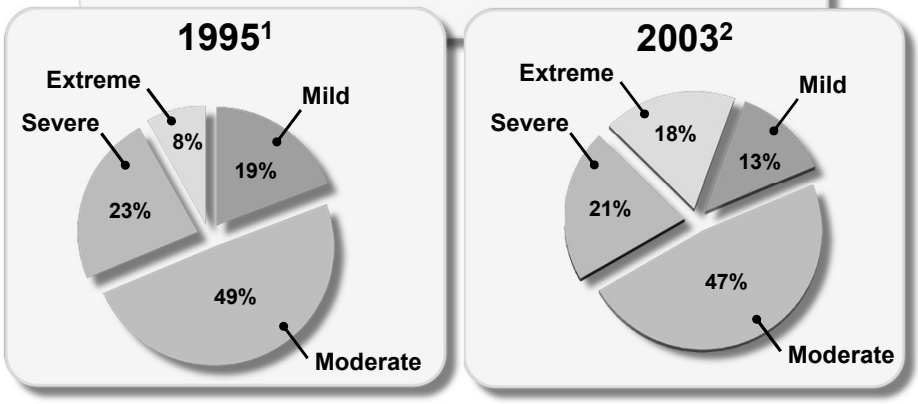
awal, MD, PhD, FRCA (Hon)
l Medicine
siology and Intensive Care

Opioids in postoperative pain – recent innovations lecture outline

- **Opioids still mainstay in postoperative pain management**
- **Drawbacks and benefits of opioids**
- **Why multimodal analgesia?**
- **Innovations in opioid therapy**
- **Transdermal and sublingual opioid PCA**
- **Recent innovations in opioid therapy- the evidence**

Postoperative Pain Continues To Be Undertreated

Despite nearly a decade of progress in pain research, 39% of patients reported severe-to-extreme postoperative pain in 2003 versus 31% in 1995



[1]Warfield CA, Kahn CH. *Anesthesiology.* 1995;83(5):1090-1094.
[2]Apfelbaum JL, et al. *Anesth Analg.* 2003;97(2):534-540.

Why opioids in postoperative pain?

- **In spite of major drawbacks opioids still mainstay treatment**
- **US survey data:**
  - **95%patients treated with opioids (380 hospitals, 300,000 patients)** ***Oderda 2013***
  - **97% patients treated with opioids (315 hospitals, 799,449 patients)** ***Ladha 2016***
- **Highly effective for moderate to severe pain**
- **Long tradition, familiarity, accumulated experience**
- **Alternatives to opioids: dissapointing (multimodal analgesia) or underused (regional techniques)**
- **Available in a wide variety of formulations: injectable (sc, im, iv (PCA), oral, sublingual, transmucosal (OTFC), rectal, transdermal, intranasal, epidural, spinal**
- **Novel non-invasive, 'high-tech' PCA systems with potent lipophilic opioids show promise (transdermal, sublingual, intranasal)**

Problems with opioids for postoperative pain management

- **Multiple side effects, bothersome to life-threatening**
- **Many patients at increased risk of respiratory depression (elderly, sleep apnoeic, obese, smokers)**
- **Efficacy better in rest pain vs movement-induced pain**
- **Less effective in neuropathic pain**
- **Risk of opioid-induced hyperalgesia (OIH)**
- **Increased overall hospital costs, LOS**
- **Immunosupressive effects (implications in infections, cancer growth)**
- **Increased risk of long-term opioid use (abuse potential) ?**

British Journal of Anaesthesia 95 (5): 584–91 (2005)
doi:10.1093/bja/aei227 Advance Access publication September 16, 2005

BJA

REVIEW ARTICLE

Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritis, and urinary retention. Evidence from published data

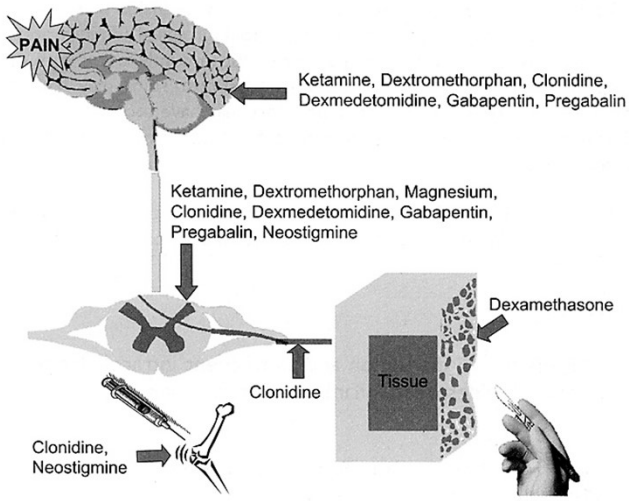
S. J. Dolin[1] and J. N. Cashman[2]*

[1]Pain Clinic, St Richard's Hospital, Chichester PO19 6SE, UK. [2]Department of Anaesthesia, St George's Hospital, London SW17 0QT, UK
**Corresponding author. E-mail: jeremy.cashman@stgeorges.nhs.uk*

- **Data from 183 studies for PONV, 89 studies for sedation, 166 studies for pruritus, 94 studies for urinary retention**
- **Pooled data, > 100.000 patients**

	I.m./s.c.	*I.v. PCA*	*Epidural*	*Overall**
Nausea	**17 %**	**32 %**	**19 %**	**25 %**
Vomiting	**22 %**	**21 %**	**16 %**	**20 %**
Pruritus	**3 %**	**14 %**	**16 %**	**15 %**
Urinary ret.	**15 %**	**13 %**	**29 %**	**23 %**
Sedation	**54 %**	**57 %**	**14 %**	**24 %**

"Acute Pain Services should aim for incidences less than this standard of care"



Anatomical sites where adjuvants can act to enhance opioid or local anesthetic activity to reduce postoperative pain.

Buvanendran A, Kroin J S
Best Practice and Reasearch Clin Anaesthesiology 2007;21:31-49

Problems with multimodal analgesia

- **No convincing evidence of benefits of combining different non-opioids (exception: combination of paracetamol and NSAIDs)**
- **Literature only on combination of two drugs, one of which is opioid (to study opioid-sparing). Common practice is to combine more than 2 drugs**
- **Large number of variables (multiple drugs and their combinations,different doses and routes of administration) makes it difficult to draw conclusions**
- **Very little literature on AEs of various combinations**

Acta Anaesthesiologica Scandinavica

Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses

M. L. Fabritius[1], A. Geisler[2], P. L. Petersen[1], L. Nikolajsen[3], M. S. Hansen[1], V. Kontinen[4], K. Hamunen[5], J. B. Dahl[6], J. Wetterslev[7] and O. Mathiesen[2]

2016;60:1188-1208

- Cochrane, sequential analysis, GRADE
- 132 RCTs, n=9498
- 13/132 trials (with low risk of bias)
  - 3.1 mg reduction of opioid in 24h
  - 1.2 mg reduction of opioid in 24h as add-on analgesic to another non-opioid

"Based on GRADE assessment…in trials with low risk of bias … Firm evidence for the use of gabapentin is lacking as clinically relevant beneficial effect of gabapentin may be absent and harm is imminent, especially when added to multimodal analgesia"

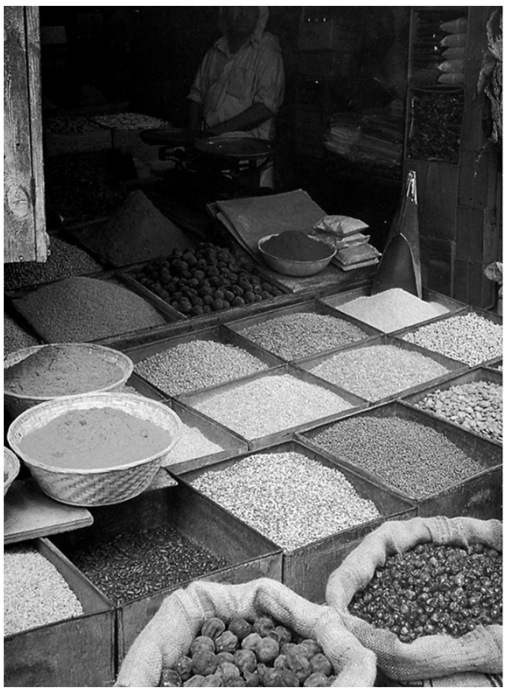
Wherefore Gabapentinoids?

Was There Rush Too Soon to Judgment?

Evan D. Kharasch, M.D., Ph.D., James C. Eisenach, M.D.

"[This] group of Scandinavian investigators raises concern of a potentially dangerous drug interaction with application of multimodal analgesia."

Anesthesiology 2016;124:10-12



EJA European Journal of Anaesthesiology

Current issues in postoperative pain management (review)

Rawal N 2016;33:160-71

"In conclusion, in spite of much rhetoric, current evidence suggests that the advantages of combining paracetamol and NSAIDs are rather modest, the benefits of combining other nonopioids overrated, the side effects generally ignored and the role of combining more than two nonopioids largely unknown".

Anesthesiology

Variations in the use of perioperative multimodal analgesic therapy *Ladha KS et al 2016;124:837-45*

- Database 2007-2014, n=799,449, 315 hospitals
- 4 procedures (open colectomy 22%, TKA 71%, open lobectomy 3%, below knee amputation 4%)

* Main findings:

- every patient received opioids (97%)
- only 2/3 patients received paracetamol (66%)
- non-opioids underutilized (more than one non-opioid 26-66%)
- very low rates of regional techniques (amputation 3%, colectomy 6%, lobectomy 27%, TKA 14%)
- nsNSAIDS used in 15%-57%, coxibs only 1-2%(exception TKA 39%)
- gabapentinoids 4-36%, ketamine 2-5%

"..tremendous variation in the utilization of multimodal therapy not accounted for by patient or hospital characteristics"

IV PCA

PROS

- **Well established in post-operative pain**
- **Rapid/improved pain control**
- **Empowers patients and avoids treatment delays**
- **Provides relatively uniform analgesia**
- **Good tolerability**
- **Improved patient satisfaction over intramuscular opioid injections**
- **Minimizes inappropriate pain assessment by health care staff**

CONS

- **Requires venous access**
- **Analgesia gaps**
- **Pumps require set-up**
  - **Time-consuming**
  - **Programming errors**
- **Cumbersome equipment**
  - **Bulky**
  - **IV lines and electric cables restrict mobility**
- **Cost of purchase and maintenance**

Rawal and Langford. *Eur J Anaesthesiol.* 2007;24(4):299-308
Halawi et al, Orthopedics, Orthopedics, 2015, vol 38 (7)

Opioid PCA by intravenous technique

- I.v opioid PCA drugs: morphine, fentanyl, tramadol, hydromorphone, oxycodone, pethidine, methadone, piritramide, remifentanil

- Opioid combinations:
  - fentanyl + morphine
  - alfentanil + morphine
  - remifentanil + tramadol

- Adjuvants:
  - antiemetics (droperidol, ondansetron, dexamethasone)
  - ketamine
  - naloxone
  - others (ketolorac, clonidine, magnesium, midazolam nalbuphine)

British Journal of Anaesthesia **104 (4):** 401–6 (2010)
doi:10.1093/bja/aeq041 Advance Access publication March 5, 2010

BJA

REVIEW ARTICLE

Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials

M. Carstensen[1]* and A. M. Møller[2]

- **11 RCT`s, n= 887**
- **Ketamine + iv opioid PCA vs iv PCA alone**
- **Improvement= 6 RCT`s, no improvement= 5 RCT`s**
- **18 diff. surgical procedures, heterogeniety of studies, small sample size, 5 diff. dosages**
- **Improvement- thoracic surgery, unclear- orthopedic, abdominal surgery**
- **Opioid-related side effects decreased in 7 RCT´s, no difference in 4 RCT´s**
- **Ketmine side effects**
  - **psychotomimetic side effects in 2 RCT´s**
  - **cognitive impairment 1 RCT**
  - **overall increase in AE (dysphoria, nausea, pruritus) 1 RCT**

Opioid analgesia by oral route

- Various formulations: tablets, suspensions, immediate release (IR), Controlled Release (CR)
- Immediate Release (IR): morphine, oxycodone, tramadol, codeine, dextropropoxyphene
- Controlled Release (CR) (slow release):
  - CR oxycodone (with paracetamol, naloxone)
- Opioid combinations(oxycodone+ morphine tablets,mixture)
- Oral PCA-Medication on Demand (MOD) dervice

Transmucosal analgesia with opioids

- Rectal (morphine, tramadol, paracetamol, NSAIDs)
- Intranasal (fentanyl, morphine, butorphanol, pethidine, ketamine)
- Sublingual and buccal:
  - Oral Transmucosal Fentanyl Citrate (OTFC)*
- - Fentanyl Buccal Tablets (FBT)
  - Sublingual Oral Disintegrating Tablets (ODT) (fentanyl, burenorphine, ketamine)
  - Fentanyl Buccal Soluble Film (FBSF)
  - Buccal spray
- Pulmonary (nebulised, inhaled) (morphine, fentanyl)

* *Not indicated for acute pain (226 deaths in USA 2004-2011)*

PCA vs non-PCA opioid administration

Patients receiving PCA:

- **had lower VAS pain intensity scores versus non-patient controlled analgesia over most time intervals**
- **were more satisfied with PCA (81% versus 61%, P value = 0.002)**
- **consumed higher amounts of opioids than controls (0 to 24 hours, 7 mg more of IV morphine equivalents, 95% CI 1 mg to 13 mg).**
- **had a higher incidence of pruritus (15% versus 8%, P = 0.01)**
- **had a similar incidence of other adverse events.**
- **no difference in the length of hospital stay.**

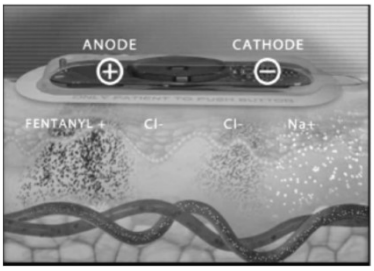
McNicol ED et al, **Cochrane Database of Systematic Reviews 2015**, 6. CD003348. DOI: 10.1002/14651858.CD003348.pub3.

PCA by other routes

- Subcutaneous PCA (morphine)
- Sublingual PCA (sufentanil)
- Transdermal PCA (iontophoretic PCA) (fentanyl)
- Intranasal (spray) PCA(PCINA) fentanyl , diamorphine
- Oral PCA (MOD device) - hydromorphone,oxycodone, morphine, paracetamol (cancer pain)

Iontophoretic Transdermal Delivery

Iontophoresis: generally imperceptible electrical field transports 40 µg fentanyl dose through intact skin and into the bloodstream



Transdermal delivery	Onset	Skin Depot	Patient-Controlled
Iontophoresis	Rapid	No	Yes
Passive Delivery	Slow	Yes	No

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

IONSYS – new version

Why is Fentanyl appropriate for iontophoretic transdermal delivery

- **Low molecular weight**
- **Available as chloride salt**
- **Skin compatible**

Optimal properties for molecular transport across the skin into systemic circulation with no skin depot

  - ***rapid penetration of CNS by potent lipophilic molecule***

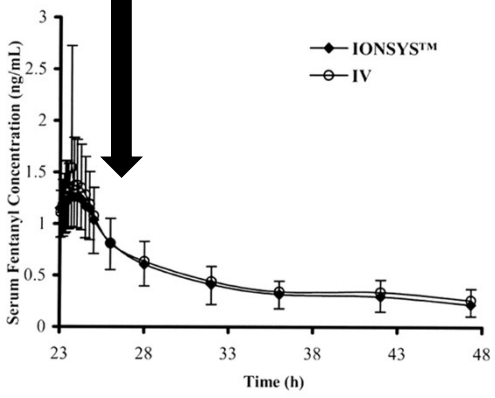
- **40 µg fentanyl over 10 min**

Peng PW, Sandler AN. Anesthesiology 1999;90:576–99

Serum Concentrations compared to IV Infusion

- **Mean systemic bioavailability is 87%[1]**
- **Rapid rise/decline in serum fentanyl concentrations similar to IV infusion[2]**

demonstrates no subcutaneous depot effect



[1]IONSYS 40 micrograms per dose transdermal system, Summary Of Product Characteristics, November 2015
[2]Herndon et al, *Pharmacotherapy* , 2007;27(5):745–754

1. Viscusi ER er al, *JAMA*. 2004;291:1333-1341. **2.** Hartrick CT, et al, *Reg Anesth Pain Med*. 2006;31:546-554. **3.** Minkowitz HS, eta l, *Pain Med*. 2007;8:657-668. **4.** Grond S, et al, *Br J Anaesth*. 2007;98:806-815.

Application-Site Reaction AEs: Phase IIIb Trials

Application-site Reactions, n (%)	Hartrick [1] (n = 395)	Minkowitz [2] (n = 252)	Grond[3] (n = 325)
Erythema	**27 (6.8)**	**24 (9.5)**	**124 (38.2)**
Itching	**3 (0.8)**	**14 (5.6)**	**23 (7.1)**
Vesicles	**7 (1.8)**	**7 (2.8)**	**20 (6.2)**
Edema	**0**	**3 (1.2)**	**11 (3.4)**

- **In the Grond study reporting of application-site reactions was actively solicited**
- **Although some application-site reactions occurred with IONSYS treatment, most cases were mild to moderate in severity and resolved without treatment**

1) Grond S et al. *Br J Anaesth*. 2007;98:806-815. 2) Hartrick CT et al. *Reg Anesth Pain Med*. 2006;31:546-554. 3) Minkowitz H et al. *Pain Med*. In press, 2007.

30

Potential Advantages of IONSYS®

- **Designed for acute moderate to severe post-operative pain in adults[1]:**
  - **rapid rate of analgesic absorption**
  - **no skin depot effect**
  - **fentanyl has some advantages over morphine (i.e. quicker onset, no active metabolites)[2]**
- **Patient controlled delivery, without a pump**
  - **not reliant on patient iv access[1]**
  - **fewer analgesia gaps due to technical problems and shorter time to resolution[3]**
  - **pre-programmed; avoids prescription or dosing errors[1]**
- **Potential for greater mobility [1,4]**
- **Potential advantage in infection control [1]**
- **Potential ease of care/workload[1,5] :**
  - **set-up; no pump tracking/retrieval; storage**

[1]Power I. *Br J Anaesth.* 2007;98:4-11,[2] Grass et al, Anesth Analg 2005;101:S44–S61, [3]Panchal SJ et al. *Anesth Analg.* 2007;105(5):1437-41, [4]Langford et al, *British Journal of Pain* 1– 11, 2016, [5] Grond et al, *Br J Anaesth.* 2007;98:806-815

British Journal of Pain SAGE

Br J Pain. 2016 Nov; 10(4): 198–208. PMCID: PMC5102101
Published online 2016 Sep 15. doi: 10.1177/2049463716668905

Comparison of fentanyl iontophoretic transdermal system and routine care with morphine intravenous patient-controlled analgesia in the management of early postoperative mobilisation: results from a randomised study

Richard M Langford,[1] Kuang-Yi Chang,[2] Li Ding,[3] and Jeffrey Abraham[3]

- Multicentre, open label, n=108, THA(72%), Abd hysterect(28%)
- Anaesthesia: GA, Spinal or epidural
- I.v morphine titrated to NRS =/< 4, followed by ITS upto 240mcg/h or iv PCA morphine upto 10mg/h(bolus and lockout times according to centre routines)
- ITS fentanyl associated with:
  - greater ability to mobilise upto 24h
  - better nurse 'ease of care'
  - similar safety profile (PONV about 50%, usual opioid AEs)
  - local effects: erythema(9%), vesicles (3%)
- Study terminated early(target n=200)..no reason given in paper

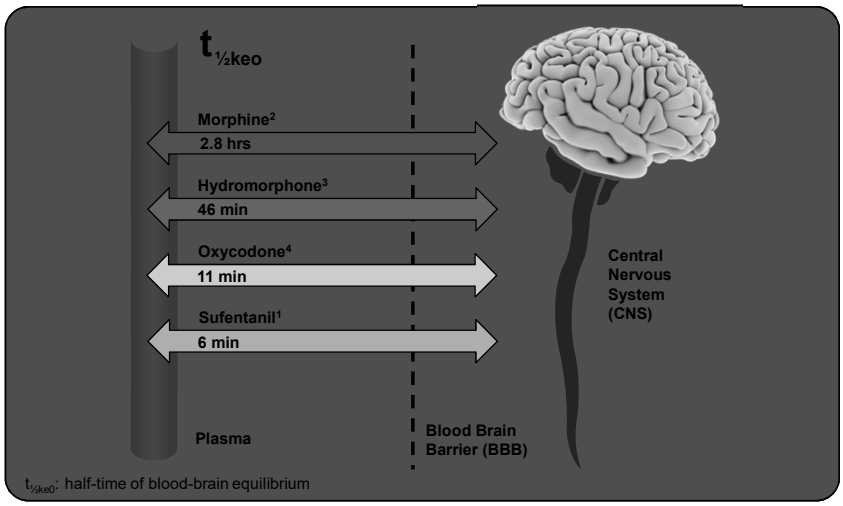
Why sublingual sufentanil PCA (vs i.v morphine PCA)?

- **Non invasive (avoids problems of i.v line and cumbersome equipment)**
- **Very potent, no active metabolites (preferable in elderly patients with compromised renal function- a problem with morphine metabolite M6G)**
- **Rapid onset: high lipophilicity facilitates sublingual absorption**
- **Pre-programmed - avoids errors**
- **Low GI bioavailability minimizes delayed effect of swallowed drug**
- **Greater sensory feed back (flashing lights, dosing sounds, dispensing vibrations)**
- **Other claimed benefits based on preliminary data: (earlier analgesia onset, fewer desaturation events, cheaper, high patient and nurse satisfaction). Further studies necessary.**

Sufentanil sublingual tablet system (SSTS)

- **Hand-held, pre-programmed, PCA system, tethered to bedside**
- **15 mcg tablet, 20 min lockout period**
- **Cartridge has 40 tablets (adequate for about 2 days)**
- **Only patient can operate device - thumb tag (RFID)**
- **Average interdosing interval 70-100 min**

Sufentanil gives rapid plasma/CNS equilibration[1]



1 Scott JC, Cooke JE, Stanski DR. *Anesthesiology*. 1991;74:34–42.
2 Lötsch J, Skarke C, Schmidt H, et al. *Anesthesiology*. 2001;95:1329–1338.
3 Schafer SL, Flood P. The Pharmacology of Opioids. In *Geriatric Anesthesiology*. New York, NY: Springer Verlag. 2007: Ch. 15, Table 15-1.
4 Lalovic B, Kharasch E, Hoffer C, et al. *Clin Pharmacol Ther*. 2006;79:461–79.

Sublingual, transdermal and intravenous patient-controlled analgesia for acute post-operative pain: systematic literature review and mixed treatment comparison

Pablo Katz MD[a], Shweta Takyar[b], Pamela Palmer[c] and Hiltrud Liedgens PhD, MaHE[a]

[a]Grünenthal GmbH, Aachen, Germany; [b]Parexel International, Chandigarh, UT, India; [c]AcelRx Pharmaceuticals, Redwood City, CA, USA

Curr Med Res Opin 2017;33:899-910

- 13 studies,2004-2016, major open abd and ortho (THA;TKA)
- Sufentanil sublingual tablet system(SSTS) associated with:
  - better global pain scores (vs iv PCA) at 24h
  - earlier onset of analgesia (vs both)
  - better adverse effect profile (vs both)

" This meta-analysis shows that SSTS….can be more effective, faster in onset and better tolerated than IV PCA (morphine) and PCTS(fentanyl)."

Novel routes of opioid administration – the evidence

- **Intranasal, sublingual and buccal fentanyl are effective treatments for breakthrough pain in cancer patients (level 1*, Cochrane review) with similar efficacy to i.v administration (level 1 PRISMA) and superior to oral morphine (level 1)**
- **Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than OTFC (level 1)**
- **Acute pain: none of these routes (buccal or transdermal patches) recommended due to safety concerns (and lack of regulatory approval**
- **Transdermal (fentanyl) PCA and sublingual (sufentanil) PCA appear promising. Further studies necessary**

* ANZCA recommendations

British Journal of Pain SAGE

Br J Pain. 2016 Nov; 10(4): 217–221. PMCID: PMC5102094
Published online 2016 Jul 25. doi: 10.1177/2049463716657363

Is tapentadol different from classical opioids? A review of the evidence

Richard M Langford,[1] Roger Knaggs,[2] Paul Farquhar-Smith,[3] and Anthony H Dickenson[4]

- Synthetic, centrally acting analgesic
- Opioid and non-opioid mechanisms of action
  - Mu-opioid receptor (MOR)
  - noradrenaline re-uptake inhibition (NRI)
- Investigated in acute, chronic (and cancer) pain (most studies)
- Similar efficacy to oxycodone but less side effects (nausea, vomiting, constipation) (postop-dental, ortho, breast surgery)
- Reduced risk of abuse potential?

To summarize...

FREE METRO 03.02.2010 metro.co.uk

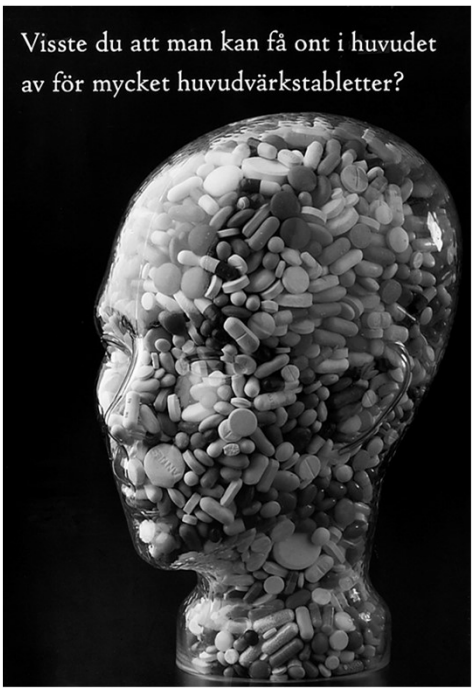
Knife? What knife is that?

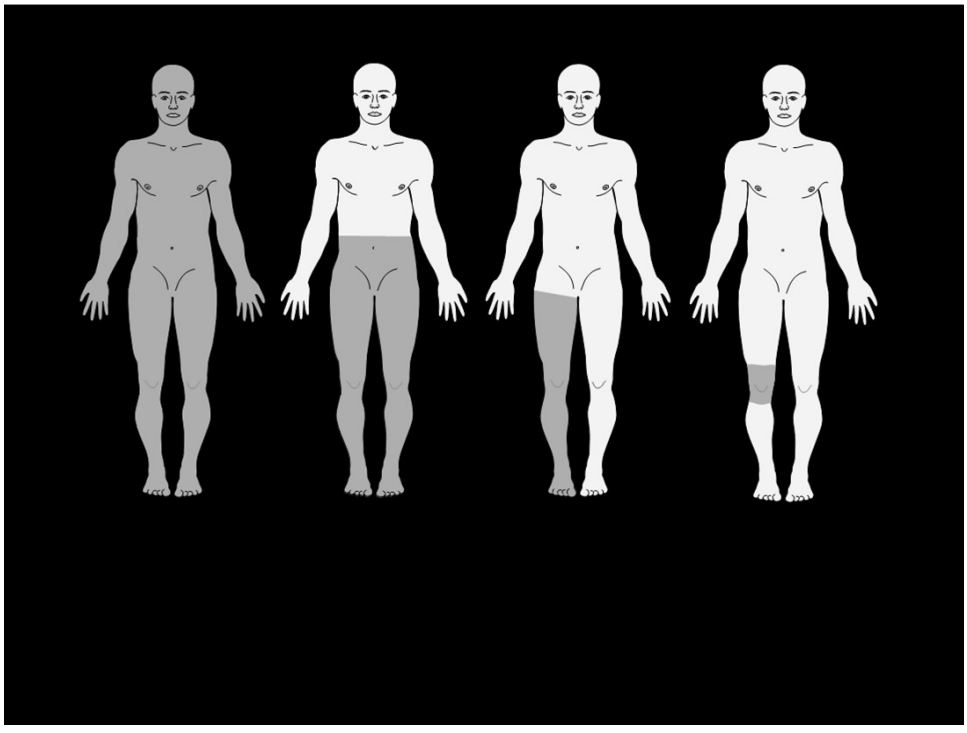
A MUGGING victim calmly walked away after being robbed – unaware she had a 15cm (6in) knife in her back. Julia Popova, 22, had no idea the thug had plunged a kitchen knife in just centimetres away from her spinal cord until her stunned parents told her. 'Shock had kicked in and her body prevented her from feeling any pain,' said a doctor in Moscow. The blade was removed without injuring her spine.

Back-stabbed: Julia Popova shows her injury to stunned hospital stuff Picture: CEN

Why opioids in postoperative pain management?

- **Highly effective for moderate to severe pain**
- **Long tradition, familiarity, accumulated experience**
- **Available in a wide variety of formulations (injectable (sc, im, iv (PCA), oral, sublingual, transmucosal (OTFC), rectal, transdermal, intranasal, epidural, spinal**
- **No ceiling effect**
- **No good alternative (no major drug breakthrough in 50 years)**


Visste du att man kan få ont i huvudet
av för mycket huvudvärkstabletter?



Opioids in postoperative pain- recent innovations

Summary

- **In spite of multiple problems opioids remain the mainstay for treating moderate-severe postoperative pain. Non-opioids generally inadequate**
- **Multimodal analgesia - much rhetoric, poor evidence. Wound infiltration (as first line)+paracetamol+NSAID with opioids as rescue analgesics is recommended**
- **No new drugs in postoperative pain in decades. Innovations generally in drug delivery systems of old drugs**
- **Multiple routes of analgesic delivery studied (oral, buccal, sublingual, transdermal, intranasal, pulmonary)**
- **For postoperative pain the two most promising recent innovations are: transdermal PCA (fentanyl) and sublingual PCA (sufentanil)**

Audits are performed annually and the results presented at meetings of different surgery sections (picture: department of general surgery)

Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review

Kathirvel Subramaniam, MD, Balachundhar Subramaniam, MD, and Richard A. Steinbrook, MD

From the Department of Anesthesiology, Critical Care & Pain Management, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Anesth Analg 2004;99:482-495

- **37 RCT's, n= 2385, 5 subgroups: i.v. ketamine single dose, cont. infusion, PCA, epidural, pediatric**
- **I.v. morphine + ketamine not better than i.v. morphine**
- **I.v. ketamine infusion decreased i.v. and epidural opioid requirements in 6/11 studies***
- **Single bolus ketamine decreased opioid requirements in 7/11 studies***
- **Epidural ketamine beneficial in 5/8 trials**
- **Adverse effects not increased with small dose (0.15-1 mg/kg bolus, 0.12-0.6 mg/kg/h infusion**

"…small dose ketamine is a safe and useful adjuvant to standard practice opioid analgesia"**

May prevent central sensitization and chronic neuropathic pain

** No reduction of opioid adverse effects, ** in 54 % studies*

Limitations of IV PCA Highlighted in Several Recent Publications

- **Institute for Safe Medication Practices (USA)[1]**
  - **IV PCA errors occur frequently**
  - **Errors can have serious consequences, including death**
- **IV PCA requires frequent patient assessment / monitoring[1,2]**
- **Ward nurses often fail to receive adequate training for IV PCA[1]**

1. Cohen MR, Smetzer J. J Pain Palliative Care Pharmacother 2005;19:45–50
2. MacIntyre PE. Brit J Anaesth 2001;87:36–46

Postoperative pain – future perspectives

- **Outcome debate – patient oriented**
- **Procedure-specific pain management (www.postoppain.org)**
- **Trend away from epidural technique and systemic opioids (alternative regional techniques, newer non-opioids)**
- **Prevention of chronic pain syndrome**
- **Postoperative recovery (short- and long term) and rehabilitation**
- **Pain management at home after ambulatory surgery**
- **APS – audits, cost-effectiveness**

Hindawi Publishing Corporation
Pain Research and Treatment
Volume 2011, Article ID 934932, 8 pages
doi:10.1155/2011/934932

Research Article

A Survey of Acute Pain Service Structure and Function in United States Hospitals

Dawood Nasir,[1] Jo E. Howard,[2] Girish P. Joshi,[1] and Gary E. Hill[1]

- **301 hospitals (101 teaching), response rate 36%**
- **Organized APS (written protocol adherence) more in university hospitals**
- **I.v PCA most common method (managed by surgeons-75%)**
- **Written protocols 55% hospitals**
- **Pain assessment at rest 97%, on activity 63%**
- **Nurses allowed to adjust:**
  - **- PCA 62%**
  - **- epidural 43%**
  - **- perineural 21%**

Opioid-related adverse effects in the postoperative period

- **In a two-week postoperative period: nausea and/or vomiting 50%, drowsiness 41%, constipation 26%, itching 10%, urinary difficulties 8%** **Apfelbaum JL** ***Anesth Analg 2003***
- **May be responsible for nearly 60% of perioperative AEs** **Oderda GM** ***J Pain Symptom Manage 2003***
- **Respiratory depression** **Overdyk FJ** ***Anesthesiology 2010***
- **Postoperative ileus** **Barletta JF** ***Ann Pharmacother 2011***
- **CNS impairment** **Wheeler M** ***J Pain 2002***
- **Increased risk of long-term opioid use** **Alam A** ***Arch Intern Med 2012***

Increased costs due to postoperative opioid use

- **Increased costs due to AEs** **Apfelbaum JL** ***Anesth Analg 2003***
- **Increased risk of ileus (even with very low doses)** **Barletta JF** ***Ann Pharmacother 2011***
- **Errors associated with opioid delivery devices(PCA) (increased LOS, mortality and overall costs)** **Classen DC** ***JAMA 1997***
- **Hospital re-admissions** **Allaudeen NA** ***J Hosp Med 2010***
- **Increased length of stay (additional medications, personell)** **Hill RP Anesthesiology 2000, Kovac AL Drugs 2000, Oderda GM Ann Pharmacother 2007**

Death from PCA due to programming errors

- **FDA (MDR database) upto July 2000, published literature**
- **Most common error-programming of drug concentration**
- **Since introduction (1988) more than 22 million patients treated (Abbott Life Care)**
- **Estimated mortality risk 1:33000 to 1:338,800 (low estimates based on 7.7 % reporting rate, high estimates on 1.2 % reporting rates – there is severe underreporting in literature)**
- **Low likehood event but relatively numerous in absolute terms – ranging from 65-667 deaths**

Vicente KJ et al
Can J Anesth 2003;50:3228-32

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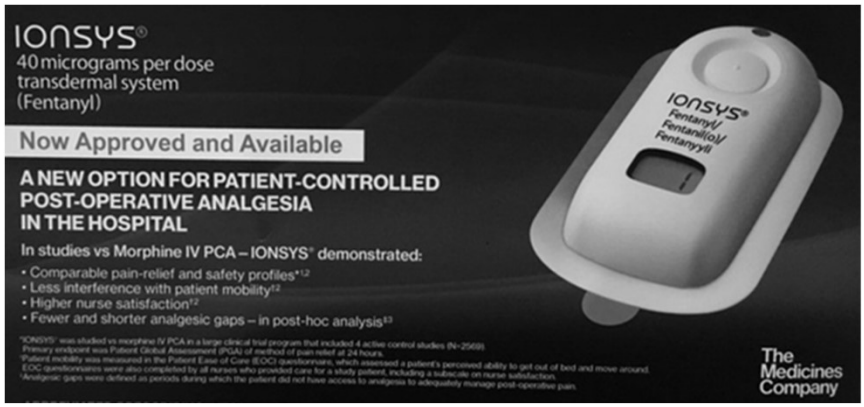


Why is Fentanyl appropriate for iontophoretic transdermal delivery

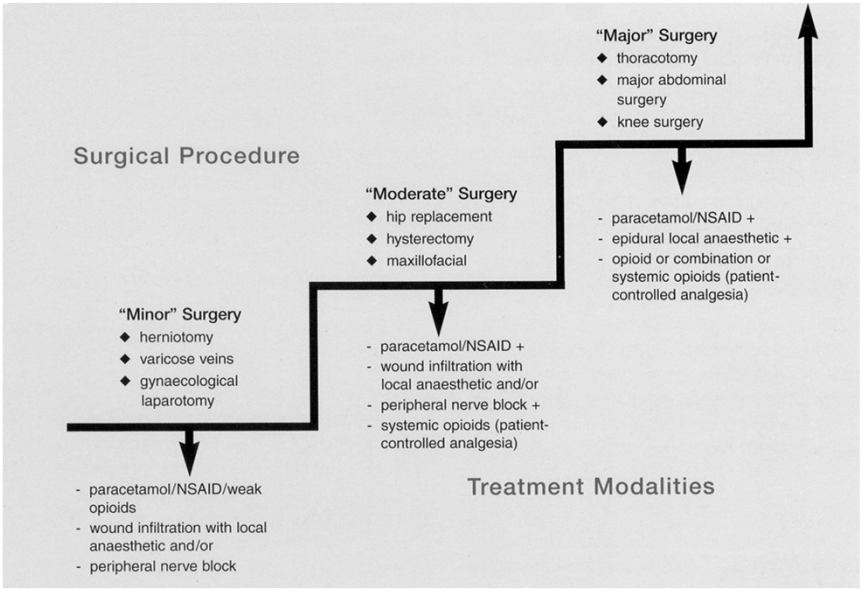
- **Low molecular weight**
- **Available as chloride salt**
- **Skin compatible**

Optimal properties for molecular transport across the skin into systemic circulation with no skin depot

  - ***rapid penetration of CNS by potent lipophilic molecule***

- **40 µg fentanyl over 10 min**

Peng PW, Sandler AN. Anesthesiology 1999;90:576–99



Trends in use of regional anesthesia. Neuraxial and peripheral nerve blocks

Cozowicz C et al ***RAPM 2016;41:43-9***

- Database study, n=959.257, THA, TKA
- Period 2006 – 2013
- Neuraxial blocks decreased:
  - from 21.7 % to 19.7 % for THA
  - from 24.7 % to 21.3 % for TKA
- Peripheral nerve blocks increased:
  - from 6.5 % to 8.7 % for THA
  - from 10.3 % to 20.4 % for TKA
- Highest neuraxial use (increasing) in rural, non-teaching hospitals. Highest peripheral blocks used in large teaching hospitals

" Thus, our data confirm that regional anesthesia remains underutilized even among orthopedic patients.."

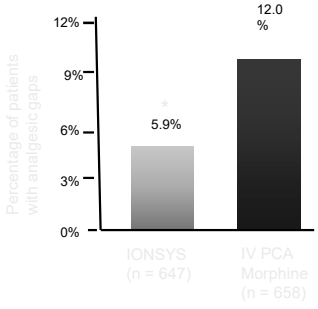
Epidural Analgesia

Benefits
Superior analgesia
Early ambulation
Reduced morbidity
Shorter hospitalization

Costs
Invasive technique
Adverse effects
Monitoring costs
Neurol. complications

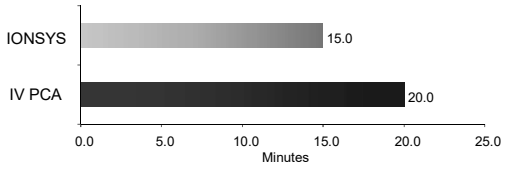
Analgesic Gaps: IONSYS vs IV PCA Morphine

A) Fewer patients had analgesic gaps with IONSYS

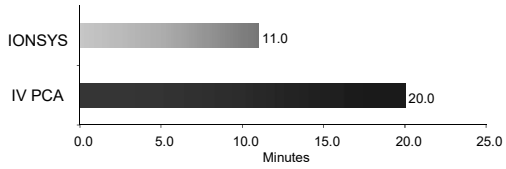


Data pooled from the Hartrick and Minkowitz studies.
* P<0.001 vs. IV PCA Morphine

B) Lower total median analgesic gap time with IONSYS



C) Lower median time to resolve gaps with IONSYS



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

Pain 136 (2008) 134–141

PAIN

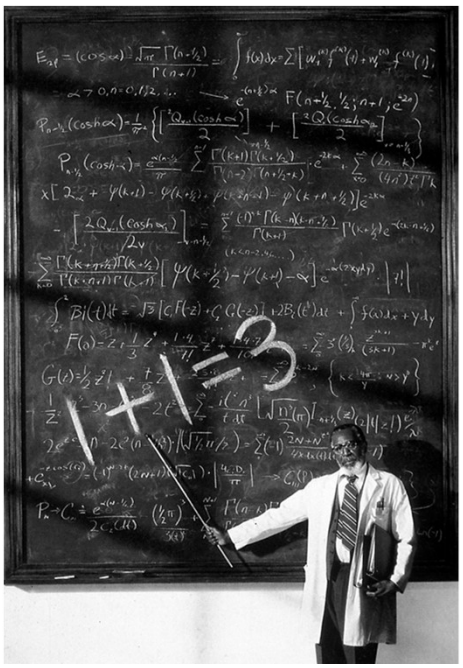
www.elsevier.com/locate/pain

Postoperative Analgesic THerapy Observational Survey (PATHOS):
A practice pattern study in 7 Central/Southern European countries

Dan Benhamou [a,*], Marco Berti [b], Gerhard Brodner [c], Jose De Andres [d], Gaetano Draisci [e], Mariano Moreno-Azcoita [f], Edmund A.M. Neugebauer [g], Wolfgang Schwenk [h], Luis Miguel Torres [i], Eric Viel [j]

- **7 countries (France, Germany, Spain, Austria, Belgium, Portugal)**
- **746 hospitals, 1558 questionnaires**
- **Responible: 59 % anaesthetists, 41 % surgeons**
- **No training programmes: 34 % institutions**
- **No written protocols: 75 % institutions**
- **Pain not assessed: 34 % institutions**
- **Pain not documented: 56 % institutions**

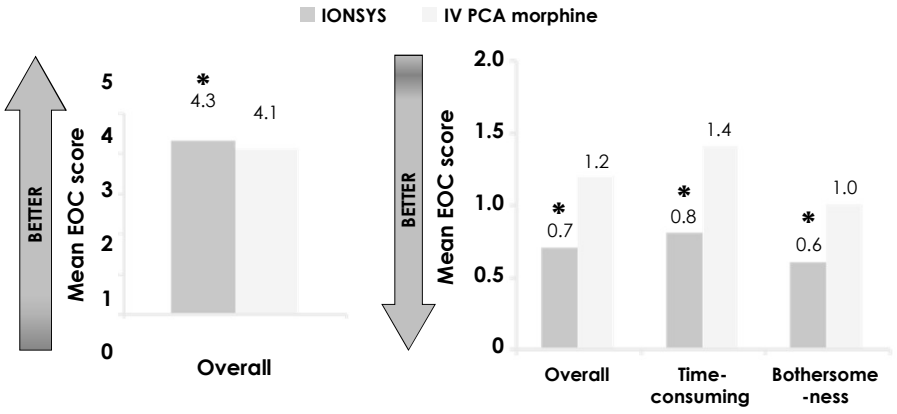
"…current POP management remains suboptimal…"



IONSYS™ vs. IV PCA

Morphine

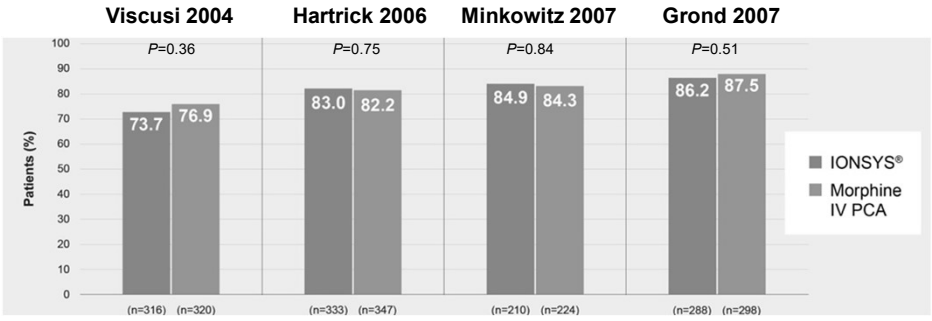
Ease-of-Care



*p<0.001

Grond et al. (2007) *B J Anaesthesia* 98:806-815

Fentanyl-ITS: Patient Global Assessment of Pain Control Method



At 24 hours or early discontinuation, patients were asked, "Overall, would you rate this method of pain control during the last 24 hours as being poor, fair, good, or excellent?

1. Viscusi ER er al, *JAMA*. 2004;291:1333-1341. **2.** Hartrick CT, et al, *Reg Anesth Pain Med*. 2006;31:546-554. **3.** Minkowitz HS, eta l, *Pain Med*. 2007;8:657-668. **4.** Grond S, et al, *Br J Anaesth*. 2007;98:806-815.