Current Issues in Postoperative Pain Management

Professor Richard Langford
Barts and The London NHS Trust

Outline

- Types of acute pain
  - issues and unmet clinical needs
- Mechanisms
- Evidence under-pinnning current strategies
- Current clinical issues
  - Safety and risk assessment in analgesic treatments
    - Neuraxial blocks; PCA
  - Emerging techniques
    - new routes / formulations of established analgesics
    - new entities
  - Emerging issues

Acute Pain

- **Trauma**
- **Medical**
- **Surgical**

Clinical characteristics of Acute Pain

- Sudden, sharp, intense, localised
- Usually self-limited
- Consequences
  - Neuro-endocrine, Cardio-Respiratory, Gastrointestinal, Urinary

    Musculoskeletal

Siddall PJ, et al. *Neural Blockade in Clinical Anesthesia and Management of Pain*; 1998:675–713.
Bonica JJ. *The Management of Pain*. Vol. 1; 1990.

Acute pain meta-analysis -165 papers 20,000 patients

Major surgery

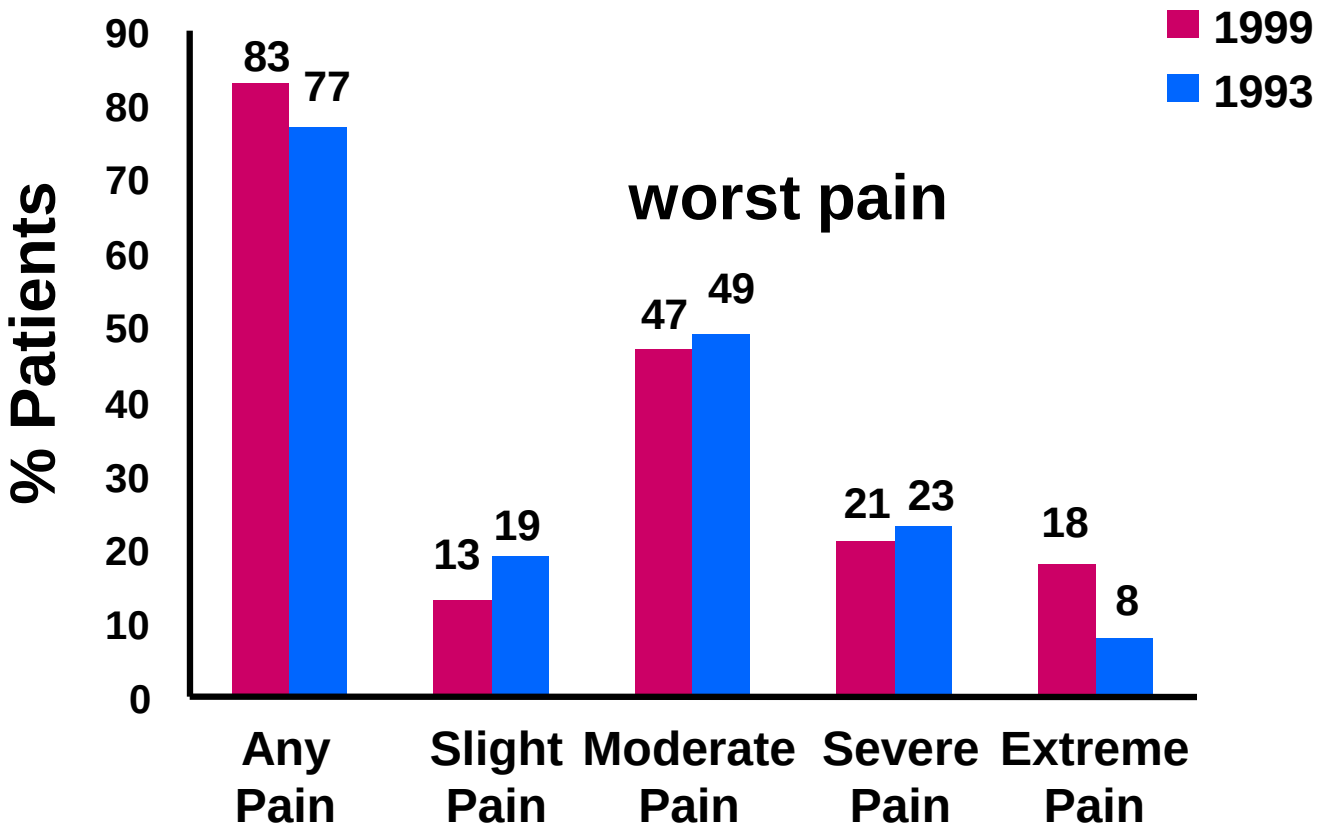
Incidence of moderately severe to severe pain

IM / PCA / Epidural analgesia

	Severe pain %	Hypoventilation % (95% CI)	Hypotension % Mean (95% CI)
IM analgesia	29.1	0.8 (0.2-2.5)	3.8 (1.9-7.5)
PCA	10.4	1.2 (0.7-1.9)	0.4 (0.1-1.9)
Epidural analgesia	7.8	1.1 (0.6-1.9)	5.6 (3.0-10.2)

Dolin SJ, Cashman JN, Bland JM. *BJA.* 2002; 89(3);409-423

Inadequate post-operative pain control *Analgesia Gaps*



Apfelbaum et al. Am. Soc. Anesthesiol. Annual Meeting October 14-18 2000

Pain – post-operative recommendations

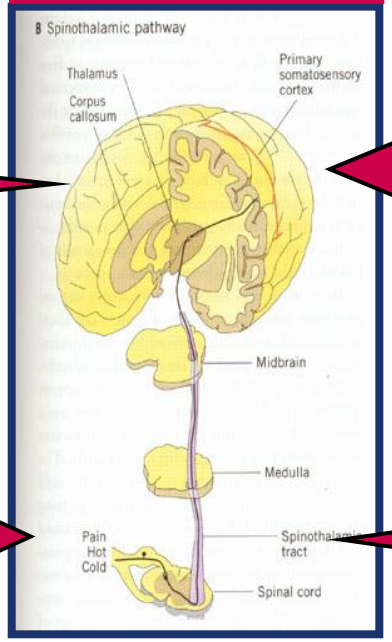
- **APS**
- **Multimodal therapy**
- **Treat early**
- **Non-opioids ‘By the Clock’**

Salicylates

inhibit prostaglandin synthesis

NSAIDs

Acetaminophen



Opioids

Improving Strategies

- Resources / Logistics / Systemic strategies
- Evidence based improvements in practice / Education:
  - Meta-analysis; NNT / NNH
  - Guidelines
  - Procedure specific recommendations (PROSPECT)
  - Pain 5th Vital Sign
  - RADAR: Responsibility, Anticipation, Discussion, Assessment, Response
  - Pain-OUT EU study:
    - Benchmarking across 11 European centres
    - Knowledge Library

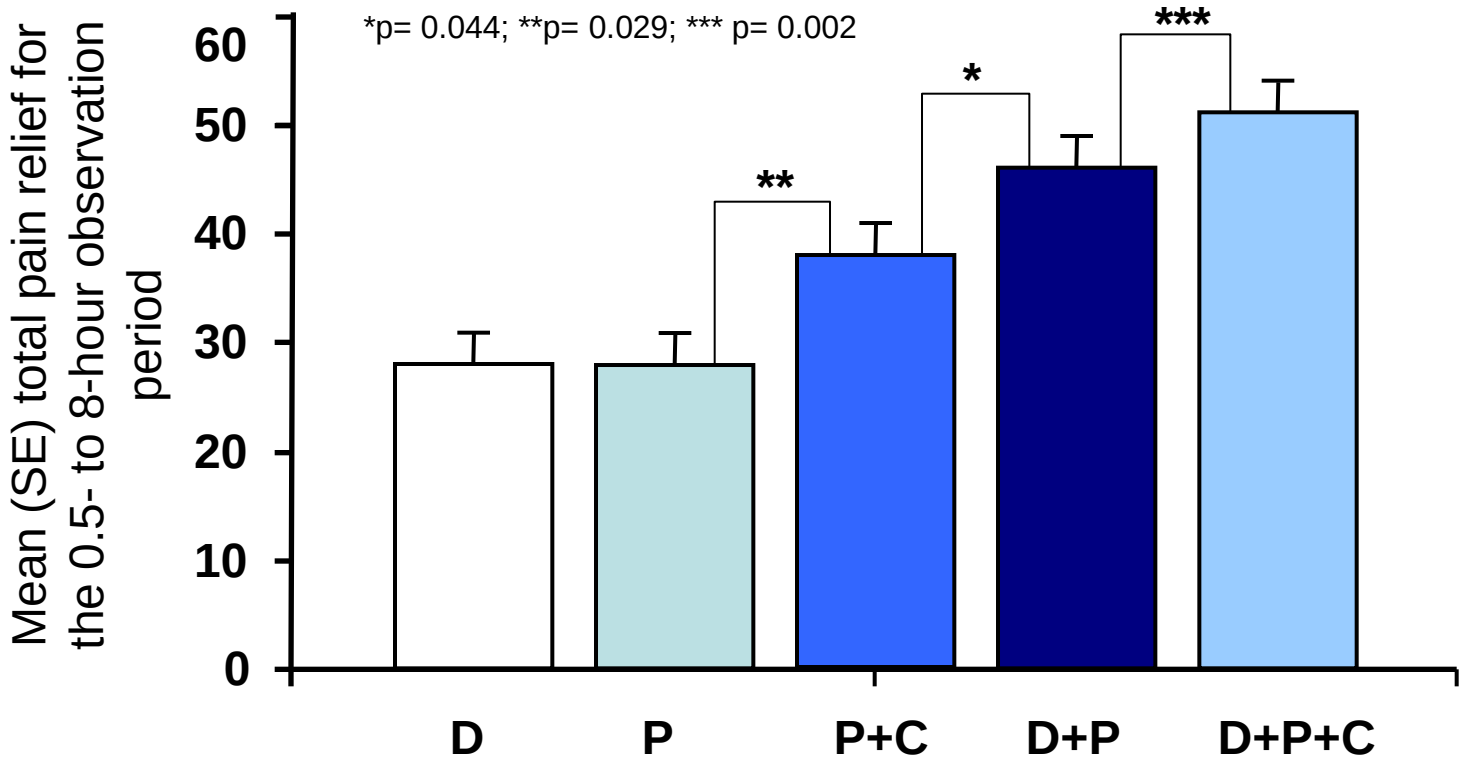
Vickers A, Bali S, Baxter A, Bruce G, England J, Heafield R, Langford R, Makin R, Power I, Trim J. Current Medical Research and Opinion'

Multimodal Analgesia

- Reduced doses of each analgesic
- Improved pain relief
- Synergistic / additive effects
- Reduces severity of side effects of each drug

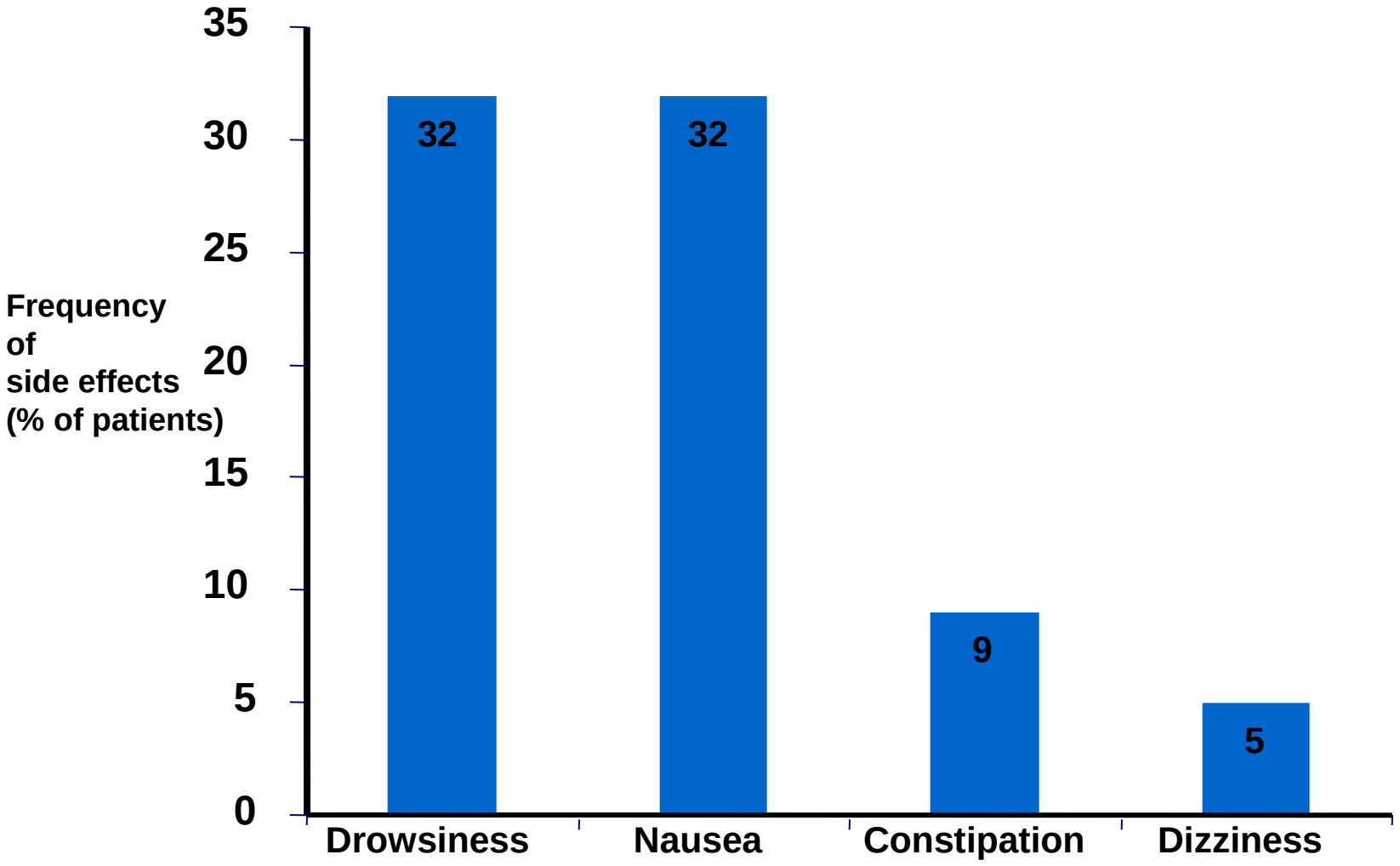
Kehlet H, Dahl JB. *Anesth Analg*. 1993;77:1048-1056.
Playford RJ, et al. *Digestion*. 1991;49:198-203.

Multimodal Therapy: Diclofenac ± Paracetamol ± Codeine



D = 100 mg diclofenac alone;
P = 1 g paracetamol alone;
P+C = 1 g paracetamol plus 60 mg codeine;
D+P = single oral dose 100-mg enteric-coated diclofenac with 1 g paracetamol;
D+P+C = 100-mg enteric-coated diclofenac with 1 g paracetamol plus 60 mg codeine

Breivik et al, *Clin Pharmacol Ther* 1999;66:625-635



Warfield CA, Kahn CH. *Anesthesiology* 1995;83:1090-1094. (Survey of 500 U.S. adults))

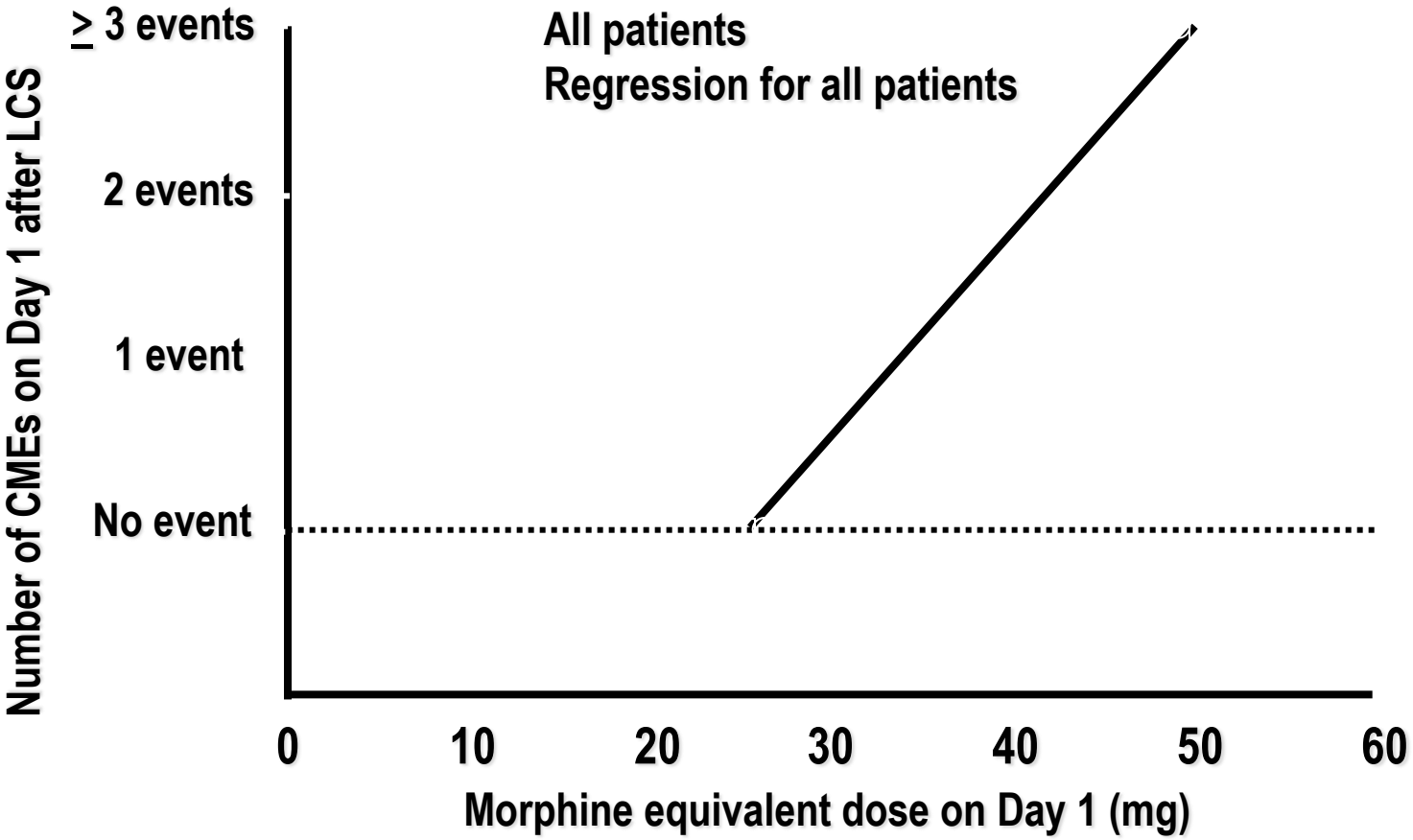
Symptom Distress Questionnaire

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(if yes), how much did it distress or bother you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A little Bit	Somewhat	Quite a Bit	Very Much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficulty with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	__ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

Apfelbaum JL et al . Reliability and validity of the perioperative opioid-related symptom distress scale. *Anesth Analg* 2004; 99: 699–709.

Dose-related opioid-associated symptoms

'Once threshold is reached, every further 3–4 mg increase will be associated with 1 clinically meaningful opioid-related symptom'



Zhao et al. *J Pain Symptom Manage 2004;28:35*

Multimodal therapy

Opioid sparing

- Much of our decision making is to avoid side effects and toxicity

Adjuvant analgesics for opioid sparing strategies

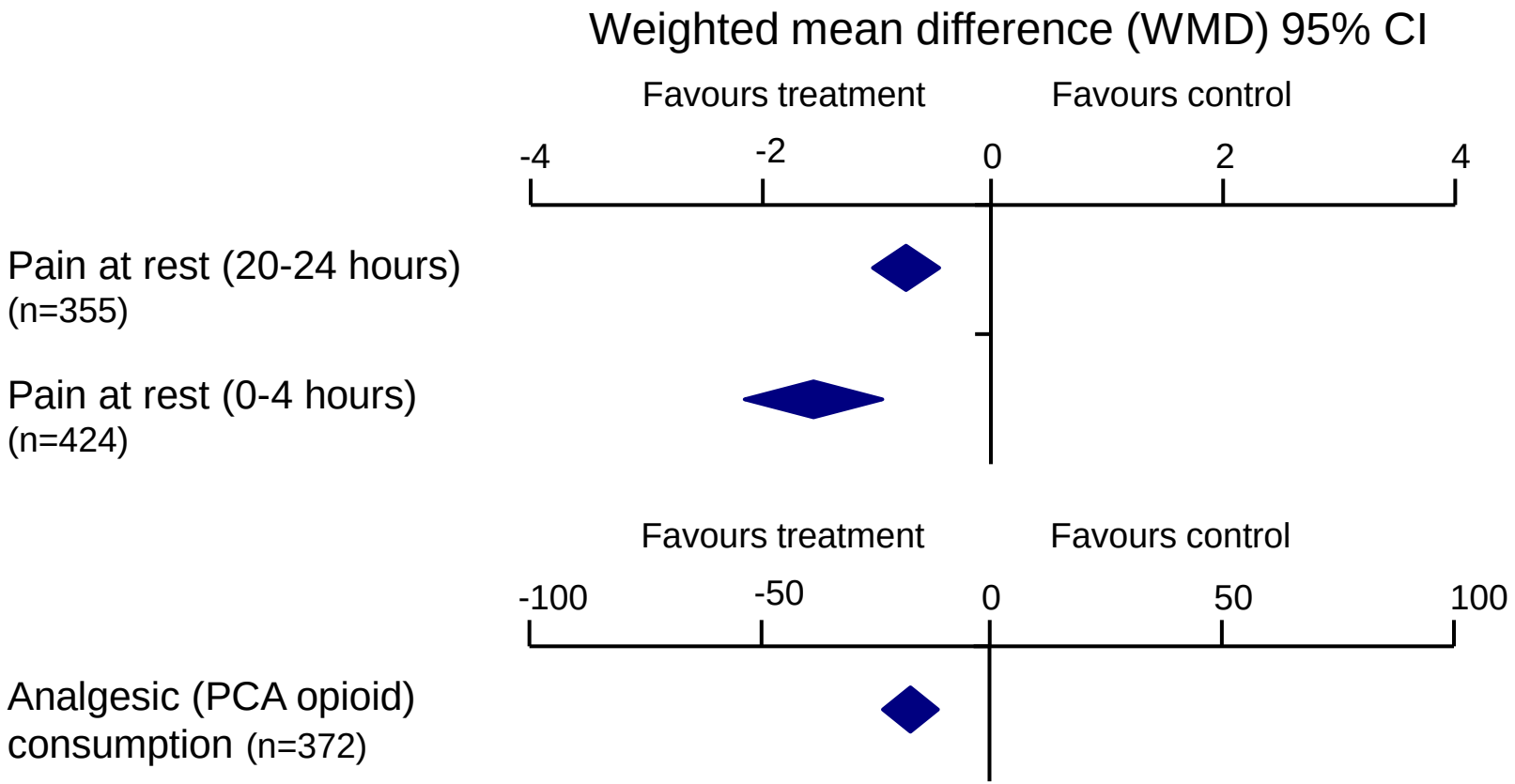
- Established
  - NSAIDs and coxibs (safety and tolerability issues)
  - Paracetamol
  - Local anaesthetic techniques
- Recent additional choices ……..?

Adjuvant analgesics for opioid sparing strategies

- Established
  - NSAIDs and coxibs (safety and tolerability issues)
  - Paracetamol
  - Local anaesthetic techniques
- Recent additional choices
  - Gabapentin
  - Low dose ketamine
  - Dexamethasone
  - Duloxetine (BJA 2010)

K.-Y. Ho et al Duloxetine reduces morphine requirements after knee replacement surgery British Journal of Anaesthesia 105 (3): 371–6 (2010)

Gabapentinin Post-operative Pain: Meta-analysis of 12 RCTs



Hurley et al. J Reg Anesth Pain Med. 2006;31:237-247

Ketamine Review

- Single IV ketamine bolus improved posto analgesia with opioids
  - side effects: not increased by a single bolus IV ketamine
- Minor surgical procedures, single dose ketamine ranging from 0.15–1 mg/kg in addition to opioids may be useful
- Despite opioid-sparing effects
  - no reduction in opioid-related side effects such as PONV, pruritus, and respiratory depression
- Small dose ketamine not associated with increased psychomimetic effects eg. hallucinations or excessive sedation
- To be researched:
  - Small dose ketamine used for acute postoperative pain to reduce long-term pain syndromes (postmastectomy, thoracotomy, and phantom pain)

Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review. K Subramaniam, B Subramaniam, R A Steinbrook Anesth Analg 2004;99:482–95

‘Recent’ Advances

- Only a few new entities
  - *in fact, we’ve lost more than we’ve gained*
- Most advances have been innovative ways to administer existing drugs:
  - local anaesthetic techniques
  - buccal
  - nasal
  - inhaled
  - controlled release
  - transdermal
    - passive & active

Postoperative Patient-controlled and Continuous Infusion Epidural Analgesia vs IV Opioid PCA

- Meta-analysis of 299 RCT's
- Epidural analgesia in every combination superior to IV PCA up to 3-days (exception – epidural morphine alone)

RCT = Randomised controlled trial; PCA = Patient-controlled analgesia; IV = intravenous; PCEA = Patient controlled epidural analgesia; PONV = Post-operative nausea/vomiting.

Wu et al. *Anesthesiology* 2005;103:1079-88

Epidural Continuous Infusion Analgesia vs IV Opioid PCA

- Meta-analysis of 299 RCT's
- Epidural analgesia in every combination superior to IV PCA up to 3-days (exception – epidural morphine alone)

- ***however, emerging safety data……***

RCT = Randomised controlled trial; PCA = Patient-controlled analgesia; IV = intravenous; PCEA = Patient controlled epidural analgesia; PONV = Post-operative nausea/vomiting.

Wu et al. *Anesthesiology* 2005;103:1079-88

Severe Neurological Complications after Central Neuraxial Blockades in Sweden 1990–1999

- Total approx. 1,260,000 spinals, 450,000 epidurals
- Severe neurological complications = 127;
  Permanent neurological damage = 85
  - Overall rate of: 1 in 8261
- Incidence after spinal = 1 in 25,000
  Obstetric epidural = 1 in 25,000
  Non-obstetric epidurals = 1 in 3,600
- Osteoporosis – previously neglected risk factor;
  common in women (↑ hip fractures, vertebral deformities, narrow spinal canal)

Moen et al. Anesthesiology 2004;101:950-9

Major complications of central neuraxial blocks:

3rd National Audit Project of Royal College of Anaesthetists (NAP3)

- **700,000 central neuraxial blocks over one year:**
  - spinals 46%
  - epidurals 41%
  - (45% obstetric indications / 44% perioperative)

- **84 major complications:**
  - 52 met all audit inclusion criteria
    - **'pessimistic' data interpretation:**
      - **1 in 24,000 incidence of permanent injury**
    - **'optimistically':**
      - **1 in 54,000 incidence of permanent injury**

Major complications of central neuraxial blocks:

3rd National Audit Project of Royal College of Anaesthetists (NAP3)

- **Deaths or paraplegias:**
  - ‘Pessimistically’ 13 cases 1 in 50,000
  - ‘Optimistically’ 5 cases 1 in 140,000

- **In the 30 patients with permanent harm:**
- More than 80% of these patients had a CNB placed for perioperative analgesia
- 60% occurred after epidural block
- 23% after spinal anaesthesia

Epidural Analgesia

Benefits

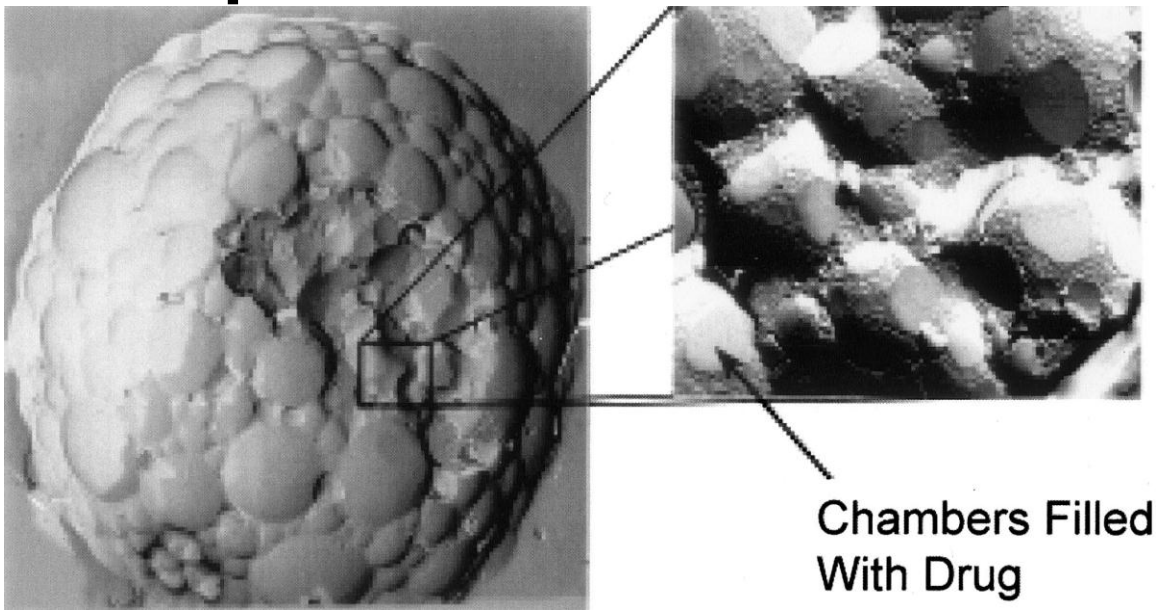
Superior analgesia
Early ambulation
Reduced morbidity
Shorter hospitalization?

Costs

Invasive technique
Adverse effects
Monitoring costs
Neurol. complications

Sustained release epidural morphine

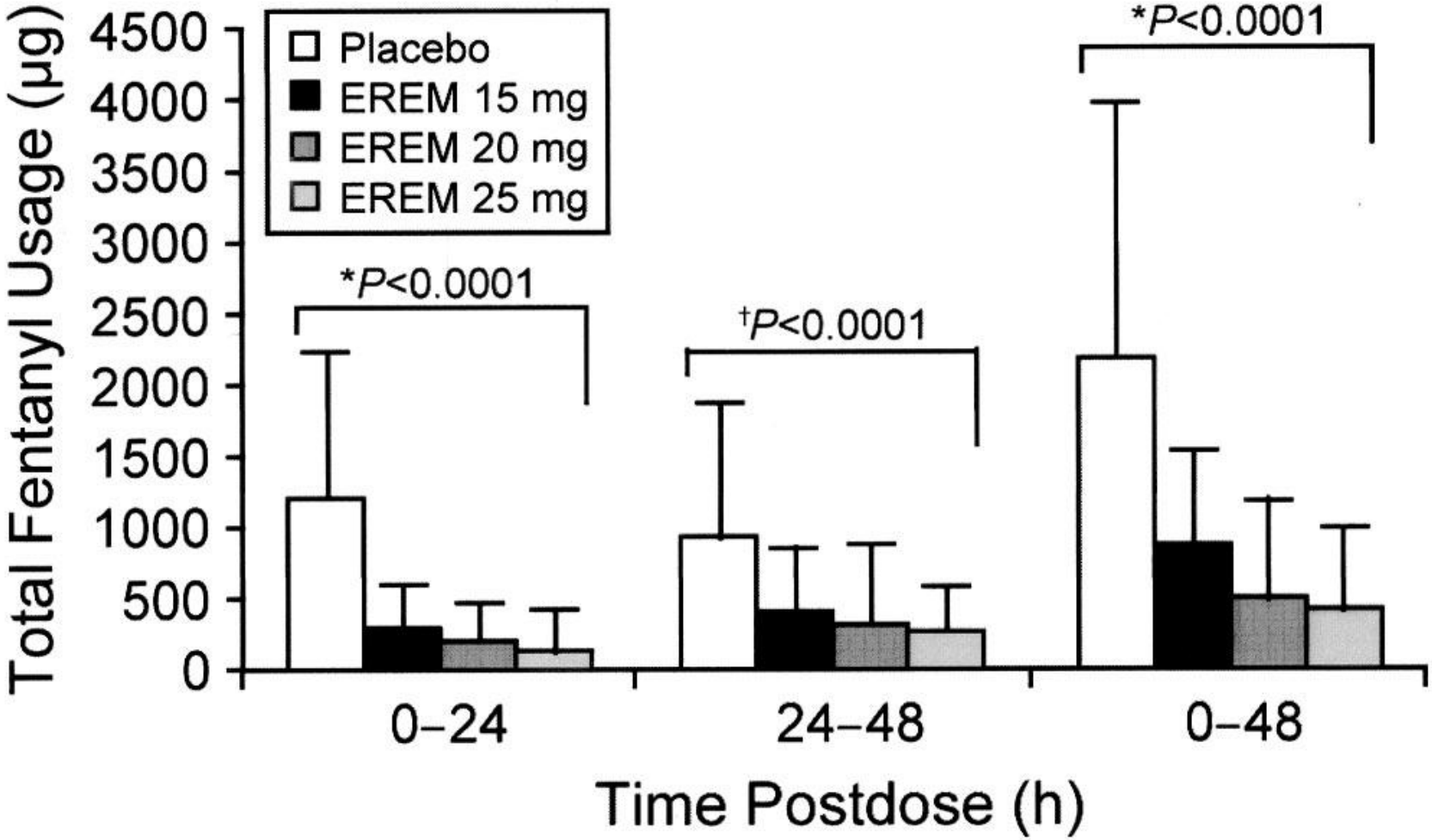
- 72 hours,
- ‘Single shot’



- No indwelling catheter
- No motor or sympathetic blockade

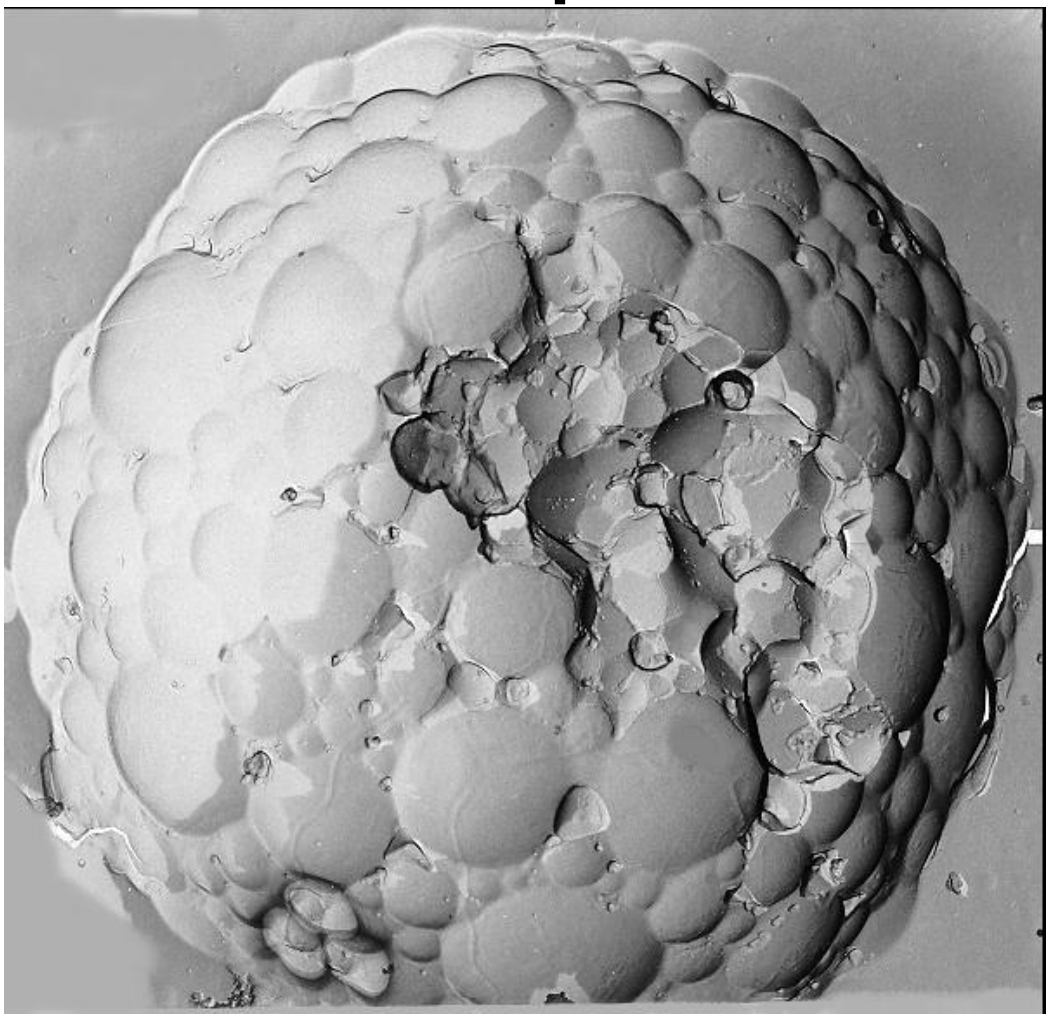
Sustained release epidural morphine

(EREM: Extended Release Epidural Morphine)



Viscusi et al. Anesthesiology. 2005 ;102

Electron Micrograph of a DepoFoam Particle



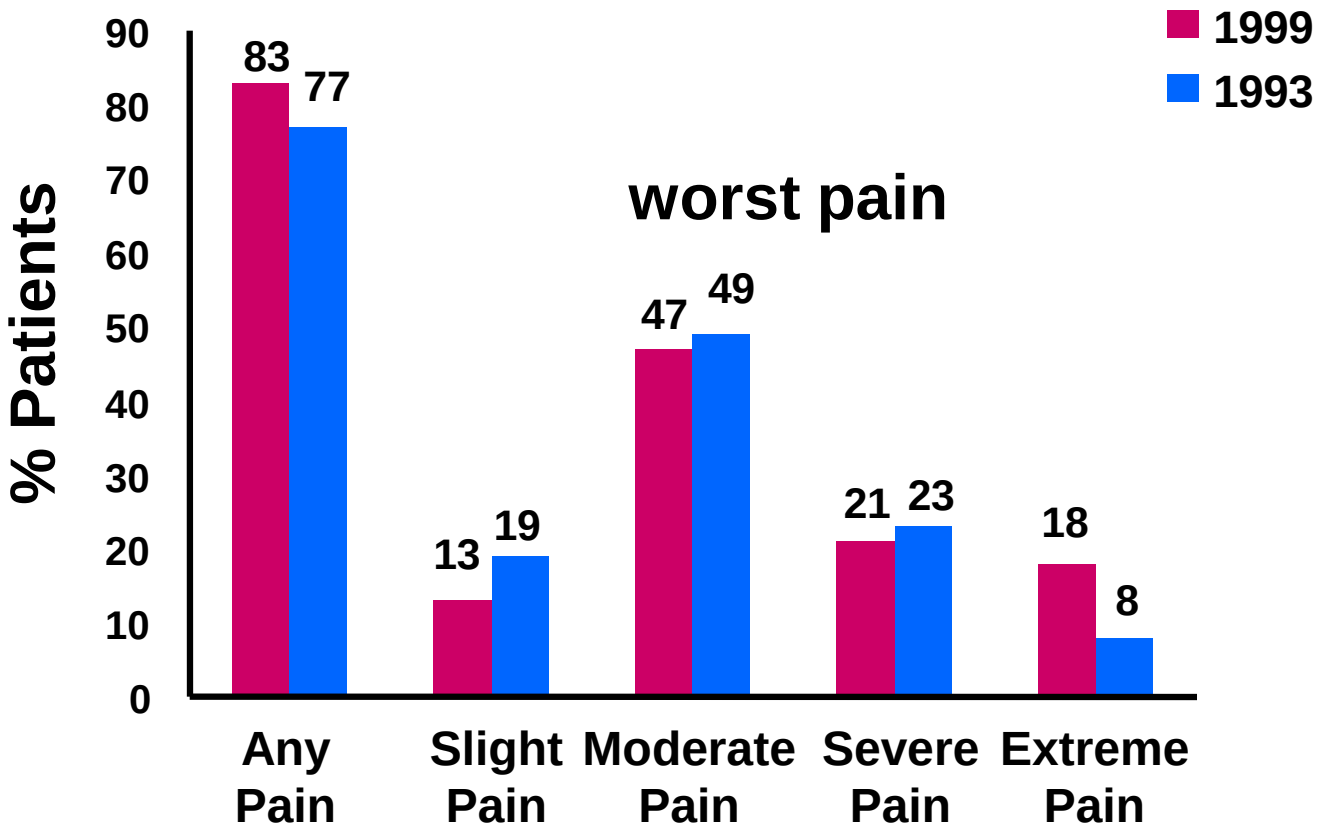
Bupivicaine for surgical wound infitration

Positive Phase 2 studies

72 hours +

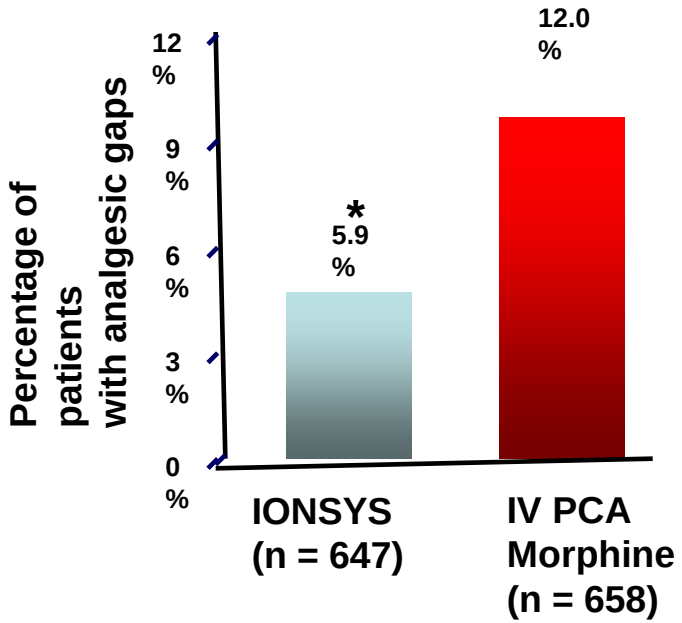
Morphine (epidural)

Inadequate post-operative pain control *Analgesia Gaps*



Apfelbaum et al. Am. Soc. Anesthesiol. Annual Meeting October 14-18 2000

IV PCA - more analgesia gaps

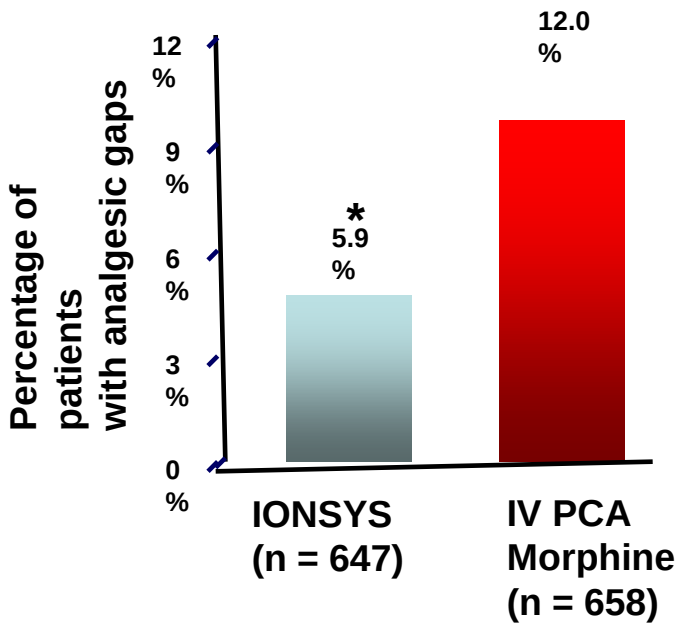


Data pooled from the Hartrick and Minkowitz studies.

*** P<0.001 vs. IV PCA Morphine**

Panchal S. et al Poster presentation. ASRA 2006
Hartrick CT et al. Regional Anesthesia and Pain Medicine Vol. 31 No. 6 Nov-Dec 2006
Minkowitz HS et al. accepted to Pain Medicine. 2006

IV PCA - more analgesia gaps



"Press the button when you feel pain"

Data pooled from the Hartrick and Minkowitz studies.

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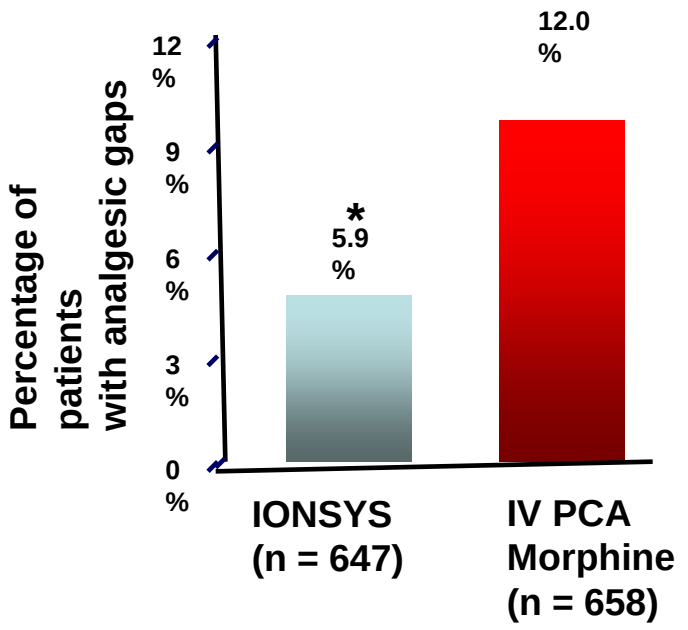


Data pooled from the Hartrick and Minkowitz studies.

*** P<0.001 vs. IV PCA Morphine**

"Press the button when you feel pain"

- First you have to feel pain

…… always playing 'catch-up',

- even worse after sleep
- and only in small increments

Panchal S. et al Poster presentation. ASRA 2006
Hartrick CT et al. Regional Anesthesia and Pain Medicine Vol. 31 No. 6 Nov-Dec 2006
Minkowitz HS et al. accepted to Pain Medicine. 2006

IV PCA: safety issues

NHS
National Patient Safety Agency

Patient safety alert 20

Alert

28 March 2007

Immediate action	☐
Action	☑
Update	☐
Information request	☐

Ref: NPSA/2007/20

Promoting safer use of injectable medicines

The National Patient Safety Agency (NPSA) received around 800 reports a month to its National Reporting and Learning System (NRLS) relating to injectable medicines between January 2005 and June 2006. This represents approximately 24 per cent of the total number of medication incidents. The majority of these resulted in no or low harm to patients. However, there were 25 incidents of death and 28 of serious harm reported between January 2005 and June 2006.

Research evidence indicates that the incidence of errors in prescribing, preparing and administering injectable medicines is higher than for other forms of medicine.[1-2] In one study, at least one error occurred in 49 per cent of intravenous medicine doses prepared and administered on hospital wards; one per cent were judged to be potentially severe errors; and 29 per cent potentially moderate errors[1] (more details about this study are included in the background section on page 6).

Using data from the NRLS and other evidence,[3] the NPSA has identified a number of latent system risks and is making recommendations that can make the use of injectable medicines safer.

Action for the NHS and the independent sector

The NPSA is recommending that all NHS and independent sector organisations in England and Wales take the following steps:

1. Undertake a risk assessment of injectable medicine procedures and products in all clinical areas to identify high risks, and develop an action plan to minimise them.
2. Ensure there are up-to-date protocols and procedures for prescribing, preparing and administering injectable medicines in all clinical areas.
3. Ensure essential technical information on injectable medicines is available and accessible to healthcare staff in clinical areas at the point of use.
4. Implement a 'purchasing for safety' policy to promote procurement of injectable medicines with inherent safety features.
5. Provide training for, and supervision of, all healthcare staff involved in prescribing, administering and monitoring injectable medicines.
6. As part of the annual medicines management audit programme, healthcare organisations should include an audit of medication practice with injectable medicines.

For response by:
- All NHS and independent sector organisations in England and Wales

For action by:
- The chief pharmacist/pharmaceutical adviser should lead the response to this alert, supported by the chief executive, medical director, nursing director and clinical governance lead/risk manager

We recommend you also inform:
- Clinical governance leads and risk managers
- Medical staff
- Nursing staff
- Pharmacy staff
- Radiographers
- Operating theatre practitioners and assistants
- Patient advice and liaison service staff in England
- Procurement managers

The NPSA has informed:
- Chief executives of acute trusts, primary care organisations, mental health trusts, ambulance trusts, local health boards in England and Wales
- Chief executives/regional directors and clinical governance leads of strategic health authorities (England) and regional offices (Wales)
- Healthcare Commission
- Healthcare Inspectorate Wales
- Business Services Centre (Wales)
- Independent Healthcare Advisory Services
- Medicines and Healthcare products Regulatory Agency
- NHS Purchasing and Supply Agency
- Welsh Health Supplies
- Royal colleges and societies
- NHS Direct
- Relevant patient organisations and community health councils in Wales
- Independent Healthcare Forum
- Commission for Social Care Inspection

PCA-related Operator Errors and Adverse Events

Nearly 50% (63/131) of possible operator errors were associated with adverse events

Type of event	Frequency
Patient death	6
Naloxone administered	41
Respiratory arrest	3
Respiratory depression	3
Oversedation	6
Unspecified	4
Total	**63**

Hankin CS, et al. *Am J Health Syst Pharm*. 2007;64(14):1492-1499.

Improved opioid strategies?

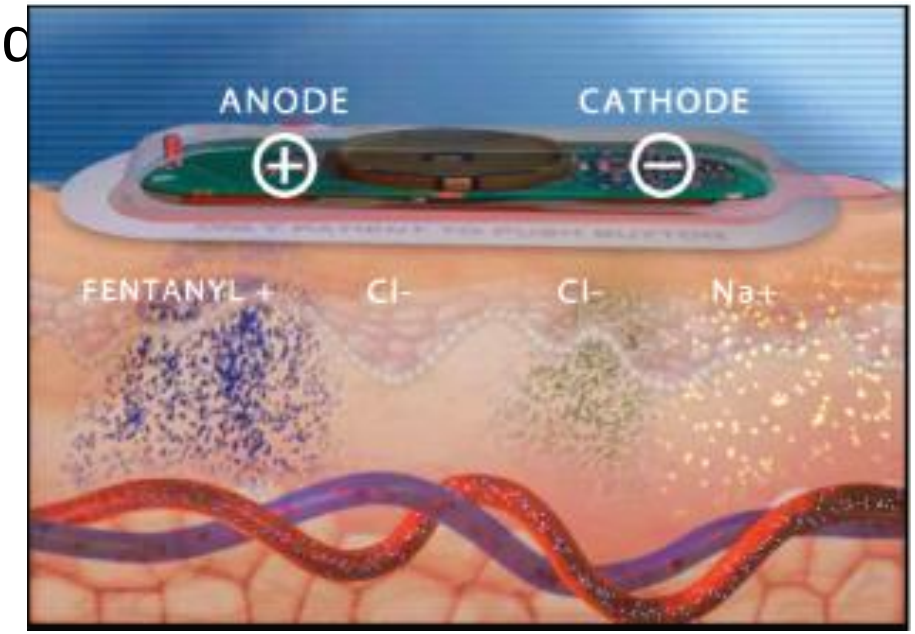
- Background, low rate infusions for PCA
- For patients able to take oral medicines
  - oral sustained release opioid plus immediate release
    - established practice in Germany

…. and with opioids, tolerability issues equally important

  - opioid sparing strategies

Iontophoretic Transdermal Delivery

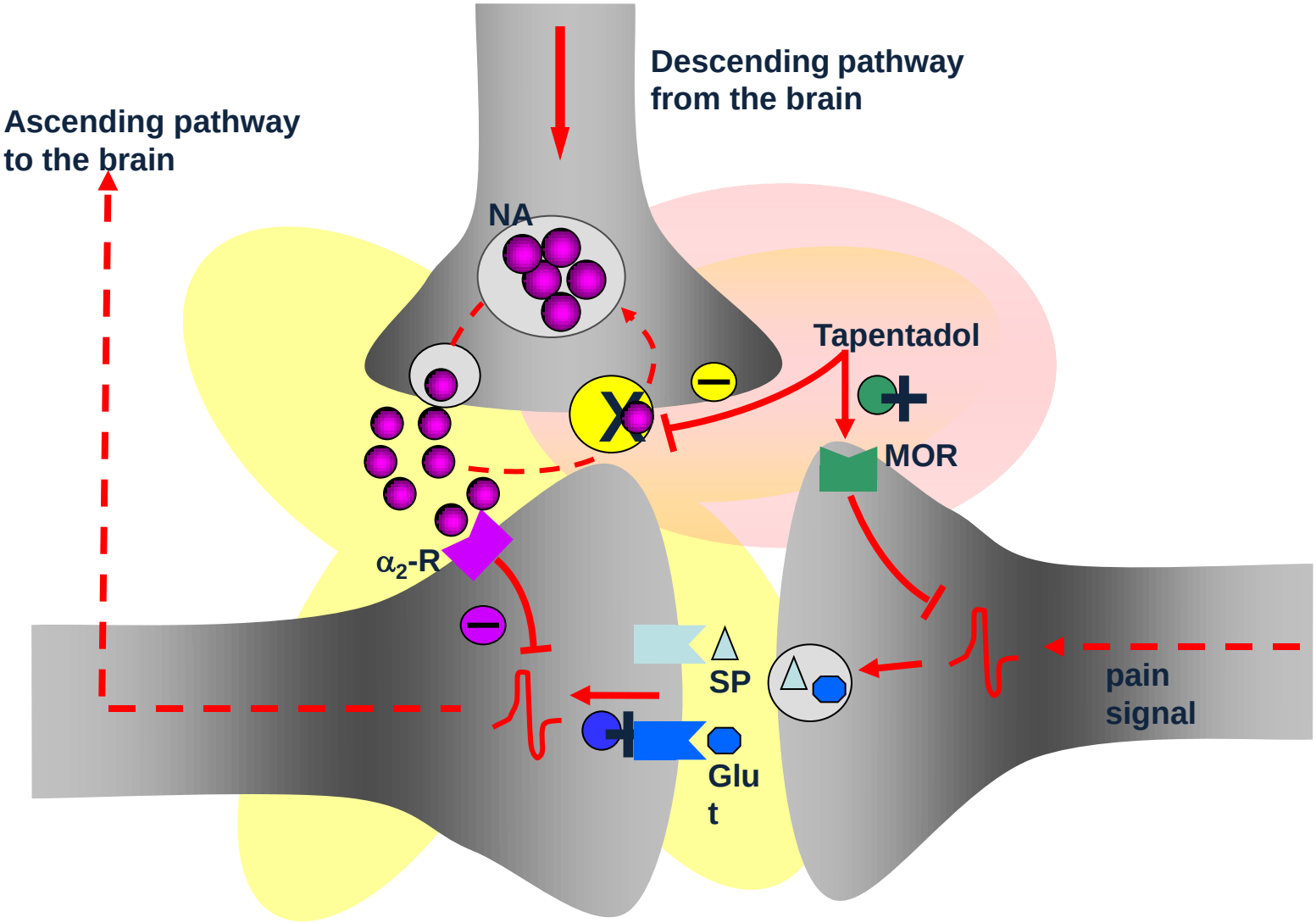
- Iontophoresis: generally imperceptible electrical field transports 40mcg fentanyl dose through intact skin and into the blood



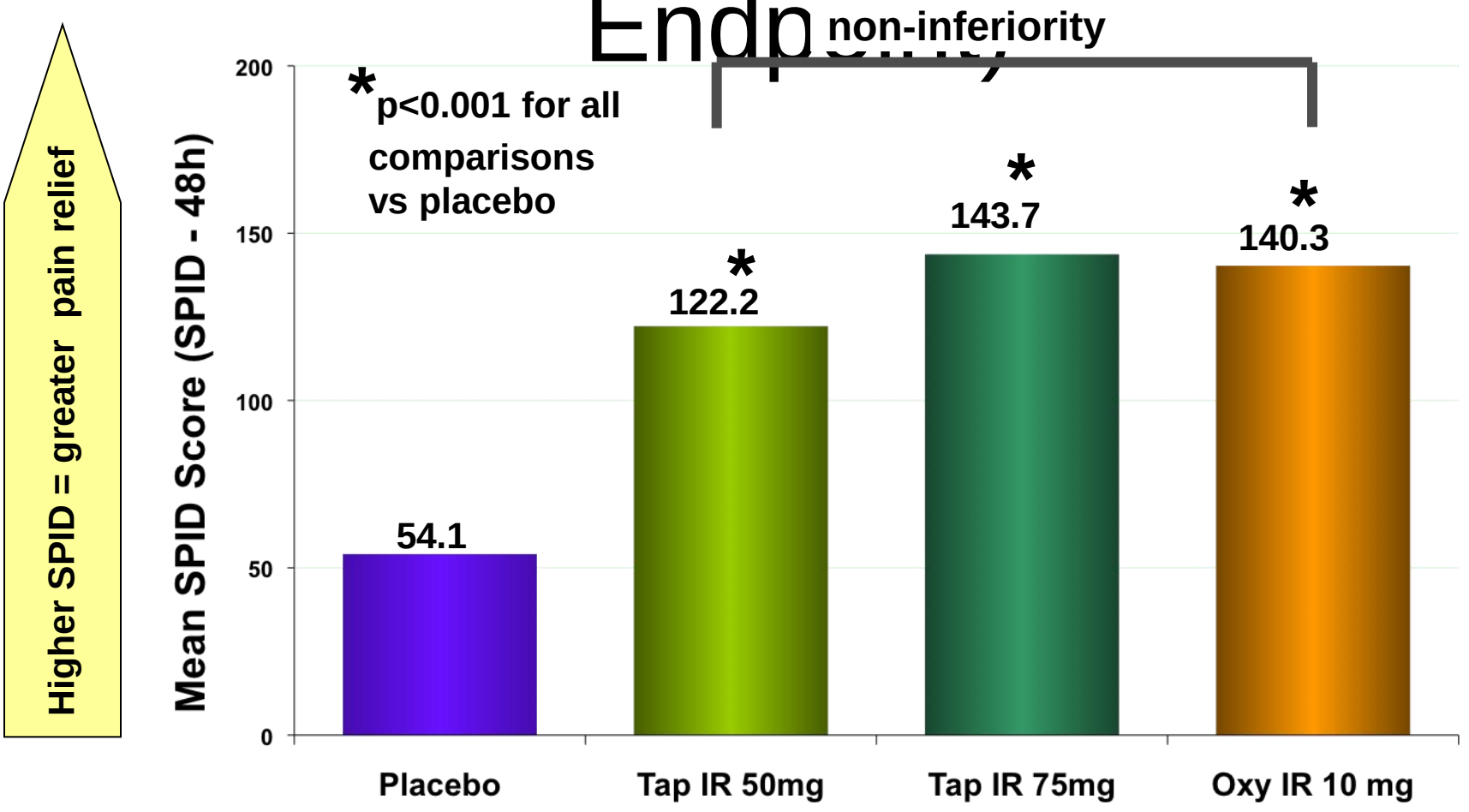
Koo PJS. Am J Health-Syst Pharm 2005;62:1171–6
Zimmer R, Ashburn MA. Comp Ther 2001;27:293–301

Tapentadol

MOR agonism and NRI in pain models



Bunionectomy: Efficacy SPID-48 Hours (Primary Endpoint)

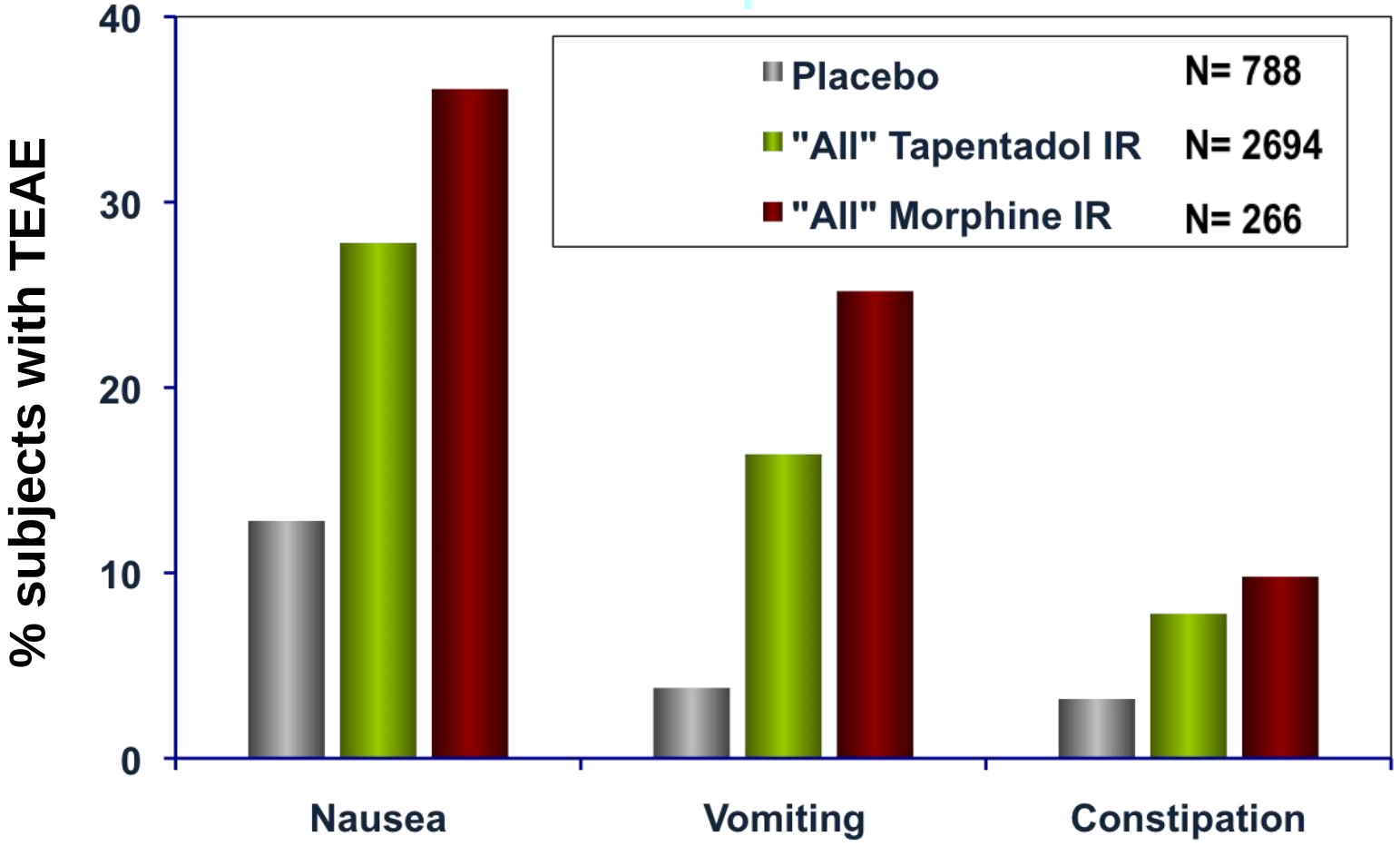


Dose dependent efficacy of Tapentadol

Daniels et al., CMRO 2009

Pooled Analysis - GI Adverse Events

Tapentadol IR Phase II/III Trials vs. Morphine



Data on file

Emerging issues in Acute Pain

Chronic Pain as an Outcome of Surgery

	Perkins & Kehlet %	Macrae %
Mastectomy	11-49	23-49
Thoracotomy	22-67	5-67
Cholecystectomy	3-56	3-27
Inguinal hernia	0-37	15-63
Vasectomy	-	0-37

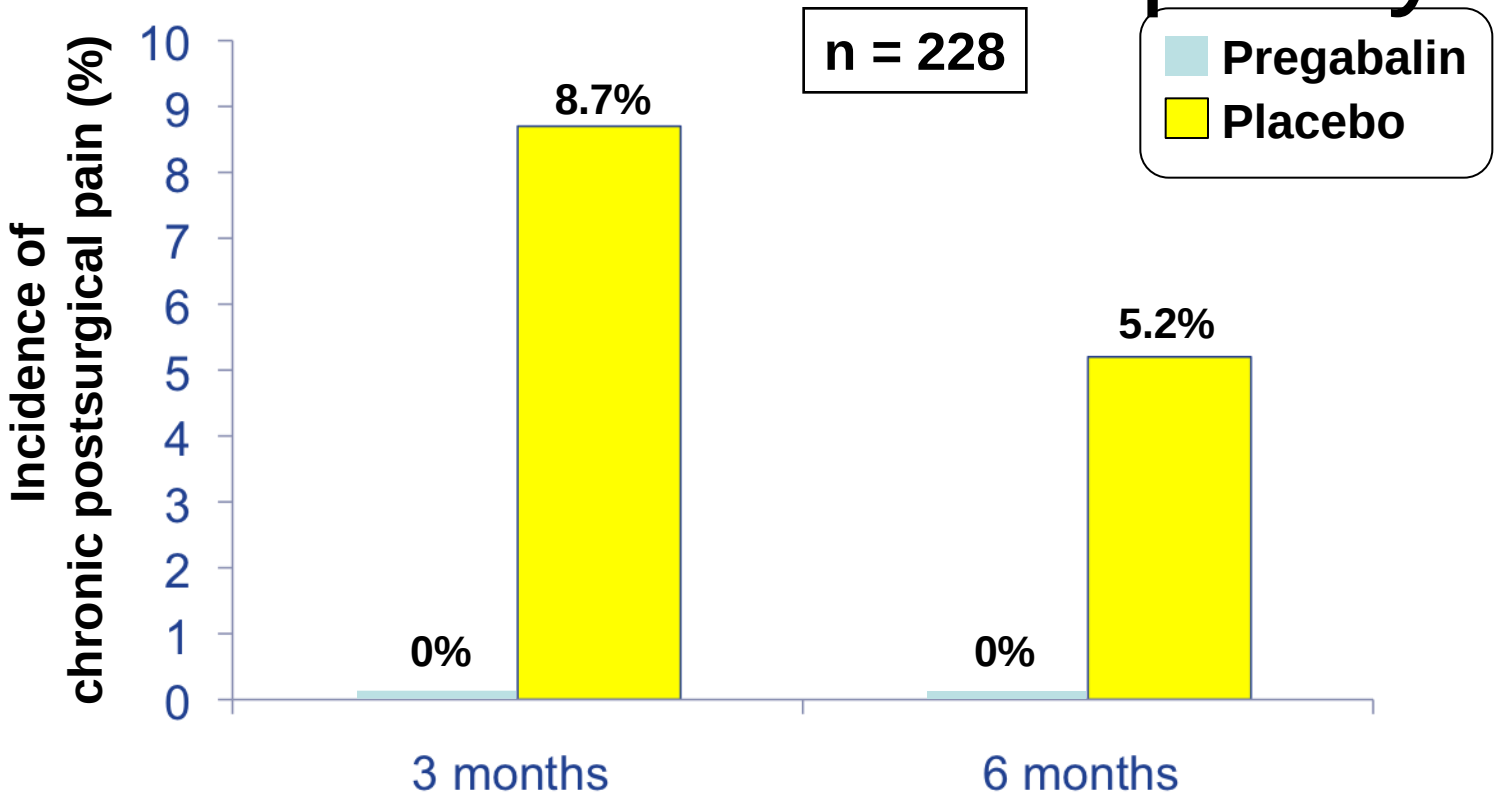
Chronic Pain as an Outcome of Surgery: A Review of Predictive Factors. Perkins, FM, Kehlet H. *Anesthesiology 2000; 93:1123-1133.* Macrae WA. *Br J Anaesth*. 2001;87:88-98.

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

- Prospective RCT double-blind trial of pregabalin (300 mg) administered before TKA and for 14 days after TKA (150–50 mg twice daily)
- Neuropathic pain screen at 3 and 6 months post surgery
  - Leeds Assessment of Neuropathic Symptoms and Signs scale
  - Secondary outcomes
    - including knee range of motion, opioid consumption, postoperative pain scores, sleep disturbance, and

Buvanendran A et al. Anesth Analg 2010;110(1):199-207

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty



Other outcomes : less opioid consumption, greater active flexion at 30 days

Buvanendran A et al. Anesth Analg 2010;110(1):199-207

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

- 240 patients randomised:
  - data for the primary outcome were obtained from 113 pregabalin patients and 115 placebo patients

At both 3 and 6 months post surgery:

- neuropathic pain was less frequent in the pregabalin group at 3 and 6 months
  - 0% vs. 8.7% and 5.2%, respectively in placebo group (P = 0.001 and P = 0.014).
- Pregabalin patients:
  - consumed less epidural and oral opioids (P = 0.003; P = 0.005)

Buvanendran A et al. Anesth Analg 2010;110(1):199-207

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

- Time to achieve hospital discharge criteria was longer for placebo patients, 69.0 ± 16.0 h (mean ± sd) vs. 60.2 ± 15.8 h (P = 0.001)
  - although no difference in actual duration of hospital stay

- Sedation (P = 0.005) and confusion (P = 0.013) were more frequent on the day of surgery and postoperative day 1 in patients receiving pregabalin

Buvanendran A et al. Anesth Analg 2010;110(1):199-207

Opioid induced immunosuppression

Effects of morphine on immune cells in animals and humans

Cell types	*In vivo* studies
T-lymphocytes	↓
B-lymphocytes	↓
Natural killer lymphocytes	↓
Monocytes/macrophages	↓

Sacerdote P et al. Experimental evidence for immunomodulatory effects of opioids. In: *Immune Mechanisms of Pain and Analgesia.* Machelska & Stein eds, 2002

Not all opioids share the same immunosuppressive properties

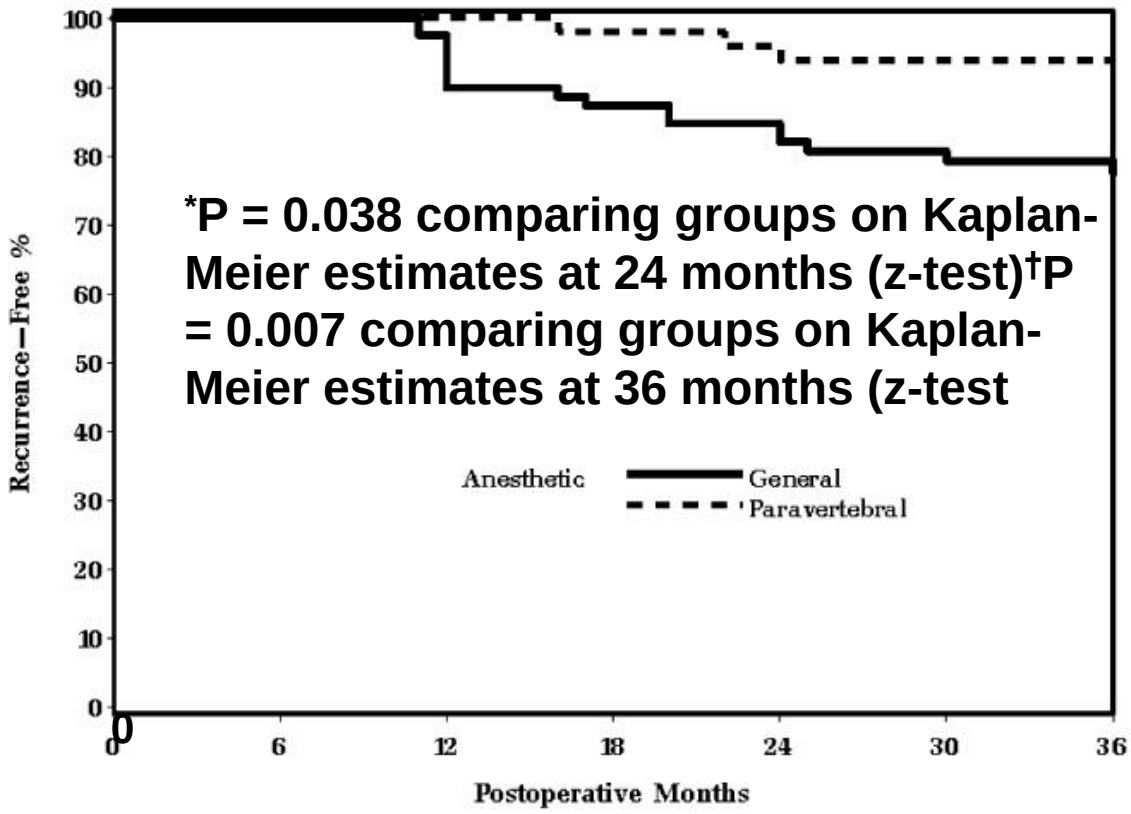
Immunosuppressive	**Less immunosuppressive**
Codeine	Buprenorphine
Methadone	Hydromorphone
Morphine	Oxycodone
Remifentanil	Tramadol
Fentanyl	

Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence: A Retrospective Survey

- GA + Epidural or Morphine PCA
- Open prostatectomy surgery with general anesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence.
- Prospective randomized trials to evaluate this association seem warranted

Biki B, Mascha E, Moriarty D, Fitzpatrick JM, Sessler D, M.D.‖; Buggy, Donal J. Anesthesiology. 2008.109(2) -180-187

Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis?



- Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha D, Sessler DI. : Anesthesiology. 2006 October; 105(4): 660–664

Messages

- **Steady improvement, but pain levels still unacceptable:**
  - need analgesic measures working before patient awakens
  - strategy for when LA wears off
  - More continuous methods of pain relief (reduce analgesia gaps)
- **~~APS~~ 'In-patient' Pain Service**
  - Medical and paediatric wards, chronic pain, etc
  - more integration with chronic pain service *(personal view)*
  - maintain education of ward staff:
    - To improve pain assessment and treatment
    - To maintain vigilance for potentially harmful complications
  - need to address training of new 'acute pain' consultants