The Complex Pain Patient in the Perioperative Setting

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Disclosure

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WARNING!
All other statements in this lecture are Eminence-Based Medicine.
Perioperative management for patients with complex regional pain syndrome

Bassem Asaad* & Peter Glass
The Lack of Evidence

‘There is no standard perioperative approach for preventing the development of, or managing existing cases of, CRPS during surgery and the postoperative period.’

Pain Manage. (2012) 2(6), 561–567
Despite the one study quoted above, the authors believe that regional anesthesia is a better choice than general anesthesia ....
Acute pain management in patients with fibromyalgia and other diffuse chronic pain syndromes
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Purpose of review
Patients with fibromyalgia are at increased risk to experience increased and prolonged postoperative pain. In this review, we will provide an overview of pathophysiological characteristics of fibromyalgia relevant for enhanced pain processing after surgery. Furthermore, we will present some potential treatment options in the perioperative period based on specific symptoms of individual fibromyalgia patients to optimize their pain management after surgery.

Recent findings
Recent evidence points towards enhanced central nervous system sensitization and decreased descending inhibition in patients with fibromyalgia. Even in patients without fibromyalgia, these two mechanisms are seen as major contributors to the severity of clinical pain.

Clinical studies addressing the perioperative outcome and management of patients with fibromyalgia are rare.
Chronic Pain is a Nervous System Disorder

[Diagram showing the brain and spinal cord pathways related to pain, with labels for the thalamus, periaqueductal gray matter, descending inhibition pathway, peripheral sensory nerve, and spinal cord section.]
Central Sensitisation in Chronic Pain

Diagram showing the brain with an 'Ouch!' thought bubble and arrows indicating an increase (+ pain) and decrease (- pain) in pain intensity compared to a Healthy person.
**Physiological Pain**

A. Nociceptive pain

- Noxious stimuli: Heat, Cold, Intense mechanical force, Chemical irritants
- Nociceptor sensory neuron
- Spinal cord
- Pain
  - Autonomic response
  - Withdrawal reflex
  - Adaptive, high-threshold pain
  - Early warning system (protective)

B. Inflammatory pain

- Peripheral inflammation
- Positive symptoms
- Inflammation
  - Macrophage
  - Mast cell
  - Neutrophil
  - Granulocyte
- Tissue damage
- Spontaneous pain
- Pain hypersensitivity
- Adaptive, low-threshold pain
- Tenderness promotes repair (protective)
Pathological pain

Neuropathic pain
- Neural lesion
- Positive and negative symptoms

CNS
Dysfunctional pain
- No neural lesion
- No inflammation
- Positive symptoms

Nociplastic pain (IASP 2017)

Spontaneous pain
- Pain hypersensitivity
  - Peripheral nerve damage
  - Injury
  - Stroke
  - Abnormal central processing

Maladaptive, low-threshold pain
Disease state of nervous system
The IASP Council has accepted the recommendation of a Presidential Terminology Task Force to approve a third mechanistic descriptor of pain. The task force defined “nociplastic pain” as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”

In July 2016, the task force published a topical review in PAIN that proposed the third mechanistic descriptor for clinical classification of chronic pain. Reactions to the article overall were positive, and the journal subsequently published three letters to the editor that discussed the new descriptor.

In an October report to the Council recommending adoption of the term, the task force suggested that implementation of the third mechanistic descriptor has the potential to:

- confer validity on the patient’s experience of pain;
- facilitate communication between patients, clinicians, researchers, and other stakeholders;
- improve diagnosis and treatment by encouraging clinicians to screen for signs of altered nociceptive function; and
- stimulate research by identifying altered nociceptive function as an important area for mechanistic studies, establishment of treatment guidelines, and development of new treatment strategies.
Pathophysiology of Maintenance:
- Radiculopathy
- Neuroma traction
- Myofascial sensitization
- Brain, SC pathology (atrophy, reorganization)

Pathology:
- Muscle atrophy, weakness;
- Bone loss;
- Immunocompromise
- Depression

Psychopathology of maintenance:
- Encoded anxiety dysregulation
- PTSD
- Emotional allodynia
- Mood disorder

Acute injury and pain

Central Sensitization
- Neuroplastic changes

Disability
- Less active
- Kinesophobia
- Decreased motivation
- Increased isolation
- Role loss
- Sleep disorder

Neurogenic Inflammation:
- Glial activation
- Pro-inflammatory cytokines
- Blood-nerve barrier disruption

Peripheral Sensitization:
New Na+ channels cause lower threshold

Gallagher RM in Ebert in Kerns, 2010
Risk stratification for the development of chronic postsurgical pain

Stephan A. Schug\textsuperscript{a,*}, Julie Bruce\textsuperscript{b}

\textbf{Keywords}: Chronic postsurgical pain, Persistent postsurgical pain, Risk stratification, Genetics, Psychosocial, Surgery
## Table 2

### Risk factors for CPSP by time line and domain.

<table>
<thead>
<tr>
<th>Domain of risk factor</th>
<th>Preoperative period</th>
<th>Intraoperative period</th>
<th>Postoperative period</th>
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<tbody>
<tr>
<td>Demographic</td>
<td>Age</td>
<td>N/A</td>
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</tr>
<tr>
<td></td>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>Multiple mutations</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Psychological</td>
<td>Depression</td>
<td>N/A</td>
<td>Depression</td>
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<tr>
<td></td>
<td>Psychological vulnerability</td>
<td></td>
<td>Psychological vulnerability</td>
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<tr>
<td></td>
<td>Stress</td>
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<td>Stress</td>
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<td></td>
<td>Anxiety</td>
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<td>Anxiety</td>
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<tr>
<td></td>
<td>Catastrophising</td>
<td></td>
<td>Catastrophising</td>
</tr>
<tr>
<td>Pain</td>
<td>Preoperative chronic pain</td>
<td>N/A</td>
<td>Severe acute pain</td>
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<tr>
<td></td>
<td>Preoperative opioid use</td>
<td></td>
<td>Acute neuropathic pain</td>
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<tr>
<td></td>
<td>Increased sensitivity to experimental pain</td>
<td></td>
<td>Acute secondary hyperalgesia</td>
</tr>
<tr>
<td></td>
<td>Increased temporal summation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased CPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>N/A</td>
<td>Type of surgery</td>
<td>Need for repeated revisions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nerve injury</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Longer duration of surgery</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Traumatic approaches</td>
<td></td>
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<tr>
<td>Clinical</td>
<td>Severity and numbers of comorbidities</td>
<td>N/A</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Disability</td>
<td></td>
<td>Chemotherapy</td>
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</table>

Compiled from multiple sources including Refs. 13,22,26.  
CPM, conditioned pain modulation; CPSP, chronic postsurgical pain.
<table>
<thead>
<tr>
<th>Psychological</th>
<th>Depression</th>
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<tr>
<td></td>
<td>Psychological vulnerability</td>
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<tr>
<td>Stress</td>
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<td>Anxiety</td>
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<td>Catastrophising</td>
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<td>Severity and numbers of comorbidities</td>
</tr>
<tr>
<td></td>
<td>Disability</td>
</tr>
</tbody>
</table>
Preoperative Considerations in Complex Chronic Pain Patients

• Is this surgery really indicated????
  • Joint decision by multidisciplinary team!
• Optimal patient information and informed consent!
• Can the psychological state of the patient be optimized?
  • Optimal clinical psychology input
  • Psychiatric input needed?
• Is the chronic pain of the patient optimally treated?
  • Optimal physiotherapy input
• Pharmacological management
  • Wean down conventional opioids!
  • Replace conventional opioids by atypical ones!
  • Consider/optimize use of medications beneficial in central sensitization
    • Pregabalin
    • TCAs
    • SNRIs
Conclusion: Patients with a history of chronic opioid use who successfully decreased their use of opioids before surgery had substantially improved clinical outcomes that were comparable to patients who did not use opioids at all.
**Sir Charles Gairdner Hospital**

**Acute Pain Service & Preadmission Clinic**

<table>
<thead>
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<th>Opioid tapering prior to joint replacement surgery</th>
<th>Version No: 2</th>
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<tbody>
<tr>
<td></td>
<td>Date of issue: 8 December 2016</td>
</tr>
</tbody>
</table>

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At SCGH, patients on high-dose opioid therapy should be referred back to their GP for preoperative opioid weaning (with pain clinic support as needed). Higher opioid doses worsen functional outcome, increase infection risk (especially in the presence of other risk factors e.g. obesity, diabetes\(^1\)) & make postoperative pain management more difficult.

**Why reduce opioid doses preoperatively?**

- Joint arthroplasty significantly improves quality of life by improving function & reducing pain.
- Peri-prosthetic infection is a serious complication, requiring painful, prolonged & costly treatment. It is associated with increased mortality & major morbidity\(^1\); thus, any factor that increases perioperative infection risk should, if possible, be optimized preoperatively.
<table>
<thead>
<tr>
<th>Postoperative period</th>
</tr>
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<tbody>
<tr>
<td>N/A</td>
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<tr>
<td>N/A</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Psychological</td>
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<tr>
<td>vulnerability</td>
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<tr>
<td>Stress</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Catastrophising</td>
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<tr>
<td>Poor coping skills</td>
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<tr>
<td>Severe acute pain</td>
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<tr>
<td>Acute neuropathic</td>
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<tr>
<td>pain</td>
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<tr>
<td>Acute secondary</td>
</tr>
<tr>
<td>hyperalgesia</td>
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</tbody>
</table>
General Principles of Management

— provision of effective analgesia
  • strategies that may help to attenuate tolerance or OIH
  • prevention of withdrawal

— physiotherapy input early as appropriate
  • Early rehabilitative approach!

— clinical psychology input early as appropriate

— smooth transition to chronic pain management
  • close liaison with other treating clinicians and specialist teams as required and appropriate discharge planning
  • ongoing care by pain medicine
  • ‘transitional pain services’
8.1.1 Multimodal postoperative pain management

**Key messages**

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control, reduces opioid consumption ("opioid-sparing") and adverse effects (N) (Level II).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑️ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (N).
Whenever Possible Use a Regional Analgesia Technique!

Catheter techniques are better than single-shot blocks:

- epidural analgesia
- peripheral nerve catheters

NB: Regional techniques do NOT prevent withdrawal!
Use Analgesics to Maximum Effect!

- Non-opioids
  - Paracetamol
  - (NSAIDs/) Coxibs

- Opioids
  - Continue background opioids to avoid withdrawal
  - Realise increased opioid requirements in tolerance

- Consider atypical opioids
  - *Tramadol*
  - *Tapentadol*
Antihyperalgesic Medications

Ketamine
Gabapentin/Pregabalin
Lignocaine ?
Normal NMDA receptor transmission

- Glycine or D-serine
- Glutamate
- Polyamine
- \( \text{Ca}^{2+} \)
- \( \text{Zn}^{2+} \)

Presynaptic glutamate + postsynaptic depolarization \( \rightarrow \text{Mg}^{2+} \) block displaced, \( \text{Ca}^{2+} \) enters cell

Inhibition of NMDA receptor by ketamine

- Glycine or D-serine
- Glutamate
- Polyamine
- \( \text{Ca}^{2+} \)
- \( 	ext{Zn}^{2+} \)
- \( \text{Mg}^{2+} \)
- Ketamine

Channel blocked by ketamine, \( \text{Ca}^{2+} \) cannot enter cell
NMDA-receptor antagonists

**Systemic**

1. Perioperative ketamine reduces the incidence of chronic postsurgical pain (N) (Level I [Cochrane Review]).

2. Perioperative IV ketamine reduces opioid consumption, time to first analgesic request and postoperative nausea and vomiting compared to placebo (S) (Level I [PRISMA]); these benefits are limited to patients after thoracic surgery, when ketamine is added to the opioid in the PCA pump (N) (Level I).

3. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (S) (Level I).

4. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (N) (Level I).

7. Ketamine is a safe and effective analgesic in the prehospital setting (S) (Level II).

8. Ketamine reduces postoperative pain in opioid-tolerant patients (U) (Level II).
Alpha-2-Delta Ligands Counteract Central Sensitisation / Hyperexcitability
Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

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*Corresponding author. E-mail: habib001@dm.duke.edu
Summary. We performed this systematic review to assess the analgesic efficacy of perioperative pregabalin. Subgroup analyses and meta-regression were performed to assess the impact of individual dose and frequency of pregabalin administration on analgesic efficacy. We included 55 studies. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 h compared with placebo {mean difference [95% confidence interval (CI)]=−0.38 (−0.57, −0.20), −0.47 (−0.76, −0.18), and −8.27 mg morphine equivalents (−10.08, −6.47), respectively}. Patients receiving pregabalin had less postoperative nausea and vomiting and pruritus compared with placebo [relative risk (RR) (95% CI)=0.62 (0.48, 0.80) and 0.49 (0.34, 0.70), respectively]. Sedation, dizziness, and visual disturbance were more common with pregabalin compared with placebo [RR (95% CI)=1.46 (1.08, 1.98), 1.33 (1.07, 1.64), and 3.52 (2.05, 6.04), respectively]. All doses of pregabalin tested (≤75, 100–150, and 300 mg) resulted in opioid sparing at 24 h after surgery. There were no significant differences in acute pain outcomes with pregabalin 100–300 mg between single preoperative dosing regimens and those including additional doses repeated after surgery. Data were insufficient to reach conclusions regarding persistent pain, but limited data available from two studies suggested that pregabalin might be effective for the reduction of neuropathic pain. In conclusion, this review suggests that pregabalin improves postoperative analgesia compared with placebo at the expense of increased sedation and visual disturbances.
Pregabalin As An Anxiolytic

![Graph showing the effectiveness of Pregabalin as an anxiolytic compared to Placebo and Alprazolam. The graph indicates the mean change in HAM-A score at endpoint for different total daily doses of Pregabalin and Alprazolam.](Image)
• In methadone-maintained patients, gabapentin increased cold-pressor pain threshold and pain tolerance.
• Pregabalin in maintenance program patients reduced methadone requirements and withdrawal symptoms.
• OIH associated with remifentanil is attenuated by preoperative pregabalin.
Pregabalin for the Treatment of Drug and Alcohol Withdrawal Symptoms: A Comprehensive Review

Rainer Freynhagen¹ · Miroslav Backonja²·³ · Stephan Schug⁴ · Gavin Lyndon⁵ · Bruce Parsons⁶ · Stephen Watt⁶ · Regina Behar⁶

- Pregabalin attenuated naloxone-induced withdrawal symptoms in opioid-tolerant rats (Hasanein 2014 BS).
- Gabapentin reduced withdrawal symptoms in patients during methadone-assisted detoxification (Salehi 2011 Level III-1).
- Pregabalin added to methadone in maintenance program patients reduced methadone requirements and withdrawal symptoms compared with placebo (Moghadam 2013 Level II, n=60, JS 5).
Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety

Martin Bailey\textsuperscript{a,b,\ast}, Tomas Corcoran\textsuperscript{a,c,d}, Stephan Schug\textsuperscript{a,d}, Andrew Toner\textsuperscript{a}

Abstract
Chronic postsurgical pain (CPSP) occurs in 12% of surgical populations and is a high priority for perioperative research. Systemic lidocaine may modulate several of the pathophysiological processes linked to CPSP. This systematic review aims to identify and synthesize the evidence linking lidocaine infusions and CPSP. The authors conducted a systematic literature search of the major medical databases from inception until October 2017. Trials that randomized adults without baseline pain to perioperative lidocaine infusion or placebo were included if they reported on CPSP. The primary outcome was the presence of procedure-related pain at 3 months or longer after surgery. The secondary outcomes of pain intensity, adverse safety events, and local anesthetic toxicity were also assessed. Six trials from 4 countries (\(n = 420\)) were identified. Chronic postsurgical pain incidence was consistent with existing epidemiological data. Perioperative lidocaine infusions significantly reduced the primary outcome (odds ratio, 0.29; 95% confidence interval, 0.18-0.48), although the difference in intensity of CPSP assessed by the short-form McGill Pain Questionnaire (4 trials) was not statistically significant (weighted mean difference, \(-1.55\); 95% confidence interval, \(-3.16\) to 0.06). Publication and other bias were highly apparent, as were limitations in trial design. Each study included a statement reporting no adverse events attributable to lidocaine, but systematic safety surveillance strategies were absent. Current limited clinical trial data and biological plausibility support lidocaine infusions use to reduce the development of CPSP without full assurances as to its safety. This hypothesis should be addressed in future definitive clinical trials with comprehensive safety assessment and reporting.

Keywords: Chronic pain, Lidocaine, Postoperative pain
The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain

Abstract: Chronic postsurgical pain (CPSP), an often unanticipated result of necessary and even life-saving procedures, develops in 5–10% of patients one-year after major surgery. Sub-
Conclusion

Taken together, the current TPS and planned expansions are designed to address the historical gaps in pain management for postsurgical patients. Our goal is to transform the management of pain in postsurgical patients by providing seamless care beginning preoperatively, continuing throughout the hospital stay and after patients return home post-hospital discharge. Finally, important next steps are to determine the efficacy of the TPS in preventing CPSP and to evaluate the extent to which the TPS reduces hospital stay, hospital readmission rates, and overall costs to the health care system.
<table>
<thead>
<tr>
<th>Table 2 Transitional Pain Service (TPS) referral criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preoperative chronic pain with or without opioid use</td>
</tr>
<tr>
<td>• Intense postoperative pain.</td>
</tr>
<tr>
<td>○ Prolonged Acute Pain Service (APS) stay based on surgical intervention</td>
</tr>
<tr>
<td>○ Patients with intense pain, who continue to be seen by the APS beyond the expected trajectory</td>
</tr>
<tr>
<td>○ Patients requiring a repeat APS consultation once discharged from the APS (initiated by the surgical team)</td>
</tr>
<tr>
<td>○ Medically stable patients unable to be discharged due to a complex pain problem</td>
</tr>
<tr>
<td>• High postoperative opioid consumption</td>
</tr>
<tr>
<td>○ Patients who consume more than 90 mg/day of oral morphine equivalents given high requirement for opioid weaning assistance after discharge</td>
</tr>
<tr>
<td>○ Patients admitted on methadone or buprenorphine who do not have access to a community pain specialist</td>
</tr>
<tr>
<td>○ Patients discharged with a prescription for a long acting opioid-based medication</td>
</tr>
<tr>
<td>○ Patients needing interventional postsurgical procedures (eg, stump catheters post-amputation)</td>
</tr>
<tr>
<td>• Emotional distress</td>
</tr>
<tr>
<td>○ Depression, anxiety, pain catastrophizing, or other psychosocial concern identified by APS or TPS screening questionnaires</td>
</tr>
</tbody>
</table>
Discharge Planning

• Close liaison with:
  — Pain Medicine
  — GP
  — Pharmacist
  — Drug Abuse Service

• Planning of ongoing analgesia in consideration of risks for the patient, but also the community (diversion → increased exposure, overdose risk!) (‘opioid stewardship’)

• Adjustment of opioid doses down to preadmission doses
Conclusion

The complex pain patient needs ‘perioperative pain medicine’ to optimize outcomes of surgery.