When Acute Pain Becomes Chronic – What Do We Know and How Can We Prevent It?

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Overview
- Impact of acute pain transitioning to chronic pain
- Focus on low back pain and postsurgical pain
- Mechanisms and factors that predict the transition from acute pain to chronic pain
- Tools to prevent the transition
Impact of the Transition from Acute to Chronic Pain

Low Back Pain and Perioperative Pain as Models

Low Back Pain: Epidemiology

- 60%–90% lifetime prevalence
- Second most common complaint to prompt a medical evaluation
- Leading cause of long-term work disability
- Estimated US direct and indirect costs: $30-50 billion/year
- Disability and costs related to pain, not to the disease process

Natural history non specific low back pain (NSLBP)

- 80% of patients with first episode NSLBP will recover in 1 month
- 10% recover within 3 months
- 10% go on to CHRONIC PAIN
- Recurrence rates high (5-80%) depending on study

Rossignol M, Suissa S, Abenhaim L, Spine 1992;17(9):1043-1047
Nordin, et al. Proceedings of the 10th World Congress on Pain, Vol 24
**Post Surgical Chronic Pain**

- Thirty-four million Americans undergo surgery each year.
- Post operative chronic pain is defined as pain that lasts longer than 3-6 months and is different in quality and location from pain prior to surgery.
- On average 10% of postsurgical patients will develop chronic pain.


**Persistent Postoperative Pain**

- Thoracotomy: 30-60%  
- Inguinal Hernia Repair: 6-11%  
- Extremity Amputations: 30-80%  
- Cardiac Surgery  
- Caesarean section: 12%  
  - Additional 11% had discomfort or abdominal skin sensitivity  
- Breast Surgery, especially with dissection: 50%  
- Spinal Surgery  
- Orthopedic Surgery  
- Gallbladder surgery: 3-56%  
- Hysterectomy  
- Nephrectomy: 24%


**How many of your surgeons consent their patients for the possibility of chronic pain?**
Factors and Biomarkers that Predict the Transition from Acute to Chronic Pain

Transition from Acute to Chronic Low Back Pain

- In prospective longitudinal studies, **catastrophizing** and **fear** were associated with increased risk of chronic back pain one year after acute low back injury.
- **Catastrophizing** over seven times more powerful than any other predictor in predicting transition from acute to chronic pain.
- **Pain-related fear** causes patients with pain to over-predict the severity of pain they will experience. This leads to over-production of avoidance behavior.


Effects of Depression and Anxiety

- 30-65% of patients with chronic pain have co-morbid depression, often with anxiety.
- Longitudinal epidemiologic studies determine that patients with depression and anxiety are between 2-5 times more likely to have a new chronic pain problem at follow-up from 1 to 8 years later.
- Patients with depression appear to be less sensitive to pain in response to experimental noxious stimuli compared to healthy controls.
- Suggests that depression and possibly anxiety may elevate the risk of chronic pain by altering pain persistence rather than by altering pain thresholds or pain severity.

Factors Predicting Postsurgical Chronic Pain

- Few studies have explored multiple psychological and physiological factors that influence a patient's post-operative pain course.
- Even fewer studies addressed how these factors contribute to the patients post-operative pain resolution and opioid and analgesic cessation.

Factors Predicting Chronic Pain

- Acute pain experience predicts chronic pain:
  - True for herpes zoster and postherpetic neuralgia
  - True for thoracotomy, hernia repair, and most surgical procedures
  - Nerve damaging operations are at greater risk for chronic pain
  - Extent of surgically induced nerve damage doesn't correlate well with chronic pain

Postsurgical Chronic Pain

- 625 patients, mixed surgical procedure.
- Many variables collected
- At 6 months, patients with high levels of pain on postop day #4 and surgery longer than 3 hours:
  - More pain
  - More functional restrictions
  - Poor "global recovery"
  - Worse quality of life
- Preoperative fear of surgery negatively associated with more pain, poor global recovery, and worse quality of life 6 months later.
- Optimism was associated with better recovery and higher quality of life.

Longitudinal Study to Characterize Post-Surgical Pain Persistence

Table C1: Patient Characteristics (n=77)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59</td>
<td>18-85</td>
</tr>
<tr>
<td>Beck Depression Inventory Score</td>
<td>9.6</td>
<td>0-54</td>
</tr>
<tr>
<td>Fear of Pain Score</td>
<td>7.5</td>
<td>1-11.14</td>
</tr>
<tr>
<td>Anxiety Sensitivity Index Score</td>
<td>10.6</td>
<td>3-59.6</td>
</tr>
<tr>
<td>SOAPP</td>
<td>10.6</td>
<td>4-68</td>
</tr>
<tr>
<td>Gender (percent male)</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Positive PTSD symptomatology</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Pre-operative Opiate Use</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>History of Unprescribed Opioid Use</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Surgery Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Total Hip Replacement</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total Knee Replacement</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Radical Mastectomy</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Table C3: Multivariate Analysis of Factors Promoting Delayed Pain Resolution

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive PTSD Symptoms</td>
<td>0.35</td>
<td>0.04</td>
</tr>
<tr>
<td>Pain Severity: Post Operative Day 1</td>
<td>0.85</td>
<td>0.24</td>
</tr>
<tr>
<td>Self-Perceived Risk of Addiction</td>
<td>0.41</td>
<td>0.05</td>
</tr>
<tr>
<td>Beck Depression Inventory Score</td>
<td>0.99</td>
<td>0.97</td>
</tr>
</tbody>
</table>

The Transition from Acute to Chronic Pain

Every Surgical Procedure

- Cuts nerves
- Cuts tissues
- Induces the injury response
- Alters peripheral and central nervous system pain processing
- Can cause chronic pain

Note: Similarly, most chronic low back pain starts with an acute pain episode
Peripheral vs Central Mechanisms of Neuropathic Pain: Experimental Effects

<table>
<thead>
<tr>
<th>Peripheral Effects</th>
<th>Central Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ectopic and spontaneous discharge</td>
<td></td>
</tr>
<tr>
<td>• Nonsynaptic conduction</td>
<td></td>
</tr>
<tr>
<td>• Alterations in ion channel expression</td>
<td></td>
</tr>
<tr>
<td>• Collateral sprouting of primary afferent neurons</td>
<td></td>
</tr>
<tr>
<td>• Sprouting of sympathetic neurons in dorsal root ganglion</td>
<td></td>
</tr>
<tr>
<td>• Nociceptor sensitization</td>
<td></td>
</tr>
<tr>
<td>• Neurogenic inflammation</td>
<td></td>
</tr>
<tr>
<td>• Central sensitization</td>
<td></td>
</tr>
<tr>
<td>• Spinal reorganization</td>
<td></td>
</tr>
<tr>
<td>• Cortical reorganization</td>
<td></td>
</tr>
<tr>
<td>• Changes in inhibitory pathways</td>
<td></td>
</tr>
<tr>
<td>• Changes in glial cell functioning</td>
<td></td>
</tr>
</tbody>
</table>


Right arm amputation below elbow

Individual Differences in Pain
Factors relevant to pain perception

- Cognition: attention, distraction, hypervigilance, catastrophizing, reappraisal, hypnotic suggestion
- Mood: depression, anxiety, catastrophizing, emotional context
- Context: beliefs, expectations, placebo
- Genetics
- Injury: peripheral and central sensitization
  - Peripheral and central sensitization

Individual Differences – Thermal Pain Sensitivity

- 500 healthy volunteers
- 49°C stimulus
- Gender, OPRD1 polymorphism, personality temperment primary determinants of pain sensitivity

**Graph:**

- Number of subjects on the y-axis
- Range of numbers from 0 to 100

Kim H, et al, Pain 2004

Individual differences in the subjective experience of pain

- Compared high vs low sensitivity subjects
- High sensitivity → more activation
  - Caudal and perigenual ACC
  - Primary somatosensory cortex
  - Prefrontal cortex

**Images:**

- HIGH
- LOW
- HIGH vs. LOW

Pain - Fear and Anxiety

- Individual’s anxiety about, and fear of, painful sensations predicts physical complaints and treatment outcomes in patients with chronic pain (McCraken, 1998, 1999)
- Patients high in anxiety more likely to develop post-herpetic neuralgia (Dworkin, 1992)
- Preop gababentin improves functional recovery after knee surgery, AND decreases anxiety (Menigaux C, Anesth and Analg, 2005)
- Psychological construct? But why? What are the neurophysiological underpinnings?

Individual difference in pain – Effects of fear of pain

Right Lateral Orbital frontal activation may reflect attempts by fearful individuals to evaluate and/or regulate possible responses to painful stimuli


Individual difference in pain – effects of somatic anxiety

Medial Prefrontal Gyrus: involved in self-focused elaboration of the negative personal implications of pain that may characterize individuals high in anxiety sensitivity

Tools to Prevent the Transition from Acute to Chronic Pain

Everything mentioned is off-label

Gabapentanoids – Should we add this to the drinking water?

Gabapentanoids – Gabapentin and Pregabalin

- Meta-analyses and systematic review: Helpful for postop pain.
  - 600–1200 mg preop decreases pain after spinal surgery, breast, hysterectomy, chole, spine, tonsillectomy
  - Menigaux et al Anesthesia & Analgesia 2005;
  - Turan et al Anesthesia & Analgesia 2005;
  - Pandey et al Can J Anaesthesiol 2004;
  - Dirks et al Anesthesiology 2002;

- Makes epidural analgesia work better
- Works pre/post incision nephrectomy
- Combined with COX-2 Inhibitor works better
- Green et al Pain 2005
- Two weeks of perioperative pregabalin reduces pain (0%, 0%) compared to placebo (8.7%, 5.2%) after TKA
- Buvanendran et al Anesthesia and Analgesia 2010
Is gabapentin working entirely as a pain med?

- Gabapentin has also been shown to reduce anxiety in a variety of circumstances including pre-operative anxiety.


Perioperative Ketamine

- Ketamine: dose before incision, low dose infusion during the surgical procedure
  - Subanesthetic dosing
  - Infrequent adverse effects

Review: "Ketamine in subanesthetic dose (that is a dose which is below that required to produce anesthesia) is effective in reducing morphine requirements in the first 24 hours after surgery. Ketamine also reduces postoperative nausea and vomiting. Adverse effects are mild or absent." Bell RF, et al. Acta Anaesthesiologica Scandinavica Volume 49 Issue 10 Page 1405-1428, November 2005

Post-surgical residual pain: Effect of subanesthetic IV ketamine

- 100 patients for rectal adenocarcinoma resection
- 5 groups compared: placebo, 2 doses IV ketamine, 2 doses epidural ketamine
- Presurgical thoracic epidural continued through perioperative period

Perioperative ketamine does not prevent chronic pain after thoracotomy

- 86 patients randomized to perioperative IV ketamine (1mg/kg at the induction, 1mg/kg h1 during surgery, then 1mg/kg during 24 h)
- IV saline
- Battery of tests to assess pain at 1-2wks, 1m and 4m after surgery
- No differences between ketamine and saline groups


A Comparison of Gabapentin and Ketamine in Acute and Chronic Pain After Hysterectomy

- 60 patients randomized to:
  - Ketamine - 0.3mg/kg IV bolus and 0.05mg/kg/hr infusion until end of surgery, PO placebo
  - Gabapentin - PO 1200mg, IV saline
  - Oral placebo, IV saline
- Assessed 1, 3 and 6m after surgery
- Postop pain decreased in gabapentin group compared with ketamine and saline
- Reduced opioids in gabapentin and ketamine
- Incidence of incisional pain reduced at 1, 3, and 6m in gabapentin group


Perioperative Multimodal Analgesia

Minimally invasive surgery along with:
- Neural Blockade or other local anesthetic
- NSAID/COX-2 Inhibitor/Acetaminophen/Steroid
- Gabapentin/Pregabalin
- NMDA antagonist
- Mexiletine
- Clonidine
- Recovery/rehabilitation plan

Together, these interventions can reduce immediate post-op pain, facilitate recovery, and possibly reduce chronic pain
Summary

- Most chronic pain started with an acute pain event.
- We are creating an epidemic of chronic pain with our surgeries.
- Factors have been identified to predict the transition of acute to chronic pain in postsurgical patients and LBP.
  - Preoperative and immediate postop pain
  - Fear, anxiety, depression, catastrophizing, PTSD
  - Exaggerated response to experimental pain stimuli
- Tantalizing data that some anti-neuropathics, Coxibs, and regional anesthesia may reduce this transition.
- We may learn much about the transition from acute to chronic postsurgical pain by applying research from other chronic pain conditions.
- Much more research needed.

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