Objectives

1. Review epidemiologic evidence of chronic post-surgical pain (CPSP) and other transitions.
2. Describe pain mechanisms of acute to chronic transition and possible impacts of early intervention.
3. Review evidence of attempts to prevent CPSP.
Case Study #1: Mr. I. M. Groan

- 40 yo male for inguinal hernia surgery.
- Healthy, working, construction.
- Symptoms: increasing discomfort at work with bulge in right inguinal area.
- Using Tylenol #3’s sparingly
Case Study #2: Mrs. F. M. Downe

• 57 yo female for thoracotomy resection of tumor.
• History of fibromyalgia, and depression
• Medications: duloxetine (FM), oxycodone (chest wall)
Case Study #3: Mr. M. B. Aches

• 46 yo man for single level L5/S1 discectomy and fusion.
• Advanced DDD, and facet OA with central and lateral stenosis. Back and right leg pain.
• Thin, anxious man. Middle manager in big bank.
• Off work for three months waiting surgery. Apply for LTD, and work claim – sitting caused it.
• Oxycodone 140 mg/d and gabapentin.
CPSP

• IASP Definition:
  – Pain that develops after surgical intervention and lasts at least two months; other causes being excluded, in particular pain from a condition preceding surgery.

  i. Pain develops after a surgery
  ii. Pain at least two months in duration
  iii. Other causes excluded (eg. ongoing malignancy, infection, complications)
  iv. The possibility that the pain is continuing from a pre-existing problem should be explored and exclusion attempted.
CPSP Definition

- Few studies use a rigorous definition
- If used, differs from study to study
- Doesn’t account for type of pain

- = widely varying prevalence
- = lack of comparable studies
Epidemiology

Table 1
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) (%)</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>Cesarian section</td>
<td>6–55</td>
<td>4</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>

Source: Reproduced with permission from: Macintyre et al.33

Table 1
Approximate numbers of operations carried out in England and the USA and incidence of CPSP

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Incidence of chronic pain</th>
<th>No. of ops in UK in 2005–6</th>
<th>No. of ops in USA in 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total operations</td>
<td></td>
<td>7 125 000</td>
<td>22 629 000</td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td>18 000</td>
<td>131 000</td>
</tr>
<tr>
<td>Caesarean section</td>
<td></td>
<td>139 000</td>
<td>858 000</td>
</tr>
<tr>
<td>Amputation</td>
<td>20–50%</td>
<td>15 000</td>
<td>132 000</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>30–55%</td>
<td>29 000</td>
<td>501 000</td>
</tr>
<tr>
<td>Hernia repair</td>
<td>5–35%</td>
<td>75 000</td>
<td>689 000</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>5–50%</td>
<td>51 000</td>
<td>667 000</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>12%</td>
<td>61 000</td>
<td>660 000</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>5–65%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

W. Macrae; BJA 101:77-86 (2008)
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Severe acute pain (at 24 h)</th>
<th>Subacute pain (from day 10 to 6–8 weeks)</th>
<th>Chronic pain (from 3 to 12 months)</th>
<th>Neuropathic component of CPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb amputation [6,7]</td>
<td>[30%]</td>
<td>50–75%</td>
<td>50–85%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Thoracotomy [8,9]</td>
<td>[30%]</td>
<td>39–50%</td>
<td>16–21%</td>
<td>&gt;46%</td>
</tr>
<tr>
<td>Breast cancer surgery [10]</td>
<td>[30%]</td>
<td>16%</td>
<td>47%</td>
<td>65%</td>
</tr>
<tr>
<td>Major abdominal surgery [11,12]</td>
<td>[30%]</td>
<td>18%</td>
<td>7–14%</td>
<td>?</td>
</tr>
<tr>
<td>Craniotomy [13]</td>
<td>20%</td>
<td>6%</td>
<td>7–29%</td>
<td>25%</td>
</tr>
<tr>
<td>Inguinal hernia [14,15]</td>
<td>7%</td>
<td>14%</td>
<td>12%</td>
<td>80%</td>
</tr>
<tr>
<td>Knee arthroplasty [16]</td>
<td>44%</td>
<td>16–52%</td>
<td>13%</td>
<td>?</td>
</tr>
<tr>
<td>Hip arthroplasty [16]</td>
<td>40%</td>
<td>20%</td>
<td>12%</td>
<td>?</td>
</tr>
<tr>
<td>Cesarean delivery [17,18]</td>
<td>17%</td>
<td>9–16%</td>
<td>4–10%</td>
<td>53%</td>
</tr>
<tr>
<td>Cosmetic breast surgery [19,20]</td>
<td>[30%]</td>
<td>25–32%</td>
<td>6–14%</td>
<td>38%</td>
</tr>
<tr>
<td>Cosmetic chest surgery [21]</td>
<td>[30%]</td>
<td>25%</td>
<td>14%</td>
<td>?</td>
</tr>
</tbody>
</table>

For acute pain, 30% is mentioned by default as the incidence of severe acute postoperative pain reported currently in the literature [22]. For chronic pain, the table mentions the incidence in general but not severe pain which concerns 4–10% of the patients reporting persistent pain [3]. CPSP, chronic postsurgical pain.
# Numbers in BC

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Procedures/year</th>
<th>New Severe Chronic Pain/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast surgery</td>
<td>5,000</td>
<td>250-500</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>2,000</td>
<td>200</td>
</tr>
<tr>
<td>Inguinal Hernia</td>
<td>6,000</td>
<td>120-240</td>
</tr>
<tr>
<td>Amputation</td>
<td>1,600</td>
<td>160</td>
</tr>
<tr>
<td>Coronary Bypass</td>
<td>6,000</td>
<td>300-600</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>10,000</td>
<td>400</td>
</tr>
<tr>
<td>Total Knee Arthroplasty</td>
<td>5,000</td>
<td>100-200</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1530-2380</strong></td>
<td></td>
</tr>
<tr>
<td><strong>All Surgeries</strong></td>
<td><strong>400,000</strong></td>
<td><strong>4,000 (1%)</strong></td>
</tr>
</tbody>
</table>
### Risk Factors for CPSP

- **Preoperative**
- **Intraoperative**
- **Postoperative**

- **Patient**
- **Environmental**
- **Surgical**
- **Anesthetic**

- **Associative vs. Causal**
Preoperative Risk Factors

• Personal
  – Younger age
  – Female
  – Anxiety
  – Catastrophizing
  – Fear of surgery
  – Preoperative pain
  – Altered pain processing
  – ?Genetic predisposition

• Environmental
  – Repeat surgery
  – Solicitous spouse/other
  – Compensation claims
Intraoperative Risk Factors

- Surgical
  - Approach risking nerve damage
  - Duration of surgery >3h
  - Open > laparoscopic
  - electrocautery > laser
  - Low volume vs. high volume unit

- Anesthetic
  - Use of short acting, high-dose opiates
  - ? Volatile anesthetics
  - Use or not of epidural/spinal in major chest/c-section (protective)
Postoperative Risk Factors

- Acute pain – moderate/severe + duration
- Bleeding/infection
- Evidence of altered pain processing
- Depression
- Catastrophizing
- PTSD symptoms
- Social: over solicitous spouse/supports
Catastrophizing

• Psychological construct:
  – Rumination
  – Magnification
  – Helplessness

• “unrealistic beliefs that the situation will lead to the worst possible pain outcome”

• “an exaggerated negative mental set brought to bear during actual or anticipated pain experience”

Pain Catastrophizing Scale


When I’m in pain ...

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

1       I worry all the time about whether the pain will end.
2       I feel I can’t go on.
3       It’s terrible and I think it’s never going to get any better.
4       It’s awful and I feel that it overwhelms me.
5       I feel I can’t stand it anymore.
6       I become afraid that the pain will get worse.
7       I keep thinking of other painful events.
8       I anxiously want the pain to go away.
9       I can’t seem to keep it out of my mind.
10      I keep thinking about how much it hurts.
11      I keep thinking about how badly I want the pain to stop.
12      There’s nothing I can do to reduce the intensity of the pain.
13      I wonder whether something serious may happen.

...Total
Catastrophizing

• Predicts pain and disability
• In addition to other psychosocial measures, can account for much of the variance in pain interference scores post amputation
• + Evidence for treating/reversing in chronic pain and disability
• We don’t have evidence about whether treating it presurgery reduces CPSP.
No other patient factor is as consistently related to development of future pain problems as is pain itself.
Pain Predicts Pain

• Why?
  – Intraoperative nerve damage
  – Peripheral sensitization of nociceptors
  – Central sensitization of 2\textsuperscript{nd} order neurons in CNS
  – Structural changes in CNS induced by perioperative nociceptive activity
  – Unidentified pain genes
  – Psychological and emotional factors
  – Social and environmental factors
  – Publication bias
Genetics

No reports of genes predisposing a transition from acute to chronic pain post surgery

Only reports of genes associated with various Chronic pain states:

5-HTTLPR.....burning mouth syndrome, migraine, IBS, FM
Several Interleukin receptor and ligands.....burning mouth, vulvodynia, Crohn’s GCH1 .....persistent radiculopathic pain after discectomy C-OMT (inactivates dopamine, epinephrine, etc........a number of CP entities.
CPSP Pain Phenotypes (Characteristics)

- Sensory-discriminative
  - Burning
  - Frequency
  - Intensity
  - Gene1
  - Gene2
  - Gene3

- Affective-emotive
  - Unpleasantness
  - Distracting
  - Maddening
  - Gene4
  - Gene5
  - Gene6

- Cognitive-evaluative
  - Means damage
  - Can’t live like this
  - This is hopeless
  - Gene7
  - Gene8
  - Gene9
Altered Pain Processing

• Quantitative Sensory Testing.
  – Static tests:
    • pain thresholds
    • pain tolerance
  – Dynamic tests:
    • conditioned pain modulation (inhibitory)
    • summation (excitatory)
Conditioned Pain Modulation (CPM)

Also : DNIC (diffuse noxious inhibitory control)

“Pain inhibits pain”

CPM (pain inhibits pain) has been shown to be deficient in a number of chronic pain syndromes: Fibromyalgia, IBS, TMD, CFS, tension Headache, atypical facial pain

In CPSP, an abnormal CPM response (i.e. less pain inhibition) is associated higher post operative pain scores. Presurgery abnormal CPM predicts CPSP.
**Inflammation**
- Peripheral sensitization
- Reduced CPM (DNIC)
- Nerve injury
- Pain
- Prolonged surgery
- Opioids (hyperalgesia)
- Genes
- Catastrophizing
- Younger age
- Female (menstrual cycle changes)

**Pro-nociceptive**

**CNS State**

**Anti-nociceptive**

**Cortical – cognitive**
- Placebo-nocebo
- Relaxation, breathing,
- Brainstem
  (Pain inhibits pain)
- Spinal -Gate theory
- Opioids (analgesia)
- Gabapentinoids
- Ketamine
Pain Models

• Before central sensitization: two models
  1. **Labeled line system** – dedicated pain pathways like telephone wire
  2. **Gate control theory** – opening or closing – enabling or preventing pain
Pain Models

• Both right:
  – have pain pathways,
  – have facilitating/inhibiting controls,

  – but the properties and architecture of CNS neurons themselves can change: Central Sensitization

  – Central Neuronal Plasticity
Central Sensitization

Hyperalgesia

Allodynia
Central Sensitization

• After injury (surgery) the CNS goes through stages:
  – Activity dependent sensitization
    • Adaptive, short lived, reversible, normal acute pain
  – Second phase sensitization
    • Ongoing inflammatory pain or nerve injury
    • Spontaneous firing, restructuring of neurons, cell death, loss of inhibitory control
    • Uncoupled from noxious stimulus – allodynia, etc
    • Pathologic pain- intermediate – long term.
Broken Part (Pain Generator)

Personal Filter

Central Nervous System

CA_corticospinal

Acute Pain

Chronic Pain
Pre-emptive vs. Preventive Analgesia

- **Pre-emptive**: theory that if you block the pain signal from reaching CNS *before* the injury you will stop the development of central sensitization.

- **Preventive**: theory that if you use aggressive, perioperative analgesia including antihyperalgesics, nerve blocks and multimodal analgesia throughout the healing period, you will reduce incidence of CPSP.
Pre-emptive vs. Preventive Analgesia

Classic acute pain service

- surgery
- discharge

Time

Pre-emptive analgesia

Preventive analgesia
Preventive Analgesia

• Remains an attractive working hypothesis, but data are inconclusive regarding effects on CPSP.
• Problems remain with study design to answer to right questions.
Evidence

• Several studies have shown reduced pain at 3-6 months postop with use of gabapentin (mas, col, hyst), pregabalin (TKR) and/or ketamine.

• Studies criticized with some design flaws
  – small numbers,
  – telephone follow-up,
  – short intervention time (<24h)
  – focus on a single intervention
  – not analyzing and stratifying all risk factors – psychosocial, preop pain, surgical approach, etc.
Evidence

• Zero evidence on effectiveness of CBT and other psychological interventions.
• Zero evidence on alternative therapies – relaxation, mindfulness, breathing exercises
• Nothing on genetics yet.
Evidence - Surgery

• Careful dissection and nerve sparing positive.
• Using lighter weight mesh in inguinal hernia (less inflammatory)
• One RCT suggesting intentional division of ilioinguinal nerve is beneficial
• Laparoscopic approaches positive
Evidence - Anesthesia

- Epidural analgesia superior to PCA alone in thoracotomy (timing of epidural unimportant), colectomy, and amputation
- Paravertebral nerve blockade in mastectomy.
- High dose remifentanyl vs. low dose in thoracotomy is bad. (80% vs. 27% at 6 mos.)
- Using nitrous oxide may be protective (?)
Case Study #1: Mr. I. M. Groan

• 40 yo male for inguinal hernia surgery.
• Healthy, working, construction.
• Symptoms: increasing discomfort at work with bulge in right inguinal area.
• Using Tylenol #3’s sparingly
Case Study #1: Mr. I. M. Groan

- What are his risk factors for CPSP?
  - Having surgery with known risk of nerve injury
  - Younger age?
  - 10% + risk CPSP
Case Study #1: Mr. I. M. Groan

• Is there anything we can do to modify his risk factors?
  – Does he really need surgery?
  – Surgeon uses a nerve sparing technique
  – Surgeon uses a lightweight mesh.
  – Laparoscopic approach
Case Study #1: Mr. I. M. Groan

• Post op 2 weeks, he has burning pain, numbness and allodynia around the wound, radiating down into groin.

• What do we do now?
  – Antineuropathic therapy
  – CPSP education, general pain education
  – Assess mental state, sleep, and treat
Case Study #2: Mrs. F. M. Downe

• 57 yo female for thoracotomy resection of tumor.
• History of fibromyalgia, and depression
• Medications: duloxetine (FM), oxycodone (chest wall)
Case Study #2: Mrs. F. M. Downe

- What are her risk factors for CPSP?
  - Highly associated surgery with nerve injury
    - 30-50% CPSP, 10% severe
  - Female
  - Pre-operative pain
  - Depression
  - Fibromyalgia (concurrent pain syndrome)
  - Probably altered pain processing system (FM)
Case Study #2: Mrs. F. M. Downe

- Is there anything we can do to modify her risk?
  - Assess, treat depression
  - Preoperative education
  - Assess anxiety, fear of surgery, treat, counsel
  - Teach techniques breathing, meditation, etc
  - Use surgical approach with least nerve injury
    - Muscle sparing incision, thoracoscopy?, place suture away from nerve, gentle retraction
  - Multimodal analgesia: periop, postop epidural, ketamine, gabapentinoids
Case Study #3: Mr. M. B. Aches

• 46 yo man for single level L5/S1 discectomy and fusion.
• Advanced DDD, and facet OA with central and lateral stenosis. Back and right leg pain.
• Thin, anxious man. Middle manager in big bank.
• Off work for three months waiting surgery. Apply for LTD, and work claim – sitting caused it.
• Oxycodone 140 mg/d and gabapentin.
Case Study #3: Mr. M. B. Aches

• What are his risk factors for CPSP?
  – Anxiety
  – Preoperative pain (with opiate usage)
  – Compensation claims
  – Screen for Catastrophizing – high
  – Opiate tolerance and sensitization?
  – QST = impaired CPM( conditioned pain modulation) Previously DNIC.
Case Study #3: Mr. M. B. Aches

• Is there anything we can do to modify his risk?
  – Treat catastrophizing – CBT, counseling
  – Preop education reassurance
  – Self relaxation techniques
  – Does he really need surgery?
  – Preop med optimization – lower opiates? More adjunctive meds – pregabalin, nortriptyline?
  – Multimodal periop, postop analgesia.
We don’t know what’s causal

• My two cents:
  – Nerve injury and neuropathic pain
  – Development of central sensitization – especially structural changes
  – Psychosocial factors – especially catastrophizing
  – Genetic factors not yet elucidated
Possible Preclinical Assessment

• History:
  – Medical, pain, psychosocial, medications, substance use
  – Specific surgical plan
• Questionnaires:
  – Depression PHQ9
  – Anxiety – GAD 7
  – Catastrophizing PCS
  – ?other
• QST:
  – CPM and other tests of CNS function
• Genetic testing:
Take Away Messages

1. CPSP develops on a background of a complex matrix of interacting factors.
   1. Psychological
   2. Social – environmental
   3. Surgical
   4. Anesthetic – pharmacologic
   5. CNS state – pain processing
   6. Genetic
Take Away Messages

2. As yet, we don’t know how these factors work together and which are causal or associative

3. Generally, the evidence of our ability to modify risk and thus change incidence of CPSP is equivocal. Except for: some surgical techniques, epidural/spinal, some limited drug trials
Take Away Messages

4. A major research initiative is needed to unravel the factors that are causal, and what interventions, for how long, will reduce risk.

5. Most studies are not carefully enough designed to elucidate this.

6. Most benefits will likely be at an organizational level of care, interdisciplinary, and longitudinal – extending beyond hospitalization. (Perioperative care)
Discussion Points

• What common sense changes could we make that will likely benefit post surgical patients?
• What organizational changes should we be undertaking?
• What steps need to be taken to begin to conduct the necessary research?
• What mindset paradigms need to change?
Thank you!

Michael Negraeff  michael.negraeff@vch.ca