Preventing chronic pain after surgery

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PSI FOUNDATION

CIHR IRSC
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Case report

"… 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."

Case report

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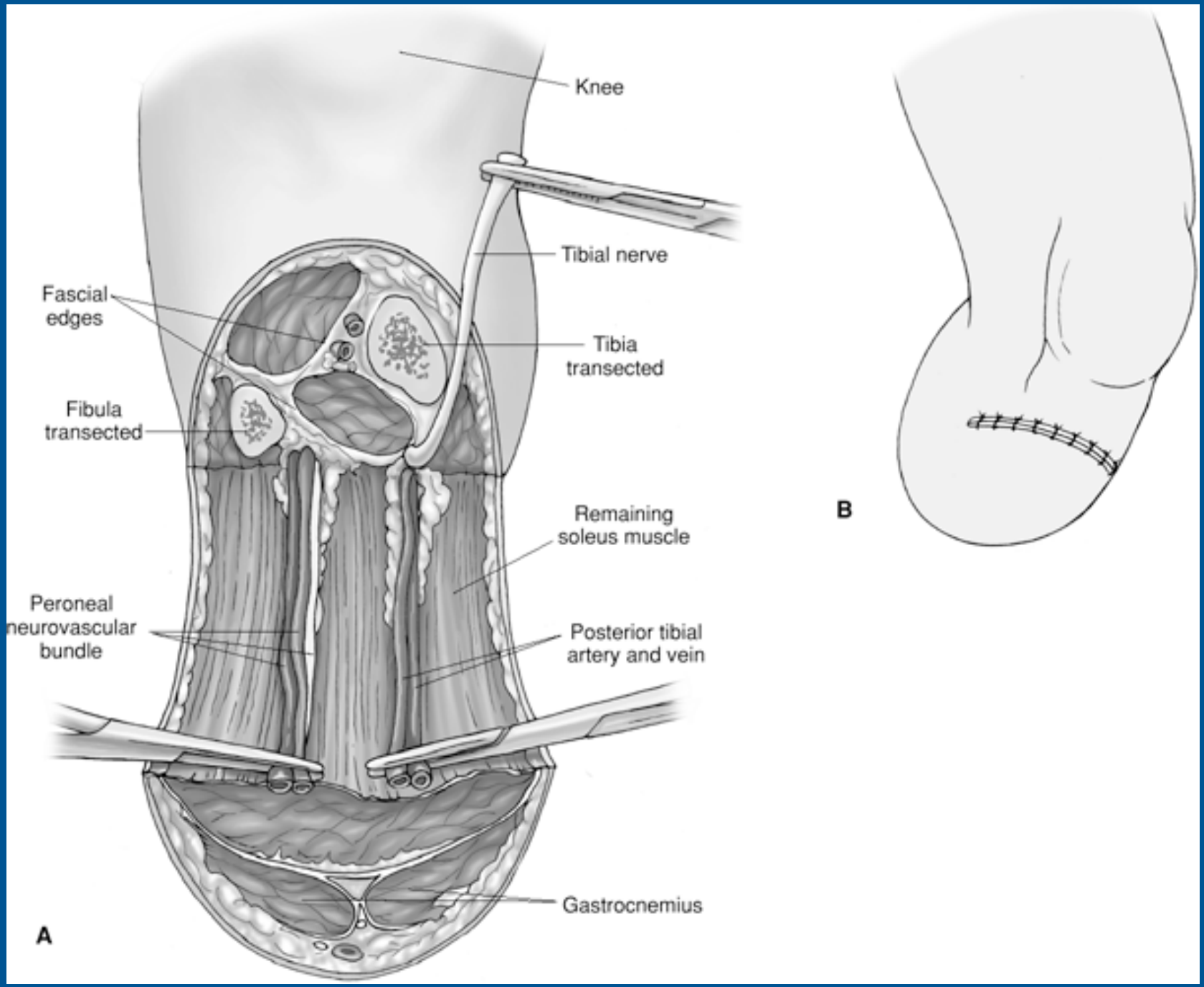
Mitchell, S.W.: Injuries of Nerves and Their Consequences, Philadelphia: J. B. Lippincott & Co., 1872


Knee
Tibial nerve
Fascial edges
Tibia transected
Fibula transected
Remaining soleus muscle
Peroneal neurovascular bundle
Posterior tibial artery and vein
Gastrocnemius
A
B

Chronic pain after surgery

Magnitude of the problem

Procedure	Chronic pain incidence (% of surgeries)		**Severe** pain (%)	U.S. surgical volume per year ('94-'96)	
	(Kehlet et. al., '06)	(Macrae, '08)	(Kehlet et. al., '06)	(Kehlet et. al., '06)	(Macrae, '08)
Amputation	30-50	50-85	5-10	159K	132K
Breast surgery	20-30	20-50	5-10	479K	131K
Thoracotomy	30-40	5-65	10	-	660K
Herniorraphy	10	5-35	2-4	609K	689K
Cardiac surgery	30-50	30-55	5-10	598K	501K
C-section	10	6	4	220K	858K
Cholecystectomy		5-50			667K

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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

The contributors to the development of pain in 5130 patients	
Putative cause	% of patients[a]
Degenerative	34.2
Surgery	22.5
No definite cause	20.2
Trauma	18.7
Infective	7.2
Inflammatory	6.7
Tumour	3.5
Others	6.2

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

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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?)

Katz & Seltzer, Expert Rev Neurother 2009.; Jung et. al., Pain 2003.
Fillingim et. al., J Pain 2009.

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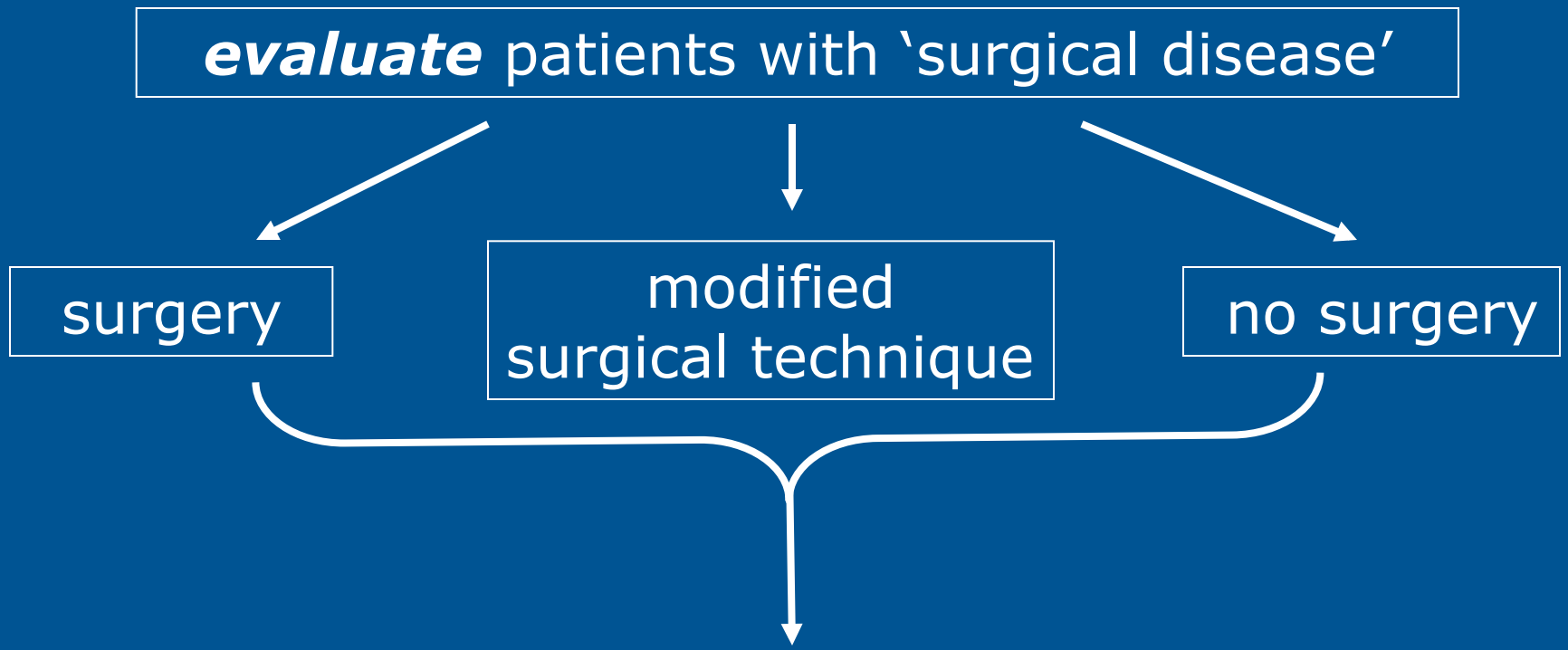
1. continued efforts to understand predictors will serve to guide future preventive efforts

2. understanding predictors could also help restrict risky and/or costly preventive therapies only to individuals at risk

Studying **chronic pain after surgery**

Effect of surgical stimulus



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)

↓

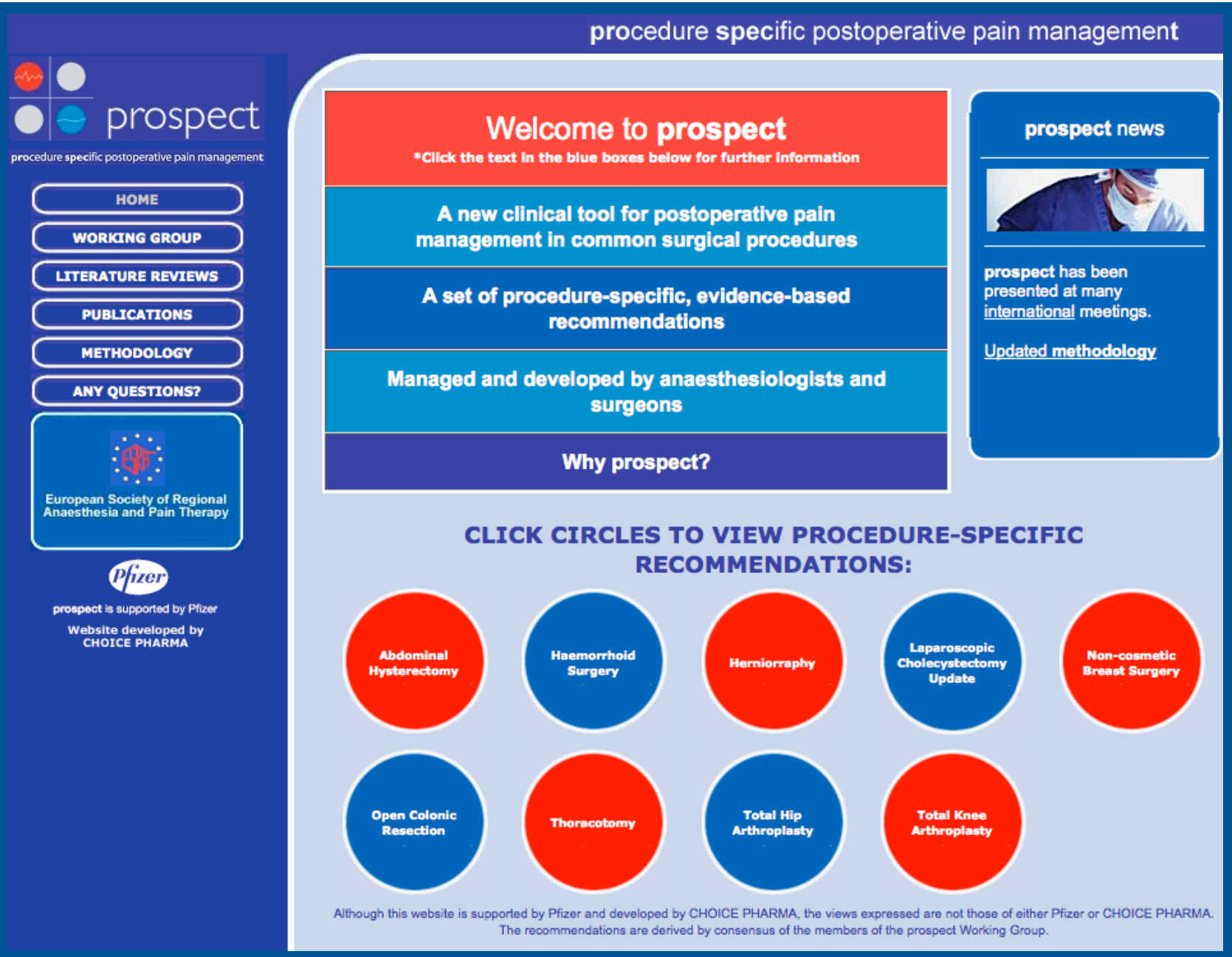
Evaluate sensory function and pain-related outcomes
from time of surgery out to timepoints of interest
(e.g. 3, 6 and 12 months)

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)



Kehlet et. al., Best Pract Res Clin Anaesthesiol, 2007

Pain, 33 (1988) 297–301
Elsevier

PAIN

Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade

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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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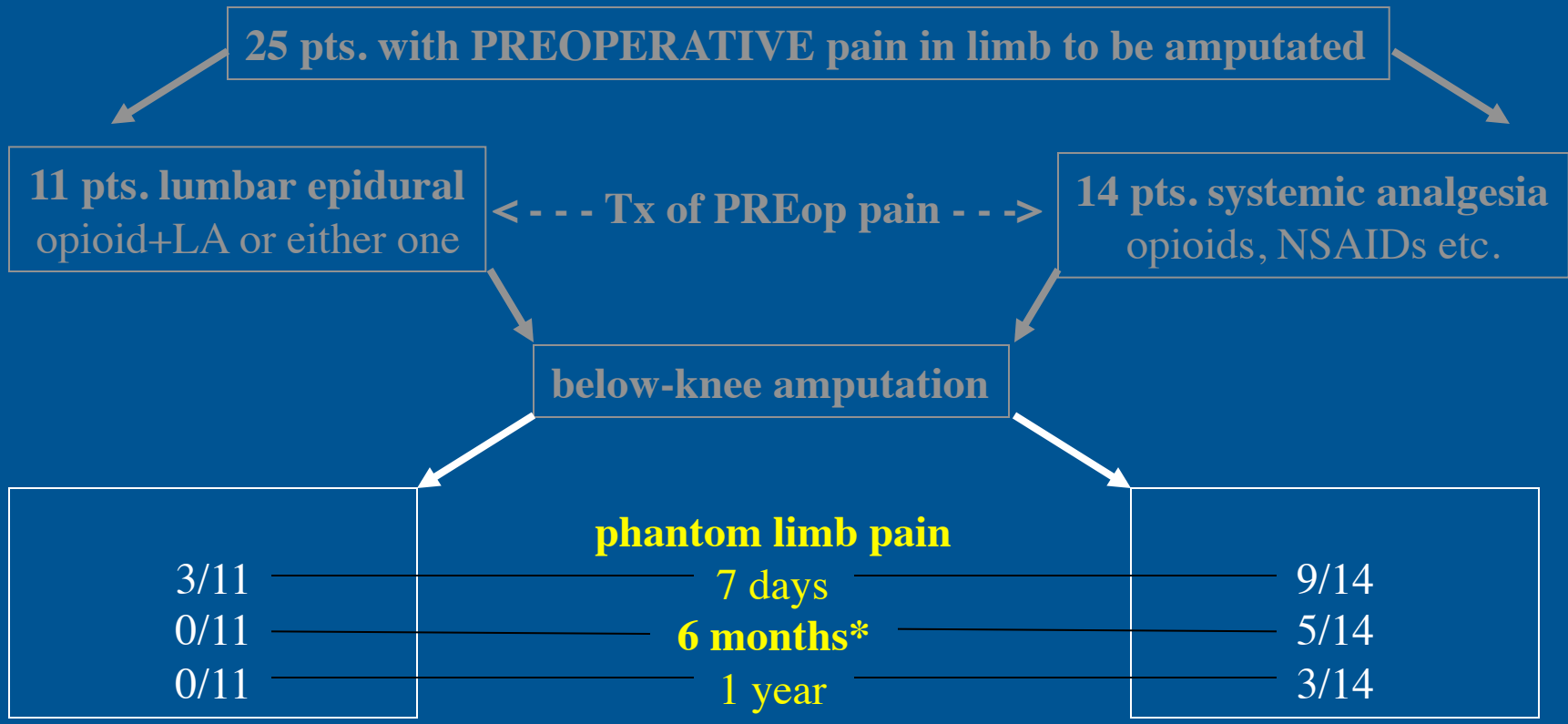

Lancet 1997; **350:** 1353–57 THE LANCET

Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation

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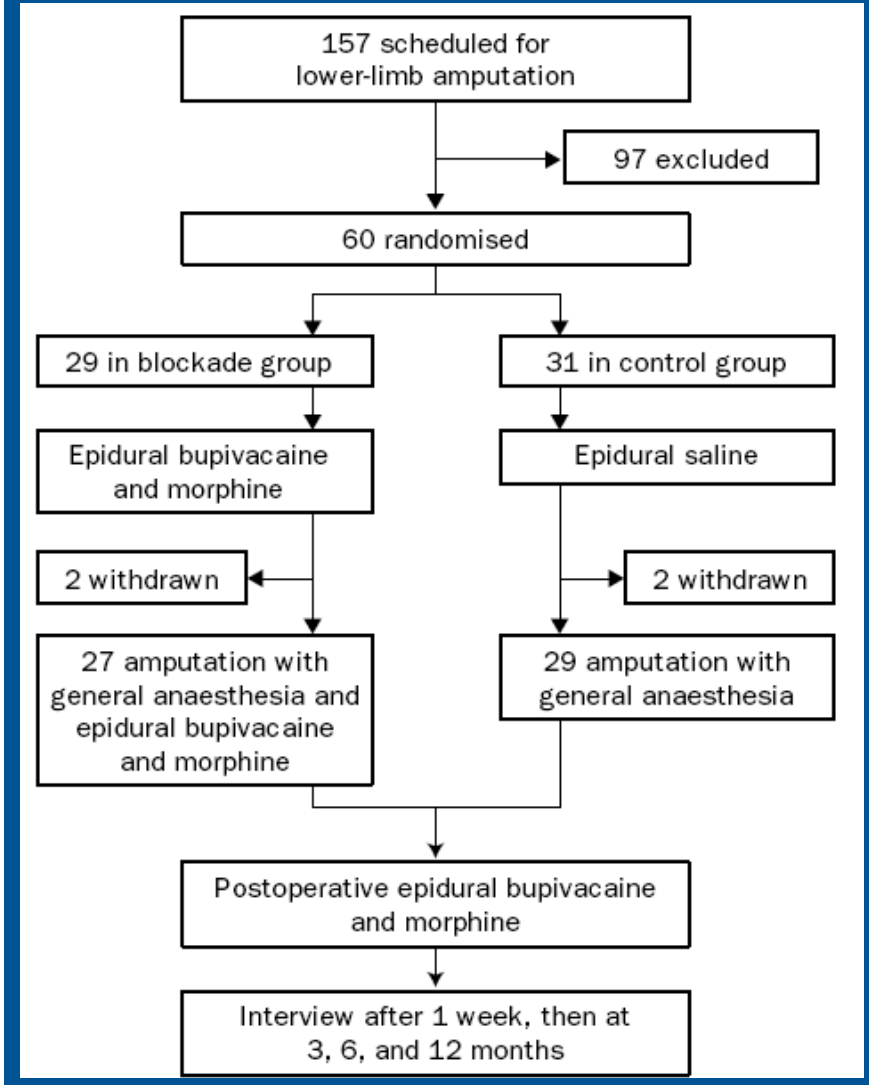

- varying levels of preop pain but randomization stratified by pain level

- "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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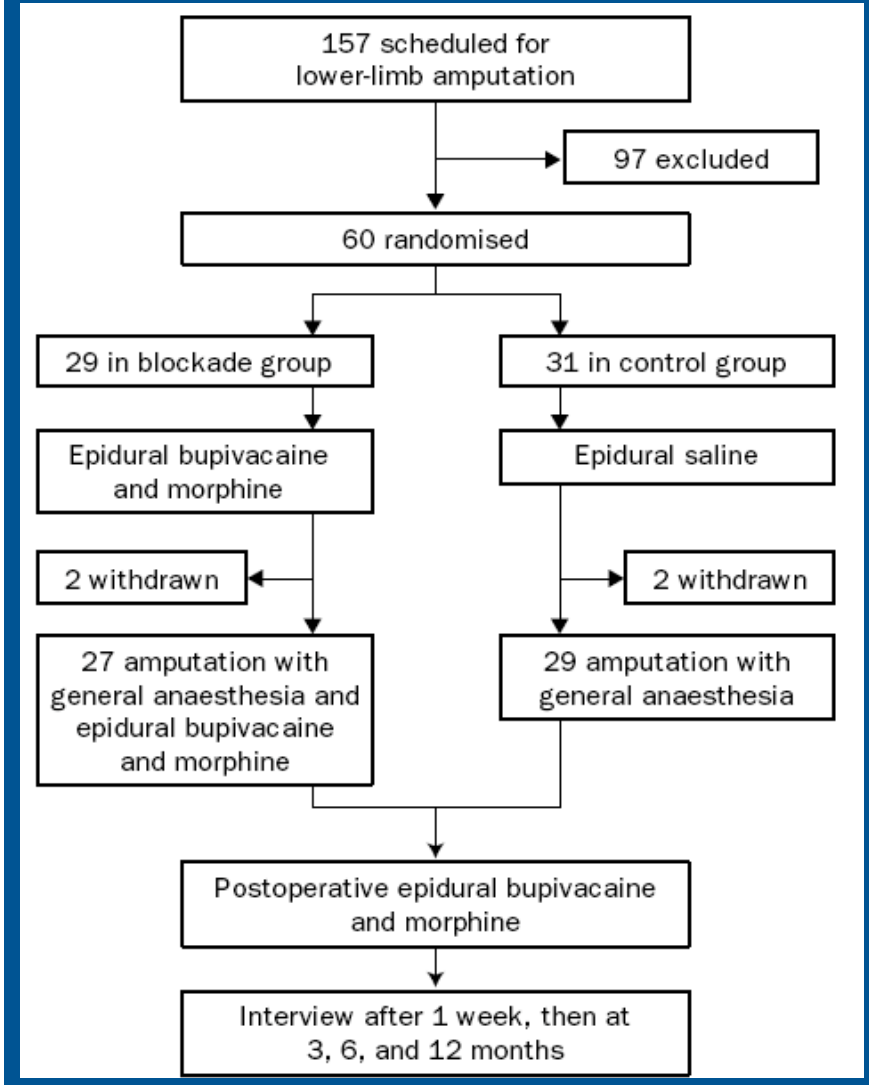

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- phantom pain (block vs not):

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
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- **gabapentin 1,600 mg/d (HS preop to 8d post)**
- **intraoperative ropivacaine irrigation**
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No. of patients	3 mo			6 mo		
	Control n (%)	Treatment n (%)	*P*-value	Control n (%)	Treatment n (%)	*P*-value
Chest pain*	7/22 (32)	7/22 (32)	1.00	5/21 (24)	3/20 (15)	0.697
Axilla pain*	10/22 (45)	3/22 (14)	0.045	6/21 (29)	3/20 (15)	0.454
Arm pain*	13/22 (59)	5/22 (23)	0.038	7/21 (33)	3/20 (15)	0.277
Chronic pain (total)*	18/22 (82)	10/22 (45)	0.028	12/21 (57)	6/20 (30)	0.151

* any reported pain regardless of severity

A Randomized Study of the Effects of Gabapentin on Postamputation Pain

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Anesthesiology 2006; 105:1008–15

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

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Time	Phantom pain **incidence**		Phantom pain **intensity** (0-10)*	
	gabapentin	placebo	gabapentin	placebo
1 month	55%	53%	1.5	1.2
6 months	59%	50%	1.0	0.5

* 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 i*mm*pacting 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 i*mm*pacting 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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R. Andrew Moore

Henry McQuay

Cochrane Collaboration, Oxford, UK:

Phil Wiffen