

Developing therapies to prevent the acute to chronic pain transition: clinical perspectives

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Models of the transition to chronic pain

1. Surgery — > chronic post-surgical pain
2. Acute low back injury — > chronic low back pain
3. Wrist fracture — > complex regional pain syndrome (CRPS)
4. Cancer chemotherapy — > painful chemotherapy-induced peripheral neuropathy (CIPN)
5. Herpes zoster — > postherpetic neuralgia (PHN)
6. Pre-diabetes, diabetes — > painful diabetic peripheral neuropathy (DPN)

	<u>Estimated incidence of chronic pain</u>	<u>Estimated chronic severe (disabling) pain (>5 out of score of 10)</u>	US surgical volumes (1000s)†
Amputation ²	30-50%	5-10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy) ³	20-30%	5-10%	479
Thoracotomy ^{4,7}	30-40%	10%	Unknown
Inguinal hernia repair ⁸⁻¹⁰	10%	2-4%	609
Coronary artery bypass surgery ¹¹⁻¹³	30-50%	5-10%	598
Caesarean section ¹⁴	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures*

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain; risk factors and prevention. *Lancet*, 2006;367:1618-1625.

Some established and some putative transition risk and protective factors

1. Severity of acute pain
2. Severity of nerve lesion and/or musculoskeletal injury
3. History of chronic pain
4. Psychosocial vulnerability (e.g., catastrophizing, anxiety, depression, poor social support, job dissatisfaction)
5. Impaired conditioned pain modulation
6. Augmented central sensitization

*But are these **causal** risk and protective factors?*

Research design considerations for chronic pain prevention clinical trials: **IMPACT** recommendations

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Example of a clinical trial design for prevention of acute to chronic pain transition



Investigational treatment

Placebo treatment

Hypothesized risk and resilience factors, transition and resolution mechanisms, and prognostic and predictive biomarkers should be included in any such clinical trial.

Primary endpoints for prevention trials

1. Incidence of any pain, for example, at 6 months
2. Incidence of clinically important pain (e.g., $\geq 4/10$) at 6 months
3. Pain intensity on an NRS or VAS at 6 months
4. Time to resolution of any pain
5. Time to resolution of clinically important pain
6. Area under a pain intensity-by-duration curve
7. Area under a “truncated” pain intensity-by-duration curve (e.g., burden of clinically important pain)

Examples of interventions hypothesized to prevent the transition to chronic pain

1. Perioperative anti-NGF antibody to prevent chronic post-surgical pain (Mantyh et al., 2011)
2. Brief psychosocial intervention (e.g., internet CBT, relaxation training) as soon as possible after acute low back injury to prevent chronic low back pain
3. Vitamin C after distal radius fracture to prevent CRPS (Evaniew et al., 2015 vs. Meena et al., 2015)

Of course, it is quite possible that the best preventive intervention would be some combination of pharmacologic and non-pharmacologic approaches.

Lifestyle Intervention for Pre-Diabetic Neuropathy

Smith AG, et al. Diabetes Care 2006;29:1294-1299

