Inadequate post-op analgesia

- 36 y female L5S1 fusion, Friday list
  - Pre-op: Zomorph 40mg bd, nefopam 90mg tid

- Anaesthetic: GA, fentanyl 100mcg, morphine 10mg. Surgery 3 h.

- Recovery: Much pain. Morphine PACU protocol

- Ward:
  - prescribed zomorph bd, nefopam 30-60mg prn and oramorph 1-2 h prn.
  - Severe pain throughout the night.
  - Seen by surgeon next morning who asked for PCA to be set up. Not done by ward staff (inexplicable).

- Referred to APT Monday
Epidural too low

• Male patient had an open cholecystectomy
  – Pre-op SR opioids

• GA + Epidural.
  Initially comfortable. Discharged to ward.

• 1st post-op night pain increased to severe. Rate 6ml/h increased by ward staff to 8ml/h.
  Ward staff unable to speak to o/c Anaesthetist as in theatre.

• S/B APT next morning: low block, bolus 10ml 0.25%Bupiv partially helpful only.
  Convert to plain bupivacaine + iv PCA with bolus 2mg
X yr old female for elective lap chole + perc jejunostomy tube.

- Takes oxynorm 50mg 4-5x daily
- Chronic abdo pain
- Bridging protocol for anticoag (PE)
- Poor nutritional status 43kg.

- Anaes: GA, iv analgesia.

- Post-op: PCA. Lot of abdominal pain for several days

- Gradually settling but developed twisted bowel: increased pain, vomiting, distension. Oxycodone s/c 160 mg/24h. INR 2.1

- Post-op oxycodone PCA: 5 mg bolus & 5mg/h background. Ist 24 h used 500mg
Oxycodone or morphine?

- Cost: oxycodone 3x morphine
- Rat data suggests oxycodone may have significant κ-receptor activity
- Small studies in man to suggest a difference in some pain modalities and visceral pain
- Palliative Care studies of opioid rotation to reduce delerium
Oxycodone

- 1.6x more potent than morphine (molar wgt)
- Lipid solubility and protein binding (38%) similar to morphine
- Receptor activity $Ki$ (nM):
  - $\mu$-opioid receptor = 18
  - $\delta$-opioid receptor = 958
  - $\kappa$-opioid receptor = 677
- Oral bioavailability > 60%
- Metabolised to noroxycodone & oxymorphone (active)
- Noroxycodone excreted unconjugated
- 8-14% oxycodone excreted unchanged
- Renal/liver impairment: prolonged effect
Intravenous morphine and oxycodone for pain after abdominal surgery
E. Kalso et al. AAS 1991;35(7):642

- Major abdo surgery, 39 patients
- Morphine or oxycodone 0.05mg/kg, 5min
- Double blind
- 2 h study period

- Dose Over 2 h - Oxy:Mor 21.8mg : 34.2mg
- Time to pain relief - Oxy:Mor 28min: 46min
- Duration of pain relief - Oxy:Mor 39min : 27min
- AEs similar
Comparison of analgesic efficacy of oxycodone and morphine in postoperative IV PCA
M. SILVAS et al. AAS 1998; 42: 576-580

- 24 h study of major breast reconstruction or spinal surgery (e.g., fusion)
- GA: volatile, fentanyl, no regional
- PCA in PACU, OX 30mcg/kg, MO 45mcg/kg, 5 min lockout

- Mean age 41

<table>
<thead>
<tr>
<th></th>
<th>Oxycodone (mg)</th>
<th>Morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recovery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>SS</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>24 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>SS</td>
<td>74</td>
<td>56</td>
</tr>
</tbody>
</table>

- Adverse effects: No difference
Oxycodone VS morphine

- No significant difference in studies of acute pain

- Palliative Care: metanalysis 2011: “There is no evidence from the included trials of a significant difference in analgesia or adverse effects between oxycodone and morphine”

- Opioid rotation for delerium in Palliative Care reports always from morphine to oxycodone

- Single nurse dispenses Oramorph
95% CI of NNT for at least 50% pain relief compared with placebo.
<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of patients</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parecoxib 40</td>
<td>(1446)</td>
<td>1.8</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Paracet 1G + Cod 60</td>
<td>197</td>
<td>2.2</td>
</tr>
<tr>
<td>Tramadol 100</td>
<td>882</td>
<td>4.8</td>
</tr>
<tr>
<td>50</td>
<td>770</td>
<td>8.3</td>
</tr>
<tr>
<td>Codeine 60 (dental)</td>
<td>1146</td>
<td>21</td>
</tr>
<tr>
<td>(other)</td>
<td>1265</td>
<td>6.8</td>
</tr>
<tr>
<td>(comb)</td>
<td>2411</td>
<td>12</td>
</tr>
<tr>
<td>Dihydrocodeine 30</td>
<td></td>
<td>8.1 (4.1-540)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNH 7</td>
</tr>
<tr>
<td>Nefopam</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Patient with colorectal cancer needs an anterior resection. He has chronic and severe back pain, high blood pressure and mild COPD.

Zomorph (morphine SR/MR) 50 mg bd (100mg daily). Oramorph 20mg 2-3x daily
Antihypertensives, 2 inhalers, statin, PPI (omeprazole).

• Post op analgesia: regional (epidural), other regional block, or iv PCA?
cutaneous layer

musculo-aponeurosis layer

parietal peritoneal membrane

multiholed catheter
Continuous Preperitoneal Infusion of Ropivacaine Provides Effective Analgesia and Accelerates Recovery after Colorectal Surgery: A Randomized, Double-blind, Placebo-controlled Study.

DOI: 10.1097/01.anes.0000278903.91986.19

Fig. 4 Pain intensity at rest (A) and during coughing (B), assessed using a verbal numerical scale (VNS). * P
US guided subcostal TAP block
Patient with colorectal cancer needs an anterior resection. He has chronic and severe back pain, high blood pressure and mild COPD.

Zomorph (morphine SR/MR) 50 mg bd (100mg daily). Oramorph 20mg 2-3x daily
Antihypertensives, 2 inhalers, statin, PPI (omeprazole).

• Total Daily Dose morphine (TDD) by oral route = 150mg
• Equivalent IV dose = 50mg per day

• Epidural: standard prescription.

• Post op iv PCA: Background dose of morphine of 1-2mg/h + PCA bolus 1mg
# Approximate conversion ratios

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability %</th>
<th>Potency 24 h Oral / TD</th>
<th>Potency 24 h IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 (20-50)</td>
<td>100mg</td>
<td>30mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>60-80</td>
<td>50mg</td>
<td>30-40mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td>25mcg/h 600mcg/24h</td>
<td>25mcg/h</td>
</tr>
</tbody>
</table>
38 yr old patient with osteomyelitis in tibia from trauma 4 yrs previously, now for below knee amputation

Fentanyl 100mcg/h, oramorph 100mg daily

- Post op analgesia: regional, pref epidural
- Maintain fentanyl patch 100mcg/h

- Regional block + PCA
- PCA drug: fentanyl
- PCA: 50-100mcg/h background + 1.5-2 ml
- Preferably manage on POSU first night on PCA
42 yr old for elective surgery. Ex IVDU, methadone 60mg daily.

- Methadone given by mouth only for drug addiction
- Good opioid analgesic
- Approx 5-10 times more potent than morphine
- Post-op analgesia: regional technique, continue oral methadone
- Calculate morphine equivalent and give IV PCA + background

- 60mg/day = 300mg morphine po = 100mg morphine iv = 2-4mg/h background + 2mg bolus
Subutex

- **Sublingual Buprenorphine up to 8mg daily**
- **Used for opioid dependency and addiction**
- **High receptor binding affinity, so other opioids cannot displace it**
- **Long half life (35-40h)**
- **Ceiling effect to analgesia**
- **Post-op analgesia: regional technique.**
Multimodal analgesia (H.Kehlet) for hip and knee arthroplasty

- Paracetamol (2G SR bd)
- COX 2 inhibitor (Celecoxib 200mg bd)
- Gabapentin (300mg + 600mg)
- Opioid upon request only: oxycodone 5-10mg (IR) or morphine 10mg (IR)
- LA infiltration (dependent on procedure)
Perioperative Gabapentinoids: Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain

- GPT & PG reduce post-op pain and opioid consumption
  - Better established for GPT

- They *may* reduce chronic post-surgical pain

- Authors believe sufficient evidence is available to recommend *1200mg GPT* or 300mg PG for either acute severe pain or prolonged pain after surgery

- And continued post-op (GPT 600mg tid, PG 150mg bd)

- As peak CSF levels take ~8h, initial dose night before surgery (but AEs?)
Perioperative Gabapentinoids: Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain

- Bind to α-2δ subunit of pre-synaptic P/Q-type VSCCs. This modulates excitatory neurotransmitter release (glutamate).
- Main difference is bioavailability. Both absorbed by AA carriers: GPT saturated, PG linear
- Minor protein binding
- Minor liver metabolism
- Excreted renally unchanged
- Drug interactions minimal except GPT absorption delayed by antacids
- Elimination half life: GPT 4.8 – 8.7h. PG 5.5 – 6.3h.
- Well tolerated
- AEs: sedation, dizziness, headache, visual disturbances, + oedema with GPT
- Large therapeutic window
Single dose oral gabapentin for established acute postoperative pain in adults

Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ

- 4 unpublished studies included, 3 dental, 1 major orthopaedic
- 177 GBT 250mg, 25 GPT 500mg (NA), 172 placebo
- >50% pain relief for 6 h: 15% GPT 250mg, 5% placebo, NNT 11
- Fewer GPT patients needed rescue meds in 6 h, NNT 5.8
- Adverse effects similar

Tiippana EM, Hamunen K, Kontinen K, Kalso E.
A & A June 2007 vol. 104no. 6 1545-1556

- 21 RCTs Gabapentin, 1 RCT pregabalin
- 786 gabapentin (300-1200mg), 99 pregabalin (50 or 300mg), 1042 placebo
- Age 18-74
- 1265 female, 509 male
- 13 studies single dose, 9 multiple dose
- Duration 4h – 10days
**Do Surgical Patients Benefit from Perioperative Gabapentin/Pregabalin? A Systematic Review of Efficacy and Safety.**

Tiippana EM, Hamunen K, Kontinen K, Kalso E. A & A June 2007 vol. 104 no. 6 1545-1556

- The opioid-sparing effect during the first 24 h after a single dose of gabapentin 300–1200 mg, 1–2 h preoperatively, ranged from 20% to 62%.

- The effect of a single dose of gabapentin was a reduction of opioid consumption equivalent to 30 ± 4 mg of morphine (mean ± 95% CI) during the first 24 h after surgery.

- Gabapentin-induced reduction in the 24-h opioid consumption was not significantly dependent on the gabapentin dose.

- Gabapentin reduced opioid-related adverse effects, such as nausea (NNT 25), vomiting (NNT 6), and urinary retention (NNT 7)

- The most common adverse effects of the gabapentinoids were sedation (NNH 35) and dizziness (NNH 12).

- **QUESTION: is GPT better than other post-op regimens? Probably not.**
Adding Gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty.

Clarke H et al. AAS2009;53(8):1073

- Double blind randomised controlled trial
- 126 patients given paracetamol 1G pO, celecoxib 400mg pO & dex 8mg iv 1-2h pre-op
- Spinal: bupiv 15mg + fentanyl 10mcg
- G1 plac/plac, G2 GPT 600 preop/plac, G3 plac/GPT 600 PACU
- Post-op para 1G 6hrly, celecoxib 200 12 h + PCA

RESULTS
- No change in morphine consumption, pain scores, chronic post-surgical pain (6mth) or AEs
Gabapentin after spinal surgery
Anesthesiology 2004;100(4):935

Table 3. Morphine Consumptions (mg) in Gabapentin and Placebo Groups

<table>
<thead>
<tr>
<th>Hours</th>
<th>Gabapentin (n = 25)</th>
<th>Placebo (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.3 ± 1.8*</td>
<td>6.7 ± 2.1</td>
</tr>
<tr>
<td>2</td>
<td>2.7 ± 1.8*</td>
<td>5.0 ± 2.4</td>
</tr>
<tr>
<td>4</td>
<td>2.4 ± 1.8*</td>
<td>6.4 ± 4.3</td>
</tr>
<tr>
<td>6</td>
<td>2.4 ± 2.4*</td>
<td>6.2 ± 3.9</td>
</tr>
<tr>
<td>12</td>
<td>2.9 ± 2.3*</td>
<td>8.0 ± 5.1</td>
</tr>
<tr>
<td>24</td>
<td>3.8 ± 4.6*</td>
<td>11.4 ± 5.4</td>
</tr>
<tr>
<td>Total morphine consumption</td>
<td>16.3 ± 8.9*</td>
<td>42.8 ± 10.9</td>
</tr>
</tbody>
</table>

Data represent interval morphine use since last measurement. Morphine doses are expressed as mean ± SD.
* P < 0.000, when compared with placebo group.

Table 2. Postoperative Pain Scores in Gabapentin and Placebo Groups

<table>
<thead>
<tr>
<th>Hours</th>
<th>Gabapentin (n = 25)</th>
<th>Placebo (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (0–5)*</td>
<td>3 (0–6)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0–5)*</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0–2)*</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0–2)</td>
<td>0 (0–4)</td>
</tr>
<tr>
<td>12</td>
<td>0 (0–3)</td>
<td>0 (0–5)</td>
</tr>
<tr>
<td>24</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
</tr>
</tbody>
</table>

Pain scores are expressed as median (upper–lower quartiles in parentheses).
* P < 0.01, when compared with placebo group.
Ketamine

- Cyclohexone derivative
- NMDA receptor antagonist
  - (Substance P antagonist)
  - (D2 agonist)
  - (Also interacts at opioid, monoaminergic, muscarinic receptors and voltage sensitive Ca ion channels)
- No action at GABA receptors
- Rapidly absorbed
- Half-life 3 h
- Hepatic metabolism cytochrome P450
- Oral bioavailability ket 20%
- OB Ket + norket = 50 - 60%
- Analgesia and dissociative anaesthesia
Perioperative ketamine for acute post-operative pain
Bell, Moore, Dahl, Kelso
Cochrane database of systematic reviews 2005

- 37 RCTs included 2240 patients up to 2004
- Subanaesthetic doses reduce morphine requirement, pain intensity of both
- Ketamine reduces PONV
- Adverse effects mild or absent
- This data cannot be translated into a specific treatment regime
Perioperative ketamine for acute post-operative pain
Bell, Moore, Dahl, Kelso
Cochrane database of systematic reviews 2005

• “The question of optimal ketamine dose is not resolved by these heterogenous trials.

• Out of interest, we wanted to see whether there was a dose-dependent effect. Using an ‘average’ weight of 70 kg, we roughly calculated the mean 24-h dose of ketamine for each of the trials....

• Interestingly, there seemed to be no increased morphine-sparing effect on increasing the ketamine dose above an estimated dose of 30 mg/24 h.”
Ketamine reduces post-op pain and hyperalgesia
AAS 1997;41(9):1124

- 20 live kidney donors randomised to receive either ketamine or placebo with GA
- Dose (for 70kg): 0.5mg/kg (35mg) bolus → 2mcg/kg/min (8.4mg/h) 24 h → 1mcg/kg/min (4.2mg/h) 48h
- Area of punctate hyperalgesia reduced by 75% Days 1,3,7
- No. patients with “wind-up” pain much less at all times
- Pain intensity less on day of surgery
- AEs: differ only with greater PONV with placebo
- 24 h dose: 237mg day 1, 101mg day 2 and 3.
- Note: approx 2 h after initial bolus plasma conc approx 0.22μM ≈ 60ng/ml and stayed roughly that for 72 h.
Ketamine in PACU

- Post op pain in PACU.
- Patients: Pain score ≥ 6 & morphine dose ≥ 7mg/30min (Exclusions apply)
- Treatment group: morphine 15mcg/kg (1mg) + ketamine 0.25mg/kg (17.5mg for 70kg)
- Control group: morphine 30mcg/kg (2mg)
- Up to 3 doses in 10 min or VAS ≤ 4
- Rescue diclofenac 75mg after 3 doses
- Control/treatment = 114/131 respectively
Figure 1. Self-rated (by a 0–10 visual analog scale [VAS]) pain intensity (mean ± sd). *P < 0.001 between the groups (by analysis of variance).

Weinbroum A A Anesth Analg 2003;96:789-795
26 y F opioid addict (heroin + methadone) 2 level spinal fusion

- Post op pain 10/10
- By 7 h post op 290mg morphine + clonidine
- By 24 h 40mg methadone 430 mg morphine
- 24 h Pain 5-7/10
- Sedated, a little confused, no resp dep
- Ketamine (mcg/kg/min) 10-7.5-5-2.5 over 45min and maintained at 2.5
- Approx bolus of 21 mg (60kg) + 9mg/h
38 yr old patient with osteomyelitis in tibia from trauma 4 yrs previously, now for below knee amputation

Fentanyl 100mcg/h, oramorph 100mg daily

- Post op analgesia: regional, pref epidural
- Maintain TD fentanyl
- Systemic equivalent = 125mcg/h fentanyl = 500mg oral morphine over 24 h = 200 mg iv over 24 h or 8mg/h
- Equivalent doses difficult to judge at high doses
- Consider Ketamine infusion if pain severe and resistant to high dose opioids
Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

Anesthesiology 2010;113:639

* Randomized, prospective, double-blinded, and placebo-controlled trial involving opiate-dependent patients undergoing major lumbar spine surgery.

* 52 patients in the treatment group were administered 0.5 mg/kg IV ketamine on induction, then infusion at 10mcg/kg/min terminated at wound closure.

* Fifty patients in the placebo group received saline.

* Patients were observed for 48 h postoperatively and followed up at 6 weeks.

* The primary outcome was 48-h morphine consumption
Periop ketamine for opiate dependent patients: Results *Anesthesiology* 2010;113:639

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ketamine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ME 24h</td>
<td>202 (176)</td>
<td>142(82)</td>
<td>0.032</td>
</tr>
<tr>
<td>Total ME 48h</td>
<td>309(341)</td>
<td>195(111)</td>
<td>0.029</td>
</tr>
<tr>
<td>PACU VAS</td>
<td>5.6 (3.0)</td>
<td>4.1(3.1)</td>
<td>0.033</td>
</tr>
<tr>
<td>PACU ME total</td>
<td>22(20)</td>
<td>18(14)</td>
<td>NS</td>
</tr>
<tr>
<td>Ward VAS 24 h</td>
<td>4.8 (2.4)</td>
<td>4.7(2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>6 wk VAS</td>
<td>4.2 (2.4)</td>
<td>3.1(2.4)</td>
<td>0.026</td>
</tr>
<tr>
<td>6 wk ME mg/h iv</td>
<td>2.8 (6.9)</td>
<td>0.8 (1.1)</td>
<td>0.041</td>
</tr>
</tbody>
</table>
Acute on chronic (abdominal) pain

- Complex surgical history
- Frequent admissions for flare up
- May be on strong opioids at home
- May be on several other psychotropic drugs
- Require high doses of opioids on the ward
- Investigations may not reveal an acute surgical problem
- Behaviour may appear inconsistent to demands for analgesia
45 yr old female, presents with acute abdominal pain. Previous colostomy for management of chronic constipation. Scan normal. Investigations normal.

Fentanyl 37mcg/h. Diazepam 10mg tid. Amitriptyline 75 mg daily, paroxetine, pregabalin.

- Sedated, yet wakes with pain and requests s/c morphine 1-2 hrly
- Reports high pain scores
- Walks around ward, may leave for cigarette
- Befriends other patients, not always helpful
- Familiar and comfortable with ward enviroment
Acute on chronic abdominal pain

- **Complex surgical history**
  - What is the diagnosis for chronic pain?
  - What is the diagnosis of acute admission?
    - Has a surgical problem been excluded?
    - Treat as “acute abdomen” until proven otherwise
    - Investigations may not reveal an acute surgical problem
  - Is pain due to the high dose of opioids?
    - Or withdrawal of strong opioids due to vomiting? (caused by opioids)
  - **Bio-psycho-social** background of patient: is psychological make up and social environment important in the presentation?
Acute on chronic abdominal pain

- Require high doses of opioids on the ward
- Investigations may not reveal an acute surgical problem
- *Behaviour may appear inconsistent to demands for analgesia*
  - Leaving ward
  - Clock watch for next dose
  - Inappropriate behaviour with staff or patients
- “A difficult patient”
Management of the “difficult” pain patient

• It is always more difficult for the patient than the staff

• Identify the “chemical coper”

• Listen to patient carefully and address specific drug related points.
  – Occasionally reflect our lack of knowledge of drugs and pharmacology.

• Rapid surgical diagnosis to avoid protracted s/c morphine

• Treat nausea aggressively, and convert back to oral route ASAP

• Frequent FU, plan changes ahead with patient

• Consider opiate withdrawal (“pain despite drugs means drugs are not working”)