OPIOID FREE SURGERY IMPLICATIONS FOR PERIOPERATIVE CARE

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DISCLOSURES

- No Disclosures

OUTLINE

- Case presentation.
- Acute exposure to opioids and chronic opioid dependence.
- ERAS protocols and multimodal pain management
- Role of regional anesthesiology
  - Thoracic Epidurals
  - Single shot intrathecal injections
  - Transverse abdominis plane blocks
- Local and regional hospital protocols and systemic pain agents.

CASE PRESENTATION:LOMA LINDA MEDICAL CENTER

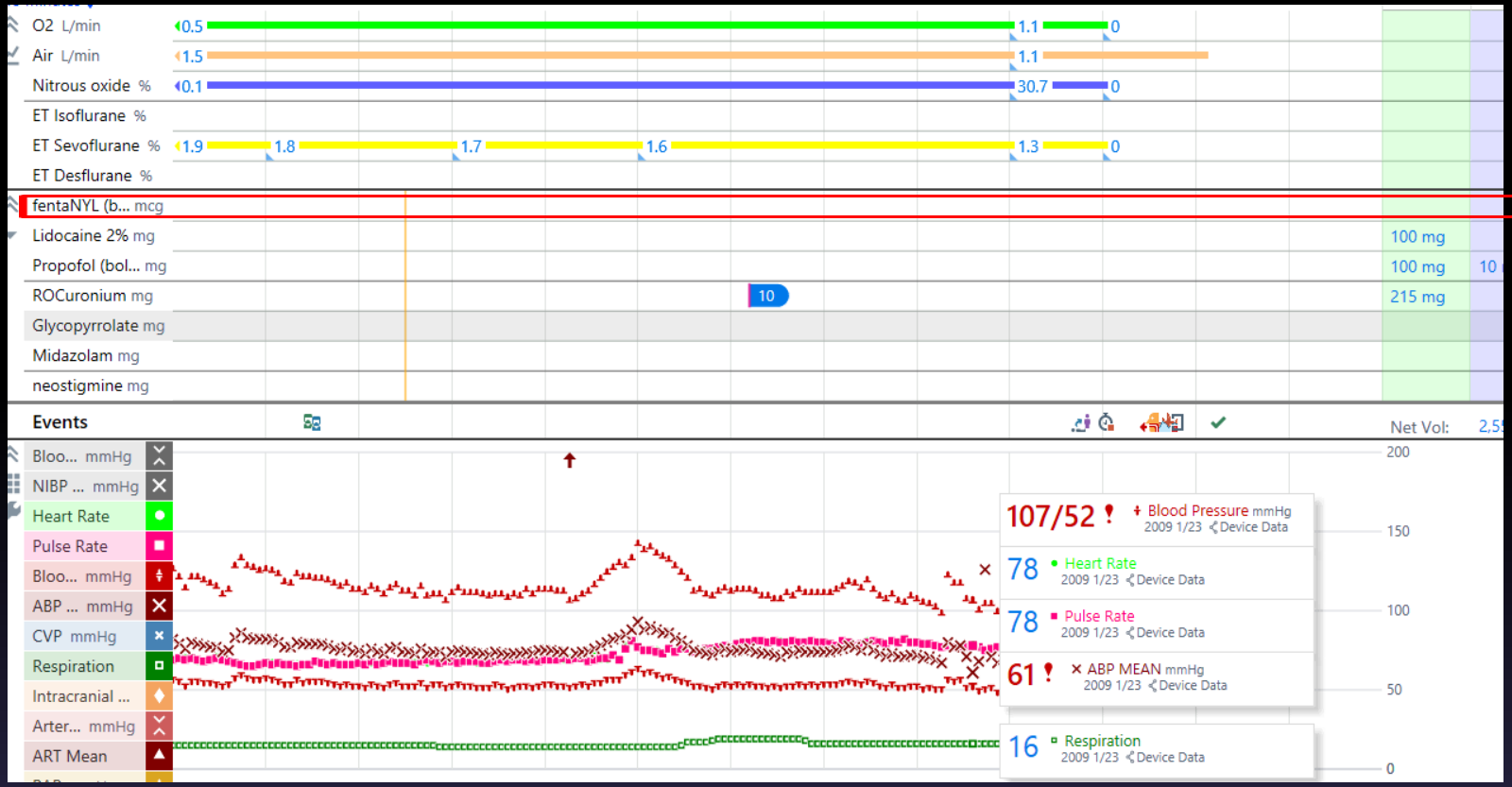
- 64 year old male with duodenal adenocarcinoma for exploratory laparotomy and Whipple surgery.
- Patient was enrolled in enhanced recovery pathway for pancreas surgery (ERAS).
- Preoperative pain medications: gabapentin, Celebrex and PO Tylenol.
- Day of surgery in preop: Thoracic Epidural at level of T8 with bolus feature.
- Intra-operative pain management: epidural infusion running. No IV opioids even on induction of anesthesia.
- Postoperative days: 2-4 gradual weaning of epidural infusion.
- Postoperative day 5: patient was discharged without requirement of any opioid medications (orally or IV).

Day of Surgery

Pre-op	Carbohydrate Loading • one bottle Ensure Pre-Surgery® 3-4 hrs before surgery. (If known diabetic, check blood glucose on arrival to Pre-op and notify anesthesia if >180 mg/dL§)
	Chlorhexidine (Hibiclens) surgical site cleaning • to be done by Pre-op nursing
	Acute Pain Consultation • if opioid tolerant
	Acetaminophen • 1000 mg, PO, once
	Celecoxib • 200 mg, PO, once (unless cardiac contraindication, CrCl <60)
	Gabapentin • 600 mg, PO, once (300 mg if CrCl <30, or >70-years-old)
	Neuraxial analgesia • PCEA/Single shot intrathecal opioid
	SCDs and Chemical VTE prophylaxis • Heparin, 5000 units, subcutaneous
Intraop	Ertapenem • 1 g IV within 1 hour of skin incision§ (ciprofloxacin/metronidazole if PCN allergy)
	Hemodynamic Management Strategy • ID as "Green", "Yellow" or "Red" at timeout* (see page 2)
	Ondansetron and dexamethasone for pre-treatment of post-operative nausea and vomiting (PONV)
	Placement of OGT vs NGT per surgeon discretion
	Placement of G tube, J tube, and drains per surgeon discretion
	If no neuraxial analgesia, Local anesthetic or consider Exparel® transversus abdominus plane (*TAP*) block
	Maintain normothermia§ • forced air warmer (Bair Hugger™) if body temp <36°C
	Anti-microbial coated suture, new gloves, and separate clean instruments for fascial/skin closure§
PACU	Maintain normothermia§ • forced air warmer (Bair Hugger™) if body temp <36°C
	Limit IVF to 1 mL/kg/hr (max 125 mL/hr)

Day of Surgery - Post-op

Pain Management	IVF/Nutrition	Activity	Drain Care
Acetaminophen, 1,000 mg, IV, Q8hr (x24 hrs) Ketorolac, 15 mg, IV, Q6hr Gabapentin, 250 mg, Jtube, BID Methocarbamol, 500 mg, IV, Q8hr Hydromorphone, 0.4 mg, IV, Q2hr, PRN breakthrough pain PCA: Hydromorphone, 0.2 mg, IV, Q15min, if no PCEA	If patient has G tube, keep to gravity If patient has NG tube, put to low wall suction Pantoprazole, 20 mg, IV, BID	Out of bed/to chair at least once the evening of surgery Incentive Spirometry SCDs	Strip & record output Qshift
Post-op Day 1			
Acetaminophen, 1,000 mg, Jtube, TID Celecoxib, 200 mg, Jtube, BID Gabapentin, 250 mg, Jtube, BID Methocarbamol, 500 mg, IV, Q8hr Oxycodone, 5 mg, Jtube, Q6hr, PRN moderate/severe pain Hydromorphone, 0.4 mg, IV, Q2hr, PRN breakthrough pain PCA: Hydromorphone, 0.2 mg, IV, Q15min, if no PCEA	NS, IV, 1 mL/kg/hr based on IBW (max 125 mL/hr) Pantoprazole, 20 mg, IV, BID Reglan, 5 mg, IV, TID Start tube feeds if feeding tube or J tube placed Impact AR®,PO, TID, if no enteral feeding access Clamp G tube (if placed), unclamp for N/V Remove or clamp NG tube (if placed), unclamp for N/V Encourage gum chewing	Remove urinary catheter Out of bed 60 minutes each shift Ambulate at least twice daily Incentive Spirometry SCDs; Lovenox, 40 mg, SQ, Qday	Strip & record output Qshift

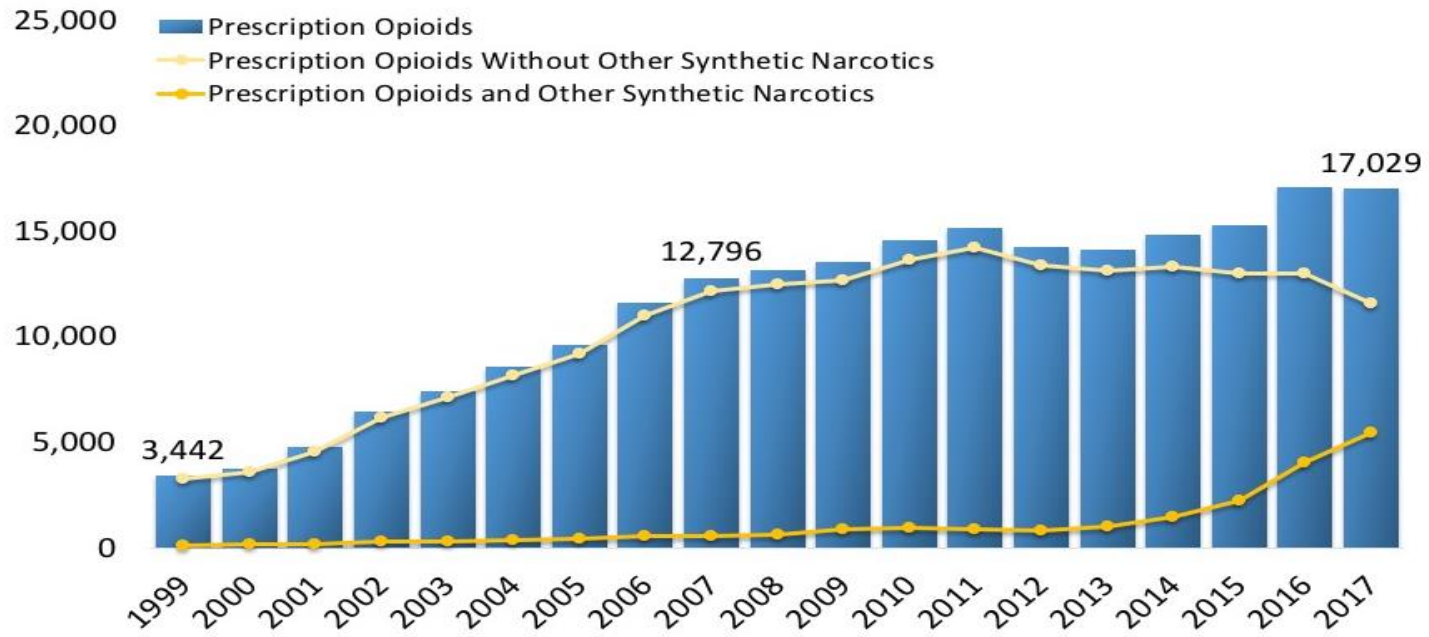

O2 L/min
0.5
1.1
0
Air L/min
1.5
1.1
Nitrous oxide %
0.1
30.7
0
ET Isoflurane %
ET Sevoflurane %
1.9
1.8
1.7
1.6
1.3
0
ET Desflurane %
fentaNYL (b... mcg
Lidocaine 2% mg
100 mg
Propofol (bol... mg
100 mg
ROCuronium mg
10
215 mg
Glycopyrrolate mg
Midazolam mg
neostigmine mg
Events
Net Vol:
Bloo... mmHg
NIBP ... mmHg
Heart Rate
Pulse Rate
Bloo... mmHg
ABP ... mmHg
CVP mmHg
Respiration
Intracranial ...
Arter... mmHg
ART Mean
200
150
100
50
0
107/52
Blood Pressure mmHg
2009 1/23 Device Data
78
Heart Rate
2009 1/23 Device Data
78
Pulse Rate
2009 1/23 Device Data
61
ABP MEAN mmHg
2009 1/23 Device Data
16
Respiration
2009 1/23 Device Data


00
2322
0000
0100
0200
0300
0330
99.1 (37.3)
Oral
88
84
NSR
18
18
132/72
105/50
Semi-Fowler
Semi-Fowler
15
15
51 kg (112 lb...
1
1
0-10
Zero
No pain
0-10
Zero

OPIOIDS IN SURGICAL PATIENTS

- 51 million Americans undergo inpatient surgery annually.
- Till 2018 Opioids have remained a primary modality
- Over 80% of patients receive opioids after low-risk surgery
- 80% involve oxycodone or hydrocodone.
- Rate of opioid prescribing was highest for specialists.
- More doses of opioids than needed or prescribing more potent opioids when other nonopioid analgesics
- Excessive or left-over opioids may be diverted or used by other members of the patient's family, including children; given away; or sold.

Figure 4. **National Drug Overdose Deaths Involving Prescription Opioids,** Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

- Opioids: 43.8 million prescriptions 2000 to 289 million prescriptions in 2012.
- Opioid overdoses roughly tripled since 1999.
- Opioids contribute to 1 death approximately every 35 minutes.
- Most commonly prescribed opioids: oxycodone and hydrocodone.
- Increase in opioid prescriptions did not improve patient pain scores.

Opioid abuse and dependence are associated with increased readmission rates and healthcare utilization after major surgery

Gupta A, et al. Opioid Abuse or Dependence Increases 30-day Readmission Rates after Major Operating Room Procedures. ANESTHESIOLOGY. May 2018.

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org

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Opioid Abuse or Dependence:

Readmissions and Care Utilization After Major Surgery

Retrospective Analysis of 16 Million Patients in the HCUP National Readmission Database (2013-14)

94,903 (0.6%) diagnosed with opioid abuse or dependence

Greater utilization of care in the opioid group study outcomes

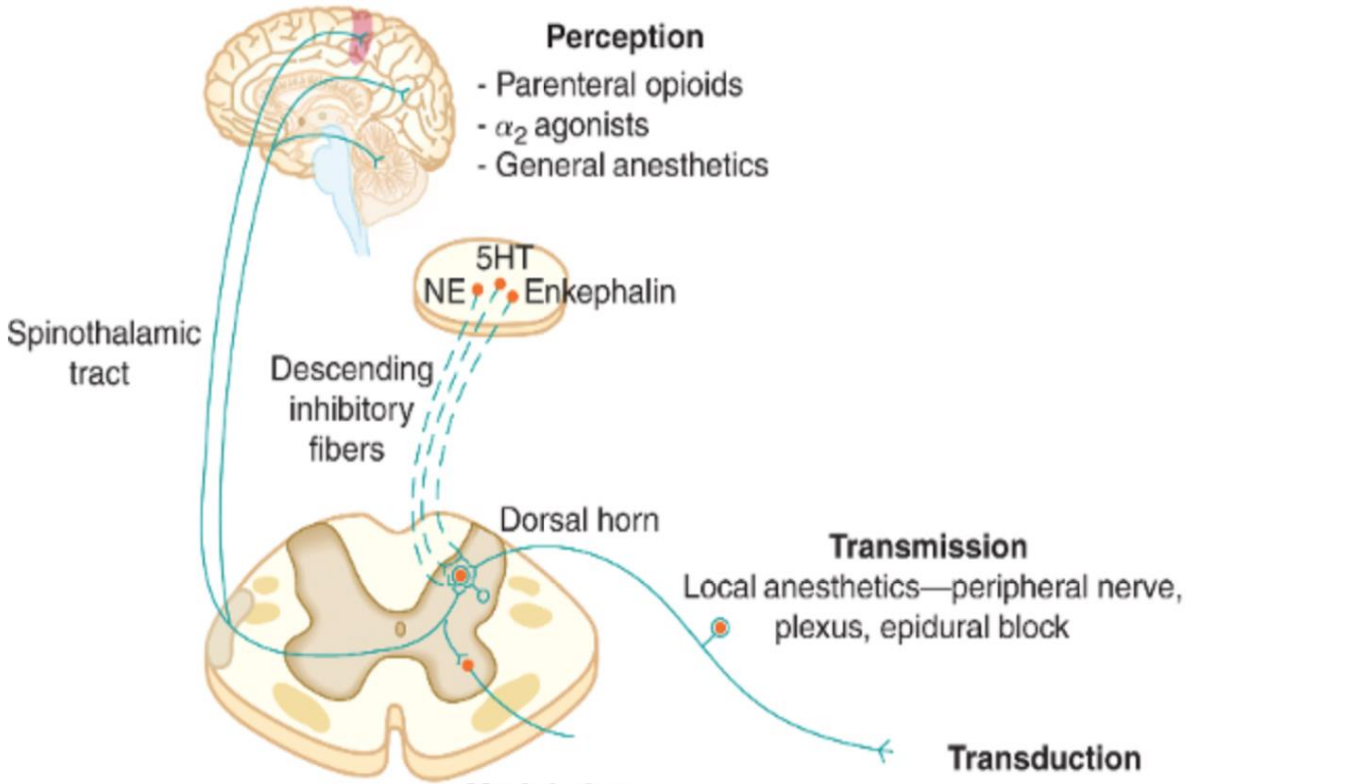
	Opioid abuse/ dependence	Control
30-day readmission	11.1%	9.1%
Mean duration of primary admission	6 days	4 days
Costs during admission	$18,528	$16,617

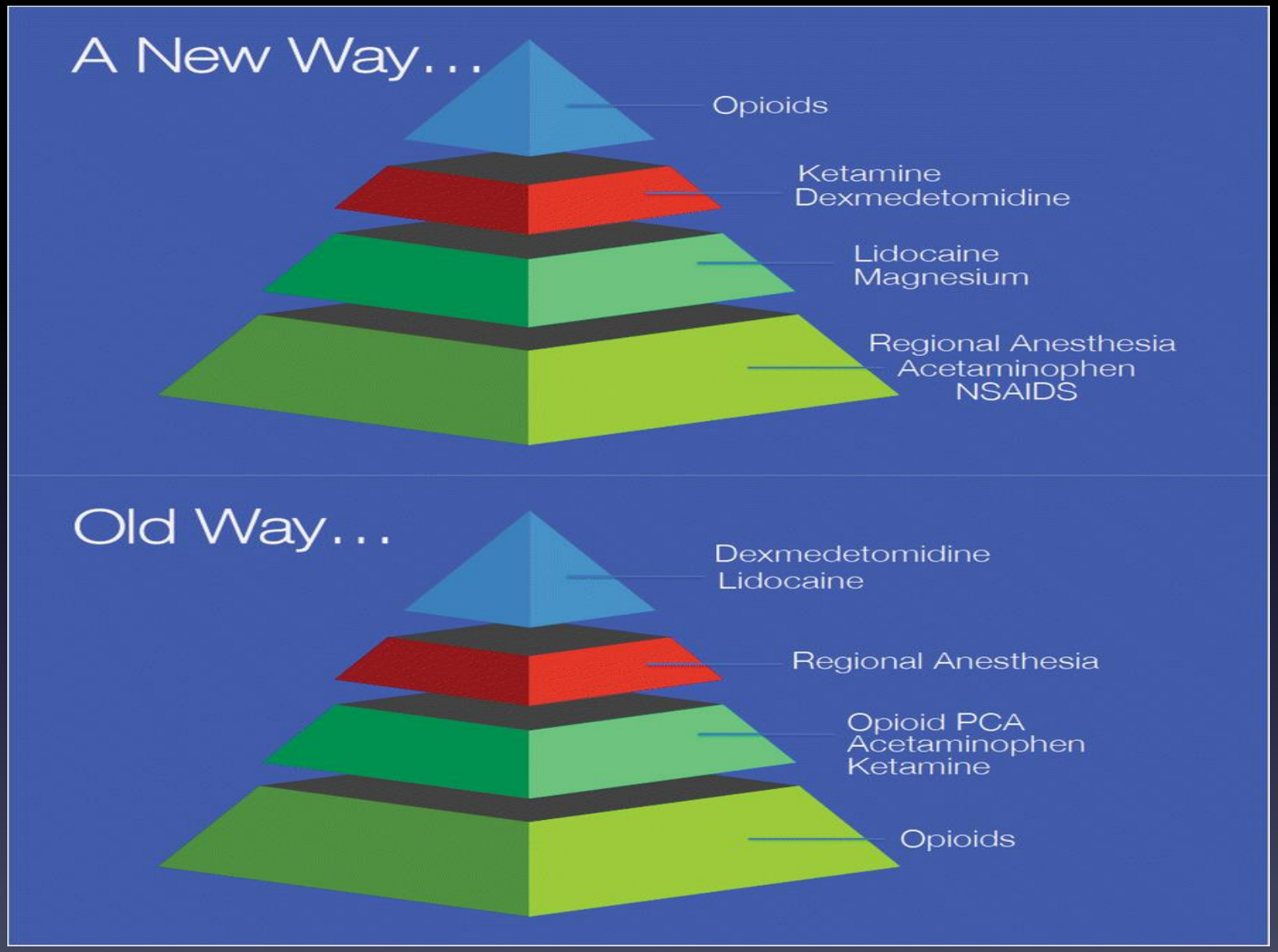
- Third postoperative day, every day of opioid therapy increases the risk of a patient becoming a chronic consumer of opioids
- Most dramatic increases after the fifth and 31st day of therapy.

SOLUTION: MULTIMODAL ANALGESIA

- Regional Anesthesia: Epidurals, single shot intra-thecal injections as well as peripheral nerve blocks
- Non-opioid medications targeting different pain receptors
- Synergistic effect of multiple medications and opioid reduction
- Acetaminophen, gabapentin/pregabalin, ketamine, magnesium, dexamethasone, non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, and lidocaine.

MULTIMODAL ANALGESIA: SYNERGISTIC EFFECTS.




A New Way…
Opioids
Ketamine
Dexmedetomidine
Lidocaine
Magnesium
Regional Anesthesia
Acetaminophen
NSAIDS
Old Way…
Dexmedetomidine
Lidocaine
Regional Anesthesia
Opioid PCA
Acetaminophen
Ketamine
Opioids

Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations☆

U.O. Gustafsson [a,b,*,q], M.J. Scott [c,d,q], W. Schwenk [e,q], N. Demartines [f,q], D. Roulin [f,q], N. Francis [g,q], C.E. McNaught [h,q], J. MacFie [h,q], A.S. Liberman [i,q], M. Soop [j,q], A. Hill [k,q], R.H. Kennedy [l,q], D.N. Lobo [m,q], K. Fearon [n,q], O. Ljungqvist [o,p,q]

Table 2 Enhanced recovery after surgery society recommendations for colonic surgery and their evidence level[6]

ERAS element with high/moderate level evidence	ERAS element with low level evidence
Stopping smoking 4 wk prior to surgery	Pre-operative information and counselling
No routine use of bowel preparation	Stopping drinking alcohol 4 wk prior to surgery
Allowing clear fluids up until 2 h before and solids 6 h before anaesthetic induction	Peri-operative oral nutritional supplements and carbohydrate loading
No routine use of sedative premedication	Standard anaesthetic that allows rapid awakening
Routine thromboprophylaxis	Post-operative nausea and vomiting prophylaxis
Antimicrobial prophylaxis and skin preparation	Routine urinary drainage
Balanced intravenous fluids guided by flow measurements	Using stress reducing elements of ERAS to minimise hyperglycaemia
Use of mid thoracic epidural blocks in open surgery	Early mobilisation
Us of spinal analgesia or PCA in laparoscopic surgery	
Laparoscopic surgery	
No routine use of nasogastric tubes	
Maintenance of normothermia	
No routine intra-abdominal drains	
Early post-operative enteral feeding	
Insulin treatment of severe hyperglycaemia in ICU	
Use of chewing gum to prevent post-operative ileus	

EPIDURAL ANALGESIA

ANNALS OF
SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

FEATURE

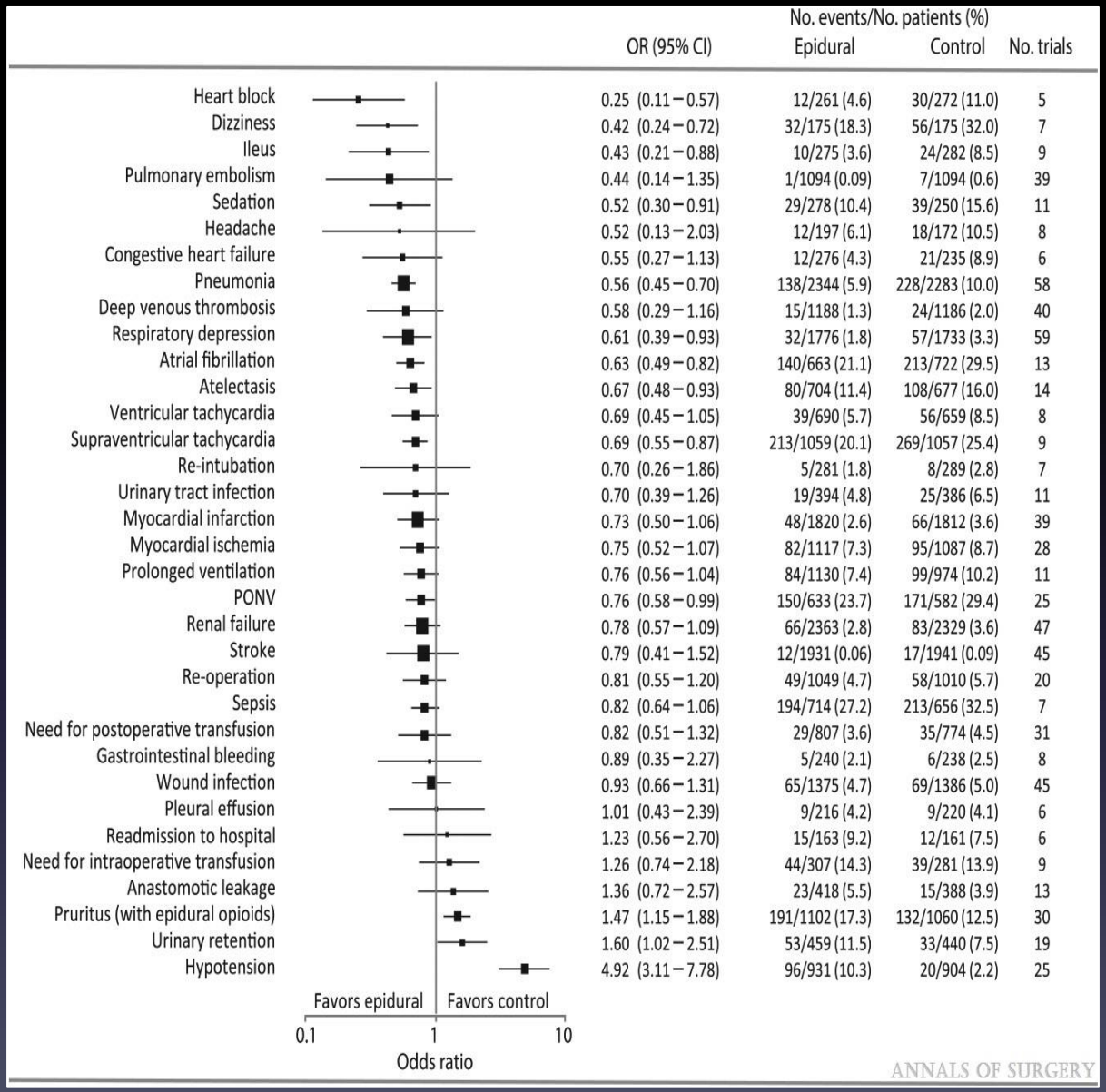
Impact of Epidural Analgesia on Mortality and Morbidity After Surgery

Systematic Review and Meta-analysis of Randomized Controlled Trials

Daniel M. Pöpping, MD, Nadia Elia, MD, MSc,† Hugo K. Van Aken, MD,* Emmanuel Marret, MD,‡ Stephan A. Schug, MD,§ Peter Kranke, MD, MBA,¶ Manuel Wenk, MD,* and Martin R. Tramèr, MD, DPhil‖*

EPIDURAL BENEFITS

- Total of 125 trials (9044 patients, 4525 received epidural analgesia).
- CENTRAL, EMBASE, PubMed, CINAHL, and BIOSIS till July 2012.
- Randomized controlled trials comparing epidural analgesia (with local anesthetics, lasting for ≥24 hours postoperatively) with systemic analgesia
- Decreased risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, and postoperative nausea and vomiting, and improved recovery of bowel function,.



Pöpping, Daniel M.; Elia, Nadia; Van Aken, Hugo K.; Marret, Emmanuel; Schug, Stephan A.; Kranke, Peter; Wenk, Manuel; Tramèr, Martin R.

Annals of Surgery259(6):1056-1067, June 2014.

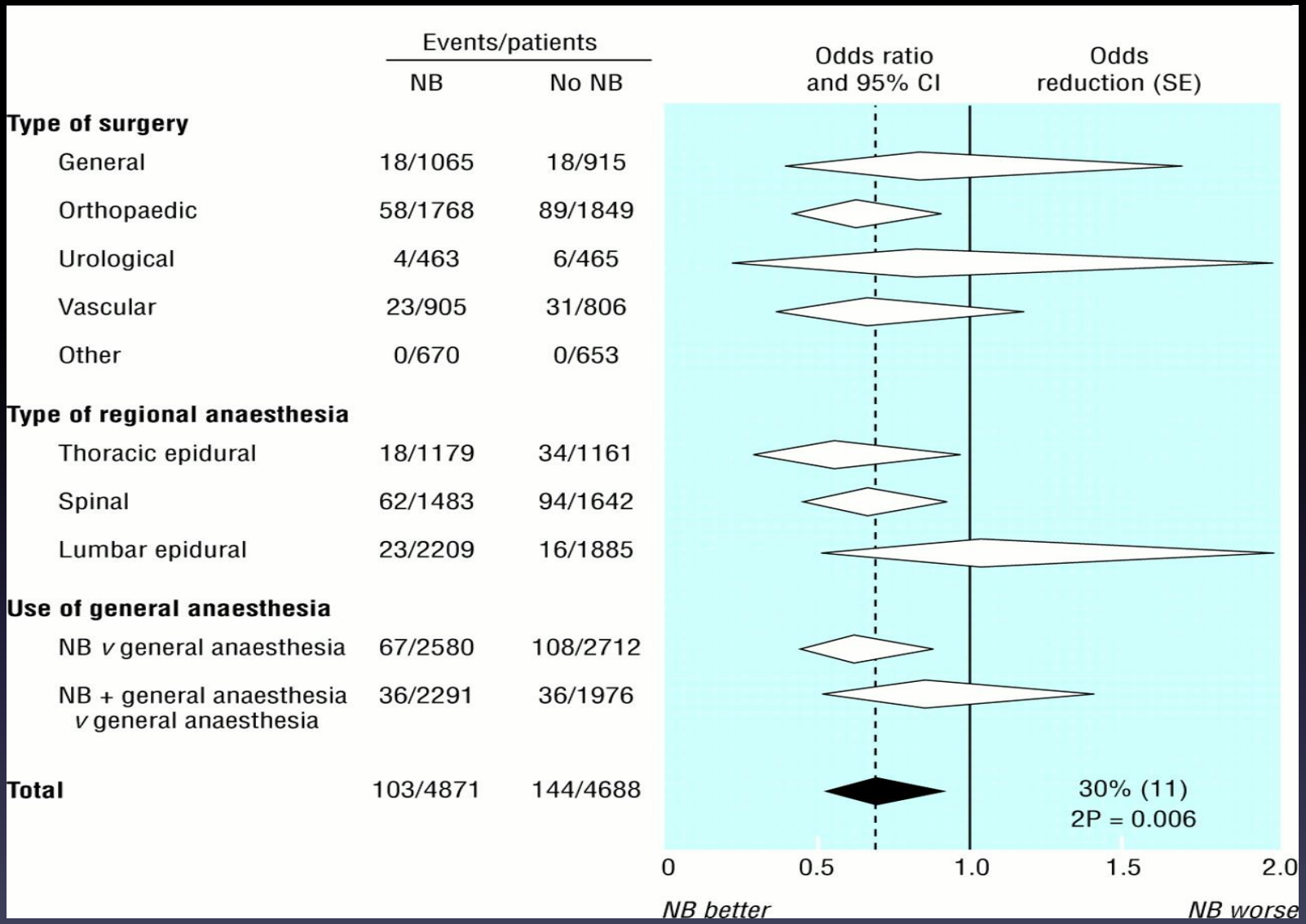
doi: 10.1097/SLA.0000000000000237

Perioperative morbidity: dichotomous outcomes. Control indicates systemic, opioid-based analgesia; PONV, postoperative nausea and vomiting.

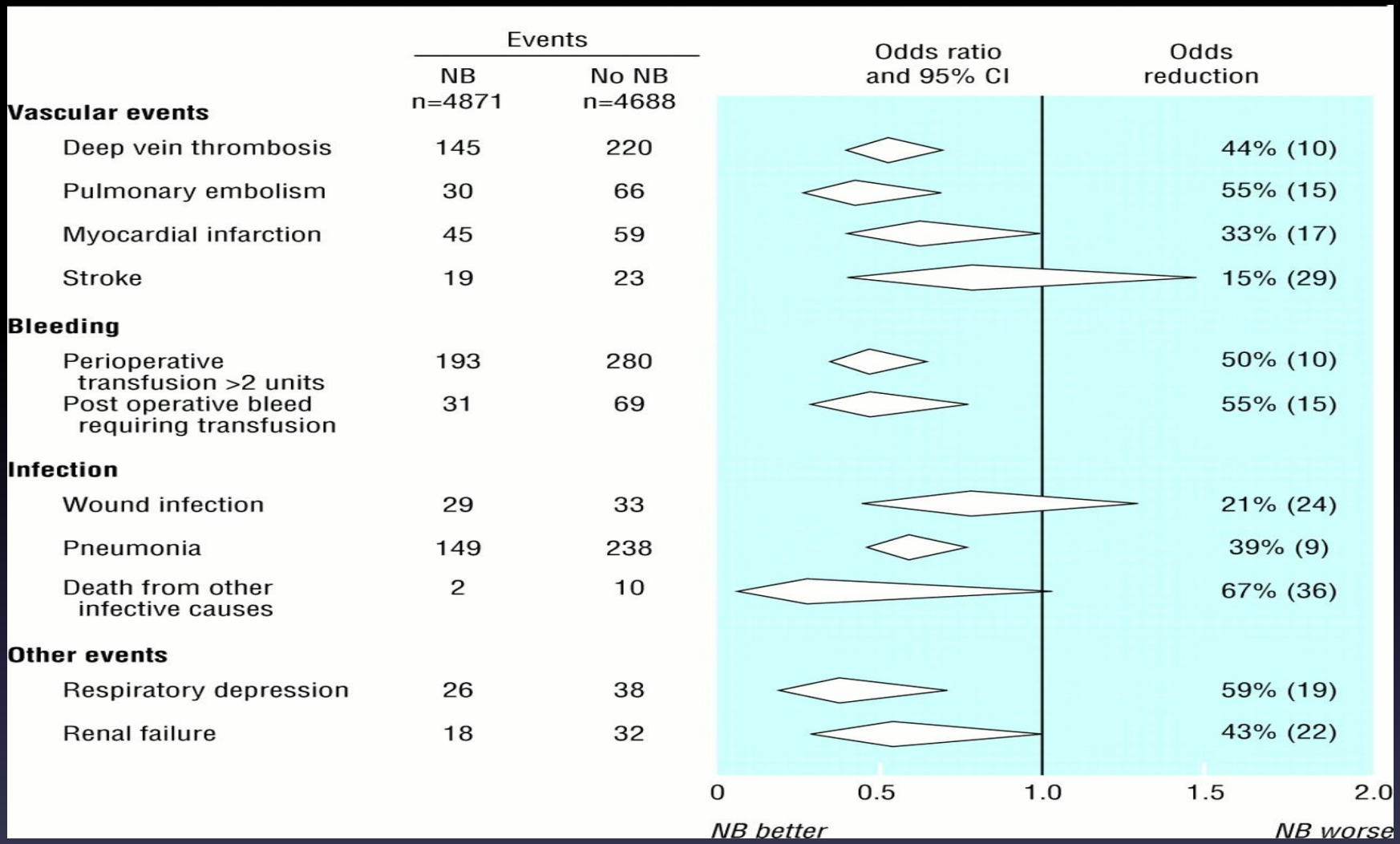
Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials

Anthony Rodgers, Natalie Walker, S Schug, A McKee, H Kehlet, A van Zundert, D Sage, M Futter, G Saville, T Clark, S MacMahon

- 141 trials 9559 patients.
- Overall mortality reduced by about a third in patients allocated to neuraxial blockade
- (103 deaths/4871 patients versus 144/4688 patients.
- Reduction odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%
- Reductions in myocardial infarction and renal failure.
- Reductions in mortality did not differ by surgical group, type of blockade (epidural or spinal),
- Neuraxial blockade was combined with general anesthesia compared with trials in which neuraxial blockade was used alone.



Effect of neuraxial blockade (NB) on postoperative mortality, by surgical group, type of neuraxial blockade, and use of general anesthesia.



Effects of neuraxial blockade (NB) on postoperative complications. Diamonds denote 95% confidence intervals for odds ratios of combined trial results.

INTRATHECAL OPIOIDS

Pain Relief by Intrathecally Applied Morphine in Man

JOSEF K. WANG, M.D.,* LEE A. NAUSS, M.D.,* JUERGEN E. THOMAS, M.D.†

In recent animal experiments, opiate receptors were identified autoradiographically in the brain and the substantia gelatinosa of the spinal cord.[1] In a corollary study, morphine administered directly into the spinal subarachnoid space of the rat produced potent analgesia.[2] Subsequent studies confirmed this finding and showed that repeated intrathecal injections of mor-

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Received from the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Accepted for publication May 9, 1978. This study has been approved by the Human Studies Committee, Mayo Clinic and Mayo Foundation.

Address reprint requests to Dr. Wang: Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901.

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The Safety And Efficacy of Intrathecal Opioid Analgesia for Acute Postoperative Pain: Seven Years' Experience with 5969 Surgical Patients at Indiana University Hospital

Kenneth H. Gwirtz, MD, Jerry V. Young, MD, Robert S. Byers, MD, Christopher Alley, DO, Katherine Levin, MD, Scott G. Walker, MD, and Robert K. Stoelting, MD

Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana

- Prospectively evaluated patients who received intrathecal opioid analgesia (ITOA) to manage postsurgical pain. 5969 adult patients who had received ITOA for major urologic, orthopedic, general/ vascular, thoracic, and non-obstetrical gynecologic surgery.

TURP, vaginal hysterectomy: 0.2–0.3 mg
Hip and knee surgery: 0.4–0.5 mg
Lower abdominal surgery (e.g., hysterectomy): 0.4–0.5 mg
Upper abdominal surgery (e.g., Whipple): 0.5–0.6 mg
Nephrectomy: 0.6–0.65 mg
Retroperitoneal lymph node dissection: 0.65–0.75 mg
Abdominal aortic aneurysm, thoracotomy: 0.65–0.8 mg

The 1% of patients receiving >25 μg of fentanyl underwent upper abdominal or thoracic procedures.

Morphine doses were established for our adult patients primarily on the basis of patient stature (average, above average, below average) and the level of surgery. Doses were routinely reduced by 0.1 mg for elderly (>65 yr old) or debilitated patients and routinely increased by 0.1 mg for extremely tall patients.

TURP = transurethral resection of prostate.

[a] Doses previously established and published by our institution (38).

- Mean satisfaction score using a 10-point numeric rating scale was 8.51.
  Control acute postoperative pain on nearly 6000 patients.
  High degree of patient satisfaction

Scores	
Data collection rate	95.6%
NRS scores (scale of 1–10)	8.51
Side effects/complications	
Pruritus	37%
Nausea/vomiting	25%
Respiratory depression[b]	3.0%
Postdural puncture headache	0.54%
Epidural blood patch for postdural puncture headache	0.37%
Patient-controlled analgesia usage complications	0
Cerebrospinal fluid infections	0
Respiratory failure requiring intubation	0
Life-threatening respiratory failure	0
Nerve injury	0
Mortality	0
Naloxone usage complications	0

NRS = numeric rating scale.

[a] Incidence of urinary retention was excluded because it was artifactually low.

[b] Criteria defined in text.

British Journal of Anaesthesia 102 (2): 156–67 (2009)
doi:10.1093/bja/aen368

BJA

REVIEW ARTICLES

Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials

N. Meylan[1], N. Elia[1 2], C. Lysakowski[1] and M. R. Tramèr[1 2]*

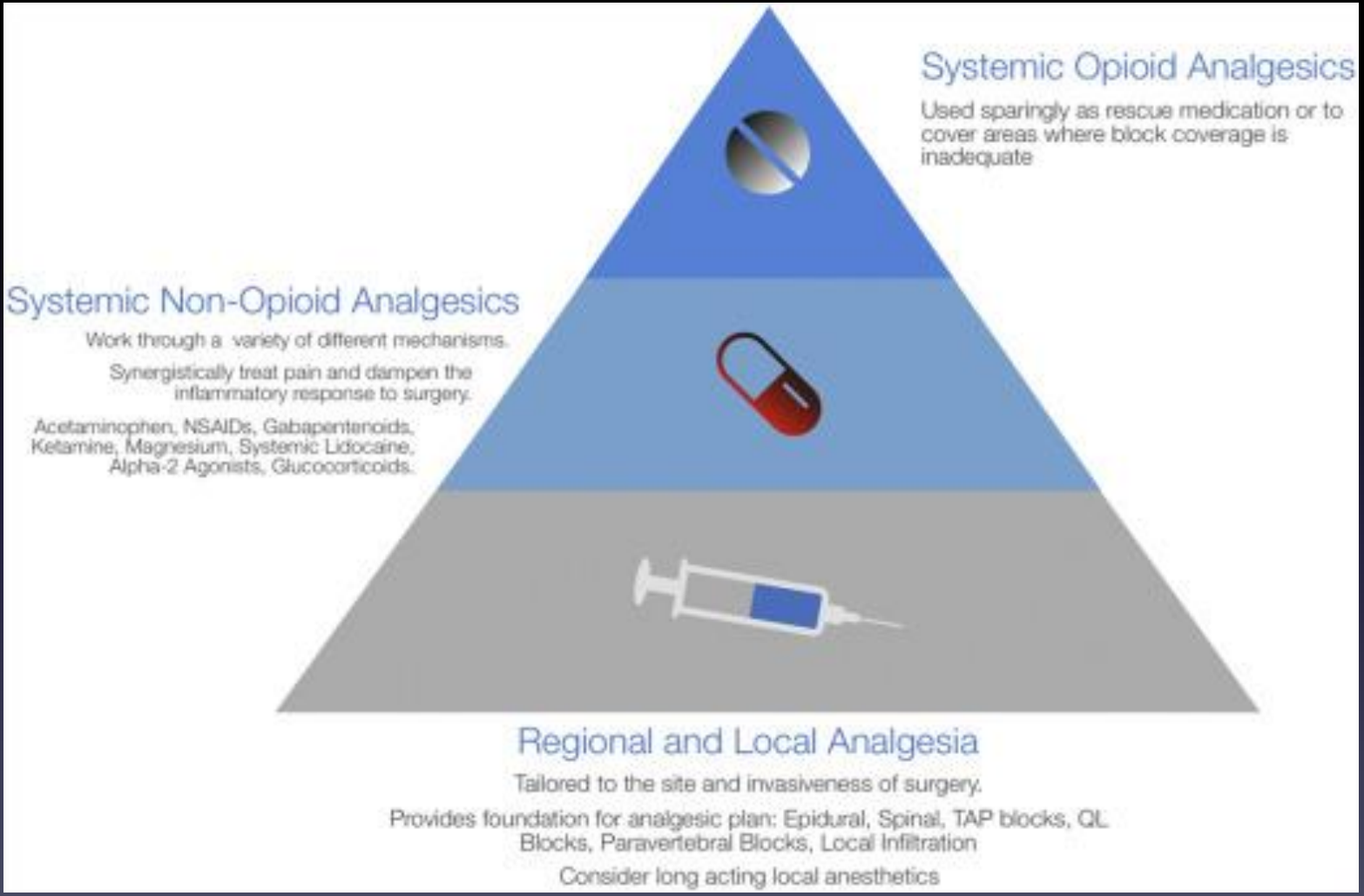
[1]Division of Anaesthesiology, University Hospitals of Geneva, 24, rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland. [2]Medical Faculty, University of Geneva, Geneva, Switzerland

*Corresponding author. E-mail: martin.tramer@hcuge.ch

- Meta-analysis of randomized trials testing intrathecal morphine alone (without local anaesthetic) in adults undergoing major surgery
- Twenty-seven studies (15 cardiac–thoracic, nine abdominal, and three spine surgery)
- 645 patients received intrathecal morphine (dose-range, 100–4000 mg).
- Pain intensity decreased by 2 cm on the 10 cm visual analogue scale up to 4 h
- Pain intensity on movement was decreased by 2 cm at 12 and 24 h.
- Opioid requirement was decreased intraoperatively, and up to 48 h after operation.
- Morphine-sparing at 24 h was significantly greater after abdominal surgery
- In conclusion, intrathecal morphine decreases pain intensity at rest and on movement up to 24 h after major surgery


Do you prefer a local anesthesia ?
I would rather prefer an imported one

PHARMACOLOGICAL MANAGEMENT



Clinical Review & Education

JAMA Surgery | Review

Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques

A Review

Elizabeth C. Wick, MD; Michael C. Grant, MD; Christopher L. Wu, MD

OBSERVATIONS Regional analgesia, acetaminophen, nonsteroidal anti-inflammatory agents, gabapentinoids, tramadol, lidocaine, and/or the *N*-methyl-D-aspartate class of glutamate receptor antagonists have been shown to be effective adjuncts to narcotic analgesia. Nonsteroidal anti-inflammatory agents are not associated with an increase in postoperative bleeding. A meta-analysis of 27 randomized clinical trials found no difference in postoperative bleeding between the groups taking ketorolac tromethamine (33 of 1304 patients [2.5%]) and the control groups (21 of 1010 [2.1%]) (odds ratio [OR], 1.1; 95% CI, 0.61-2.06; *P* = .72). After adoption of the multimodal analgesia approach for a colorectal ERAS pathway, most patients used less opioids while in the hospital and many did not need opioids after hospital discharge, although approximately 50% of patients received some opioid during their stay.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

- Potent analgesics (600 mg of ibuprofen as efficacious as 15 mg of oxycodone)
- Inhibition of cyclooxygenase and prostaglandin synthesis.
- Intravenous or oral route
- Administered on a scheduled rather than on PRN
- Superior analgesia and an opioid-sparing effect.
- Decrease in adverse events, such as postoperative nausea or vomiting and sedation.
- Potential risks: platelet dysfunction, gastrointestinal tract irritation or bleeding, and renal dysfunction.
- Cochrane review: 23 trials (comprising 1459 patients): NSAIDs clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function.

NSAIDS

Nonsteroidal anti-inflammatory agents are not associated with an increase in postoperative bleeding. A meta-analysis of 27 randomized clinical trials found no difference in postoperative bleeding between the groups taking ketorolac tromethamine (33 of 1304 patients [2.5%]) and the control groups (21 of 1010 [2.1%]) (odds ratio [OR], 1.1; 95% CI, 0.61-2.06; $P = .72$). After adoption of the multimodal analgesia approach for a colorectal ERAS pathway, most patients used less opioids while in the hospital and many did not need opioids after hospital discharge, although approximately 50% of patients received some opioid during their stay.

- Meta-analysis 27 randomized clinical trials (comprising 2314 patients undergoing a variety of surgical procedures)
- No difference in postoperative bleeding between the group taking ketorolac.

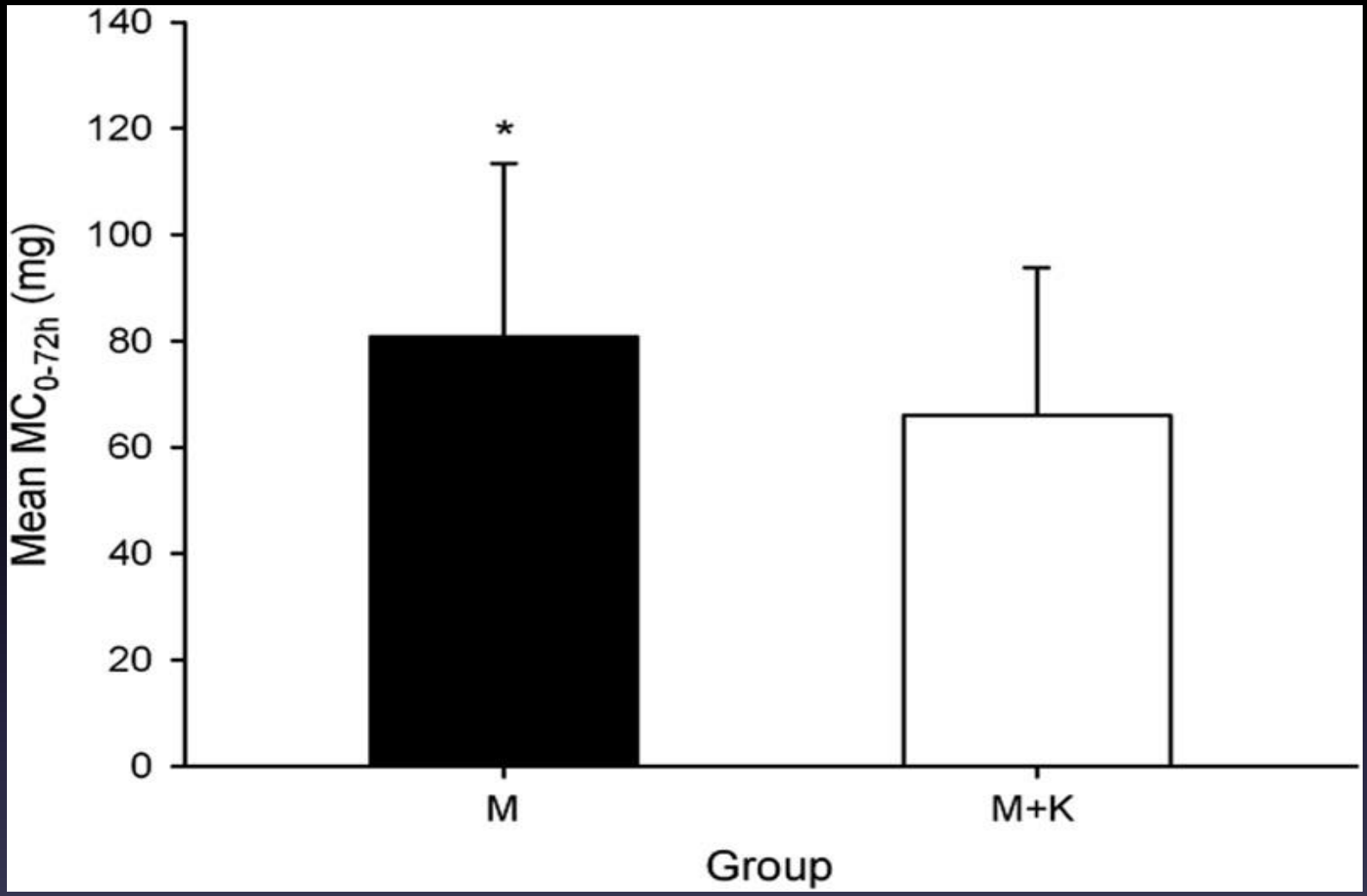
Opioid-sparing Effects of Ketorolac and Its Correlation With the Recovery of Postoperative Bowel Function in Colorectal Surgery Patients

A Prospective Randomized Double-blinded Study

Jui-Yuan Chen, MD,† Tsung-Lin Ko, MD,* Yeong-Ray Wen, MD,* Shu-Ching Wu, MSc,‡ Yenn-Hwei Chou, MD, PhD,§ Hwey-Wen Yien, MD, PhD,† and Cheng-Deng Kuo, MD, PhD†‖*

Downloaded from https://journals.lww.com

- 102 patients received elective colorectal resection.
- 2 groups and received intravenous patient-controlled analgesia (IVPCA) morphine (M group) or IVPCA morphine plus ketorolac (M+K group).
- Patients in the M+K group received 18.3% less morphine than those in the M group within 72 postoperative hours.
- maximal opioid-sparing effects of ketorolac appeared in 12 to 24 postoperative hours.
- onset of first bowel movement and passage of flatus significantly less in the M+K group than in the M group.
- The M group showed a 5.25 times greater risk of inducing PI, a result comparable with the M+K group in colorectal surgery patients.
- ketorolac to IVPCA morphine clear opioid-sparing effect and benefits in regards to the shortening of the duration of bowel immobility.



Total morphine consumption between groups was significantly different. Ketorolac addition could reduce the total morphine consumption as much as 18.3%. Error bar indicates SD; M, morphine group; MC, morphine consumption; M+K, morphine plus ketorolac group. *P<0.05.

ACETAMINOPHEN

- Acetaminophen administered on a scheduled rather than on an as-needed basis.
- Acetaminophen produces superior analgesia and an opioid-sparing effect
- Decrease in some opioid-related adverse events, such as postoperative nausea or vomiting and sedation.
- Concurrently administered with NSAIDs on a scheduled basis (assuming no contraindications)
- Administration of both agents will result in an additive and synergistic analgesic effect.

Decreased opioid consumption and enhance recovery with the addition of IV Acetaminophen in colorectal patients: a prospective, multi-institutional, randomized, double-blinded, placebo-controlled study (DOCIVA study)

Amir H. Aryaie[1] · Sepehr Lalezari[2] · Wallace K. Sergent[2] · Yana Puckett[1] · Christopher Juergens[3] · Craig Ratermann[3] · Cari Ogg[2]

Results 105 patients were enrolled and 97 remained in the study after exclusion (control group $n=50$; study group $n=47$). Mean ± SEs of opioid consumption in the study group was 21.5 ± 1.8 mg of morphine equivalent (ME) and 35.0 ± 3.3 mg ME at 24 and 48 h, respectively, versus 36.4 ± 4.1 mg ME and 59.7 ± 6.7 mg ME in the control group ($p=0.002$ and 0.002). PVASS levels were lower in the study group at all intervals at 3, 8, 24, and 48 h ($p=0.02$, 0.006, <0.01, and 0.02). ROGIF, TTDO, and LOHS were also found to be lower in the study group ($p \leq 0.01$, <0.01, and 0.002). The rate of ileus was reduced by using IV acetaminophen (22% vs 2.1%; $p=0.004$).

Conclusions IV acetaminophen helps to reduce opioid consumption for patients undergoing colorectal surgery. Additionally, there appears to be a shortened length of hospital stay, better pain control, reduced time to return of bowel function, and lower rate of post-operative ileus in patients receiving IV acetaminophen.

GABAPENTIN

- Initially developed as an antiepileptic drug.
- Gabapentin possesses analgesic properties
- α-2-δ-subunits of voltage-gated calcium channels
- Decreasing the release of excitatory neurotransmitters.
- Treatment of chronic neuropathic pain
- Contemporary evidence: use in the management of acute postsurgical pain

Do Surgical Patients Benefit from Perioperative Gabapentin/Pregabalin? A Systematic Review of Efficacy and Safety

Elina M. Tiippana, MD*

Katri Hamunen, MD, PhD*

Vesa K. Kontinen, MD, PhD*#

Eija Kalso, MD, PhD*#

BACKGROUND: Gabapentin and pregabalin have antiallodynic and antihyperalgesic properties useful for treating neuropathic pain. These properties may also be beneficial in acute postoperative pain. In this study we evaluated randomized, controlled trials examining the analgesic efficacy, adverse effects, and clinical value of gabapentinoids in postoperative pain.

METHODS: A systematic search of Medline, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) databases yielded 22 randomized, controlled trials on perioperative administration of gabapentinoids for postoperative pain relief.

RESULTS: Pain relief was better in the gabapentin groups compared with the control groups. The opioid-sparing effect during the first 24 h after a single dose of gabapentin 300–1200 mg, administered 1–2 h preoperatively, ranged from 20% to 62%. The combined 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. Metaregression analysis suggested that the 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, vomiting, and urinary retention (number-needed-to-treat 25, 6, and 7, respectively). The most common adverse effects of the gabapentinoids were sedation and dizziness (number-needed-to-harm 35 and 12, respectively).

CONCLUSIONS: Gabapentinoids effectively reduce postoperative pain, opioid consumption, and opioid-related adverse effects after surgery. Conclusions about the optimal dose and duration of the treatment cannot be made because of the heterogeneity of the trials. Studies are needed to determine the long-term benefits, if any, of perioperative gabapentinoids.

(Anesth Analg 2007;104:1545–56)

British Journal of Anaesthesia **114** (1): 10–31 (2015)
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BJA

REVIEW ARTICLES

Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

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- 55 studies (4155 patients) pregabalin associated with a significant reduction in pain scores at rest and during movement.
- Decrease of opioid consumption at 24 h compared with placebo.
- Less postoperative nausea and vomiting and pruritus compared with placebo.
- Sedation, dizziness, and visual disturbance were more common with pregabalin.
- All doses of pregabalin tested (≤75, 100–150,and 300 mg) resulted in opioid sparing at 24 h after surgery.
- No significant differences in acute pain outcomes with pregabalin 100–300 mg between single preoperative dosing regimens and those including additional doses repeated after surgery.

NMDA ANTAGONISTS

- N-methyl-D-aspartate (NMDA) class of glutamate receptor involved with nociceptive processing and development of chronic pain.
- Inhibition of NMDA receptors provides a nonopioid mechanism of analgesia.
- Ketamine hydrochloride, magnesium sulfate, dextromethorphan hydrobromide (found in cough syrup), and methadone.
- Ketamine given postoperatively in sub-anesthetic doses as an infusion: decreases intravenous patient-controlled analgesia morphine use, postoperative nausea, and postoperative vomiting.
- Magnesium also can be administered in the perioperative period
- Perioperative magnesium infusion: associated with decrease in postoperative pain and opioid consumption without clinical toxic effects caused by toxic serum levels of magnesium.

Pain Medicine
Pain Medicine 2015; 16: 383–403
Wiley Periodicals, Inc.

ACUTE & PERIOPERATIVE PAIN SECTION

Original Research Article

The Use of Intravenous Infusion or Single Dose of Low-Dose Ketamine for Postoperative Analgesia: A Review of the Current Literature

- 39 RCTs (2482 subjects) utilizing low-dose intravenous ketamine for postoperative analgesia after a variety of surgical interventions.
- Bolus dose: 0.35 mg-0.5 mg/kg and infusion 0.2-0.6 mg/kg/hr
- Ketamine provides a 40% opioid-sparing effect.

Postoperative Ketamine Administration Decreases Morphine Consumption in Major Abdominal Surgery: A Prospective, Randomized, Double-Blind, Controlled Study

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David Samarcq, MD*
Emmanuel Lorne, MD*
Mona Moubarak, MD*
Philippe Montravers, MD, PhD†
Sadek Beloucif, MD, PhD‡
Hervé Dupont, MD, PhD*

BACKGROUND: Ketamine decreases postoperative morphine consumption, but its optimal dosing and duration of administration remain unclear. In this study, we compared the effects of ketamine administration on morphine consumption limited to the intraoperative period, or continued for 48 h postoperatively.

METHODS: Eighty-one patients scheduled for abdominal surgery were prospectively randomized under double-blind conditions to three groups: (1) PERI group receiving intraoperative and postoperative ketamine for the first 48 h after surgery ($2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ after a 0.5 mg/kg bolus); (2) INTRA group receiving intraoperative ketamine administration only ($2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ after a 0.5 mg/kg bolus); and (3) CTRL group receiving placebo. Morphine consumption, visual analog scale scores and side effects (sedation score, nausea-vomiting score, nightmares, psychiatric disorders, or delusions) were recorded for the first 48 h.

RESULTS: Cumulative morphine consumption 24 h after surgery was significantly lower in the PERI group (median = 27 mg, interquartile range = [19]) than in the INTRA group (48 mg [41.5]) and CTRL group (50 mg [21]) ($P < 0.005$). Postoperative visual analog scale scores were significantly lower in the PERI group and INTRA group than in the CTRL group ($P < 0.001$). A higher rate of nausea was observed in the CTRL group compared with the PERI group (27% vs 4%, $P = 0.005$). No difference in sedation scores or psychiatric disorders was observed among groups.

CONCLUSIONS: Low-dose ketamine improved postoperative analgesia with a significant decrease of morphine consumption when its administration was continued for 48 h postoperatively, with a lower incidence of nausea and with no side effects of ketamine.

(Anesth Analg 2008;106:1856–61)

A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively

Kanupriya Kumar, MD,* Meghan A. Kirksey, MD, PhD,* Silvia Duong, BScPharm, PharmD,† and Christopher L. Wu, MD‡

Table 1. Nonopioid Adjuvants

Adjuvant	Purported Mechanism of Action	Duration/Magnitude of Opioid-Reduction Effect
Dexmedetomidine, clonidine	Stimulation of α-2 adrenoreceptors located in the dorsal horns of the spinal cord and locus coeruleus	Up to 24 h, with a greater effect with dexmedetomidine
Ketamine, amantadine, dextromethorphan	Decreased nociceptive and inflammatory pain transmission due to N-methyl-d-aspartate receptor blockade	Up to 40% opioid sparing with ketamine, unclear data on benefit with amantadine, up to 24 h with dextromethorphan
Gabapentinoids	Decreased release of excitatory neurotransmitters (eg, glutamate, substance P, and calcitonin genre-related peptide) due to interaction with α-2-δ-subunits of voltage-gated calcium channels	Reduction of opioid use postoperatively after gabapentin likely overestimated previously but still some effect Up to 24 h with pregabalin for some surgical procedures
Duloxetine	Modulating effect on descending inhibitory pain pathways in the brain and spinal cord	Up to 48 h
Tricyclic antidepressants	Suppression of central pain sensitization through the inhibition of reuptake of norepinephrine and serotonin as well as antagonism of peripheral sodium channels and spinal N-methyl-d-aspartate receptors	No clear benefit of use
Lidocaine	Decreased release of proinflammatory cytokines (eg, IL6, IL8), NF-kB–modulated downregulation at the mRNA level, and inhibition of N-methyl-d-aspartate receptors	Intraoperative and immediately postoperative (PACU), with possible greatest effect in open and laparoscopic abdominal procedures
Esmolol	Blockade of the excitatory effects of pain signaling in the central and peripheral nervous system and modulation of the central adrenergic (pronociceptive) activity	Significant but clinically small effect on postoperative opioid consumption in meta-analysis of small trials; more studies needed
Caffeine	Improved analgesic drug absorption (due to increased gastric blood flow), reduced drug clearance (due to decreased hepatic blood flow), blockade of peripheral pronociceptive adenosine signaling, and activation of the central noradenosine pathway	Addition to commonly used analgesics significantly increased the number of patients experiencing good pain relief (50% over 4–6 h)

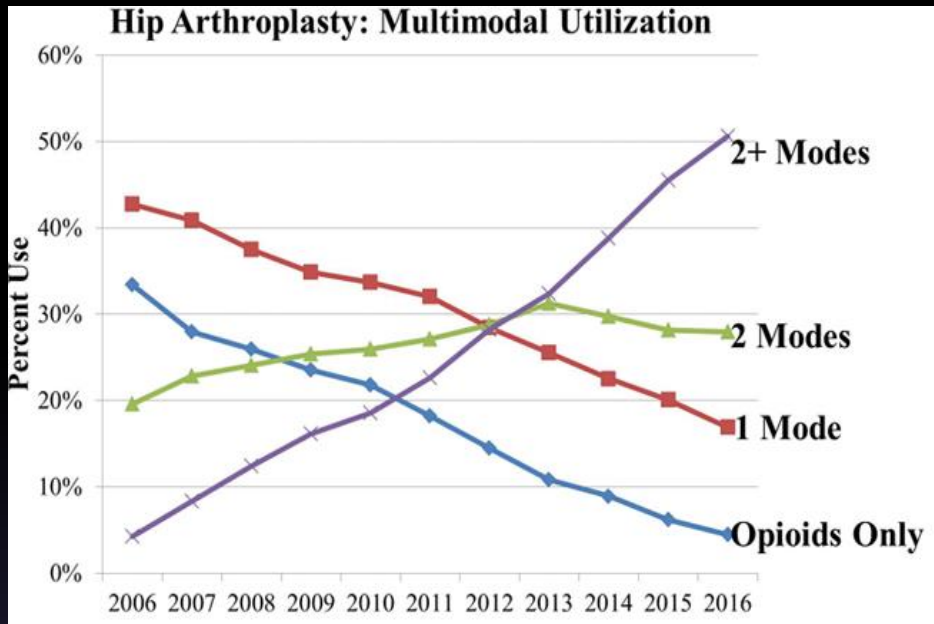
Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization

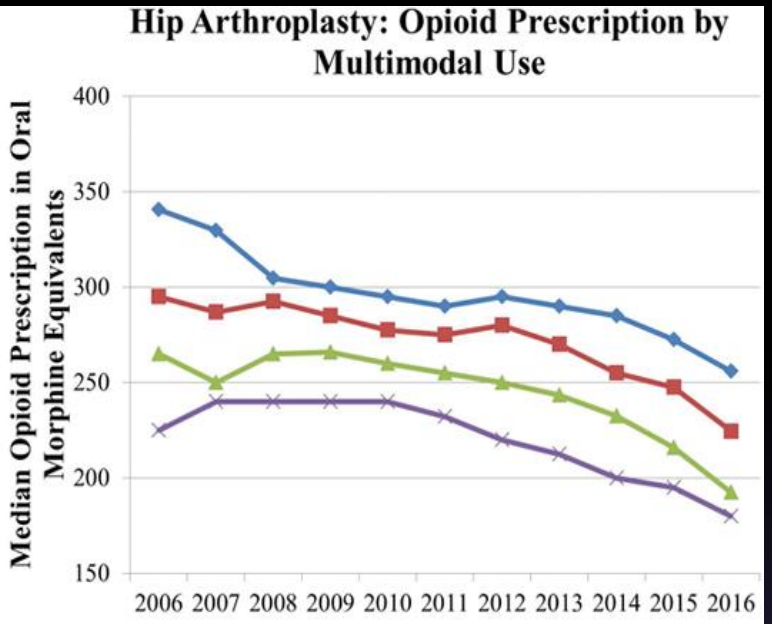
A Population-based Study

Stavros G. Memtsoudis, M.D., Ph.D., F.C.C.P., Jashvant Poeran, M.D., Ph.D., Nicole Zubizarreta, M.P.H., Crispiana Cozowicz, M.D., Eva E. Mörwald, M.D., Edward R. Mariano, M.D., M.A.S., Madhu Mazumdar, Ph.D.

CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

- Total hip/knee arthroplasties (N = 512,393 and N = 1,028,069, respectively)
- Opioids, peripheral nerve blocks, acetaminophen, steroids, gabapentin/pregabalin, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or ketamine.
- "Opioids only" and 1, 2, or more than 2 additional modes.
- Multimodal analgesia and opioid prescription, cost/length of hospitalization, and opioid-related adverse effects.
- Patients receiving more than 2 modes (compared to "opioids only") experienced 19% fewer respiratory, 26% fewer gastrointestinal, up to a –18.5% decrease in opioid prescription and a –12.1% decrease in length of stay (all $P < 0.05$).
- Total knee arthroplasty analyses showed similar patterns.
- Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors seemed to be the most effective modalities used.


Hip Arthroplasty: Multimodal Utilization
Percent Use
60%
50%
40%
30%
20%
10%
0%
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
2+ Modes
2 Modes
1 Mode
Opioids Only


Hip Arthroplasty: Opioid Prescription by Multimodal Use
Median Opioid Prescription in Oral Morphine Equivalents
400
350
300
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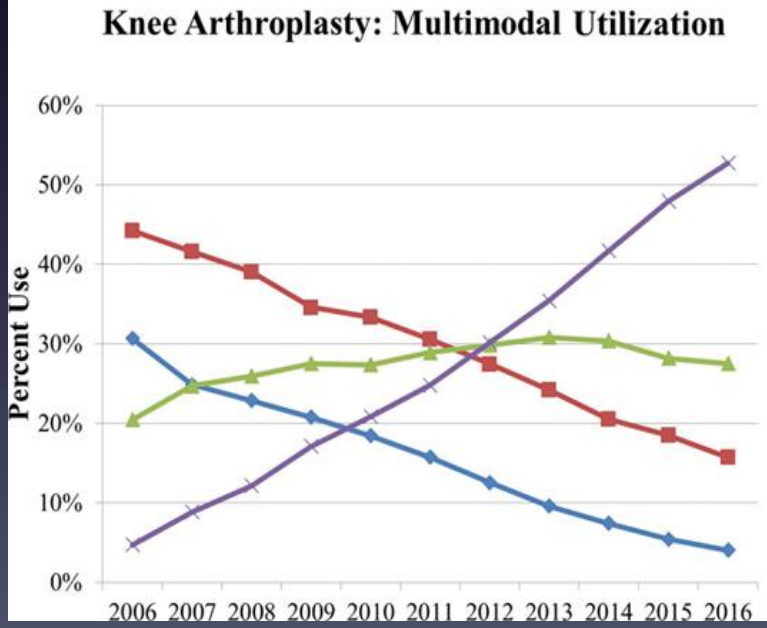
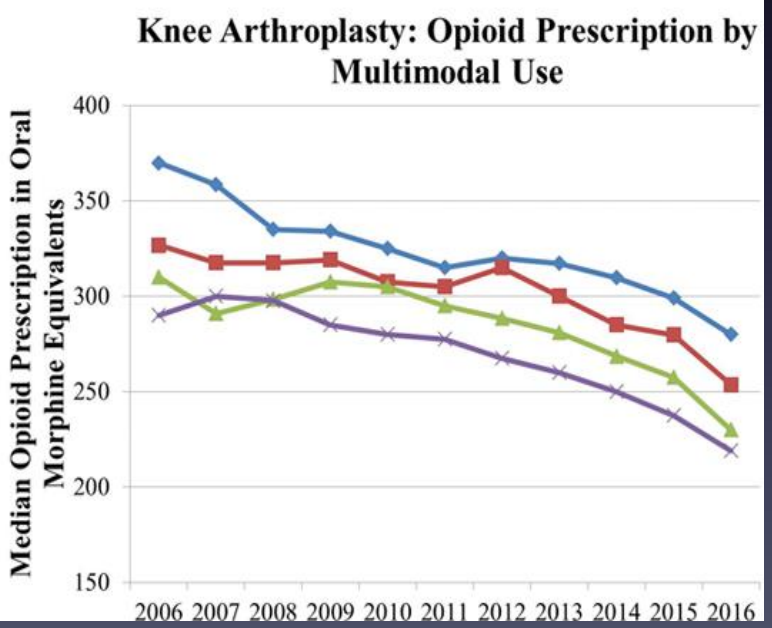
200
150
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016


Knee Arthroplasty: Multimodal Utilization
Percent Use
60%
50%
40%
30%
20%
10%
0%
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016


Knee Arthroplasty: Opioid Prescription by Multimodal Use
Median Opioid Prescription in Oral Morphine Equivalents
400
350
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250
200
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2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

Opioid-Free Analgesia in the Era of Enhanced Recovery After Surgery and the Surgical Home: Implications for Postoperative Outcomes and Population Health

Nirav V. Kamdar, MD, MPP, Nir Hoftman, MD, Siamak Rahman, MD, and Maxime Cannesson, MD, PhD

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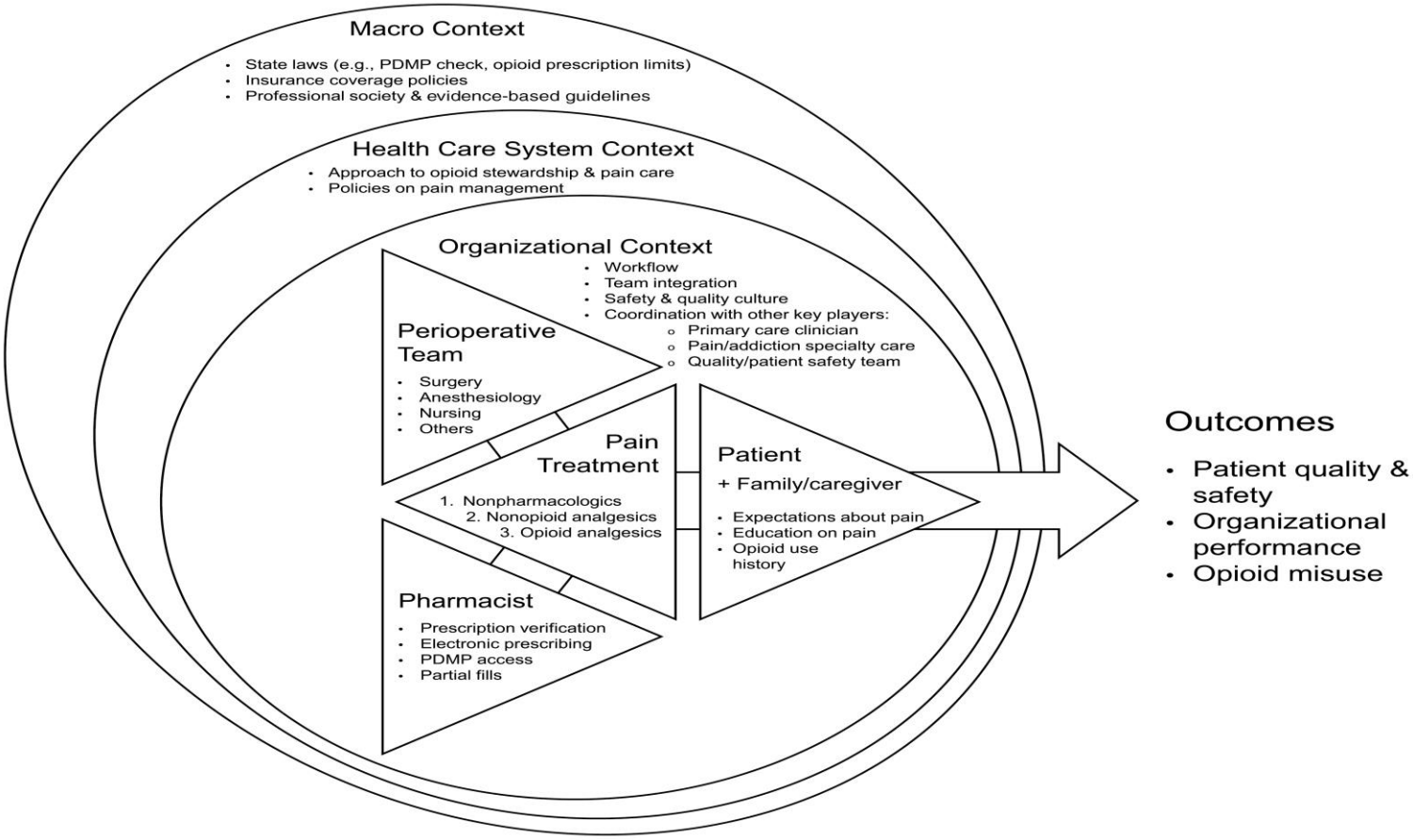

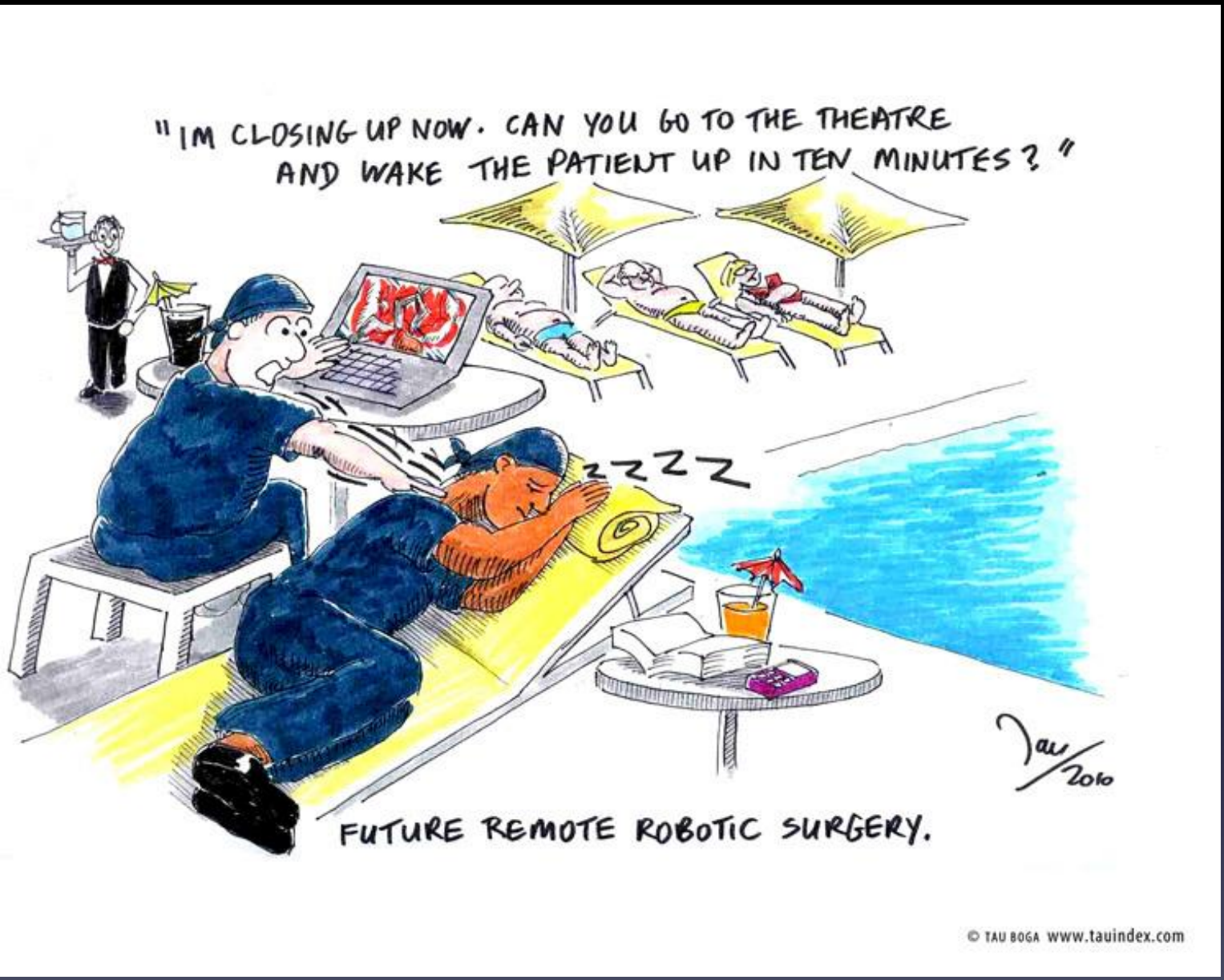
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