthetic blockade prevent chronic pain after surgery?

- populations with PREOPERATIVE pain should be considered separately
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- blocking afferent input from periphery to spinal cord suppresses spinal sensitization which could help prevent chronic pain, however:
  - blockade for how long? how ‘strong’?
  - what about peripheral events that occur after surgery? (e.g. neuroma, Na\(^+\) channels)
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- neuraxial anesthesia with local anesthetics which obliterates peripheral sensation does NOT necessarily block all afferent input (Lund *et. al.* 1987)
Multimodal Analgesia with Gabapentin and Local Anesthetics Prevents Acute and Chronic Pain After Breast Surgery for Cancer

Argyro Fassoulaki, MD, PhD, DEAA*, Argyro Triga, MD†, Aikaterini Melemeni, MD*, and Constantine Sarantopoulos, MD, PhD, DEAA‡

Anesth Analg 2005;101:1427–32

50 pts. undergoing breast cancer surgery

- placebo
- placebo
- placebo

- gabapentin 1,600 mg/d (HS preop to 8d post)
- intraoperative ropivacaine irrigation
- topical EMLA (day of surgery to 3d post)
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<tr>
<th>No. of patients</th>
<th>3 mo Control n (%)</th>
<th>Treatment n (%)</th>
<th>P-value</th>
<th>6 mo Control n (%)</th>
<th>Treatment n (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Chest pain*</td>
<td>7/22 (32)</td>
<td>7/22 (32)</td>
<td>1.00</td>
<td>5/21 (24)</td>
<td>3/20 (15)</td>
<td>0.697</td>
</tr>
<tr>
<td>Axilla pain*</td>
<td>10/22 (45)</td>
<td>3/22 (14)</td>
<td>0.045</td>
<td>6/21 (29)</td>
<td>3/20 (15)</td>
<td>0.454</td>
</tr>
<tr>
<td>Arm pain*</td>
<td>13/22 (59)</td>
<td>5/22 (23)</td>
<td>0.038</td>
<td>7/21 (33)</td>
<td>3/20 (15)</td>
<td>0.277</td>
</tr>
<tr>
<td>Chronic pain (total)*</td>
<td>18/22 (82)</td>
<td>10/22 (45)</td>
<td>0.028</td>
<td>12/21 (57)</td>
<td>6/20 (30)</td>
<td>0.151</td>
</tr>
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* any reported pain regardless of severity
A Randomized Study of the Effects of Gabapentin on Postamputation Pain

46 pts. undergoing lower limb amputation

- gabapentin 2,100 mg/d (1st postop day to 30d postop)
  - 8/10 preop pain
  - postop epidural LA+ opioid

- placebo

Lone Nikolajsen, M.D., Ph.D.,* Nanna B. Finnerup, M.D., Ph.D., † Steffen Kramp, M.D., ‡ Anne-Sofie Vimtrup, § Johnny Keller, M.D., Ph.D., † Troels S. Jensen, M.D., Ph.D., ||

Anesthesiology 2006; 105:1008–15
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<th>Phantom pain incidence</th>
<th>Phantom pain intensity (0-10)*</th>
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<tr>
<td></td>
<td>gabapentin</td>
<td>placebo</td>
</tr>
<tr>
<td>1 month</td>
<td>55%</td>
<td>53%</td>
</tr>
<tr>
<td>6 months</td>
<td>59%</td>
<td>50%</td>
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* data include scores from subjects with NO PAIN
Another crisis of definition?

**Pain:**
- New since surgery? Different from preop pain? Related to ‘surgical’ disease?
- ≥ moderate? *versus* > zero?
- primary cause for a new healthcare visit? vs. measured outcome in a research study?

**Chronic / persistent / long-term:**
≥ 2 months? ≥ 3 months? ≥ 6 months? ≥ 1 yr?
Questions impacting on future RCT design

- is there a difference between chronic pain post-nerve injury and post-‘other’ tissue injury re: pathophysiology & potential prevention strategies?

- when do neurobiological events leading to chronic pain occur? operating room? 1st 14d? 1st 60d?

- can treatments known to diminish established chronic pain also prevent induction of chronic pain after surgery?

- should ‘prevention’ trials be limited to subjects at greatest risk? (i.e. tx risk-benefit assessment)
Questions impacting on future RCT design

- Q: is the incidence of *subclinical* pain 6-12 mos. after surgery higher than we think?

- If yes, some treatments may be *suppressive* (e.g. of pain or sensitization) rather than *curative*

- should the primary outcome be pain intensity? (i.e. continuous measure) *OR* presence of a pre-defined severity of pain (i.e. dichotomous measure)
Acknowledgments

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**Nuffield Department of Anaesthetics, Oxford University, UK:**

R. Andrew Moore

Henry McQuay

**Cochrane Collaboration, Oxford, UK:**

Phil Wiffen