

Perioperative Nonopioid Analgesic Adjuncts

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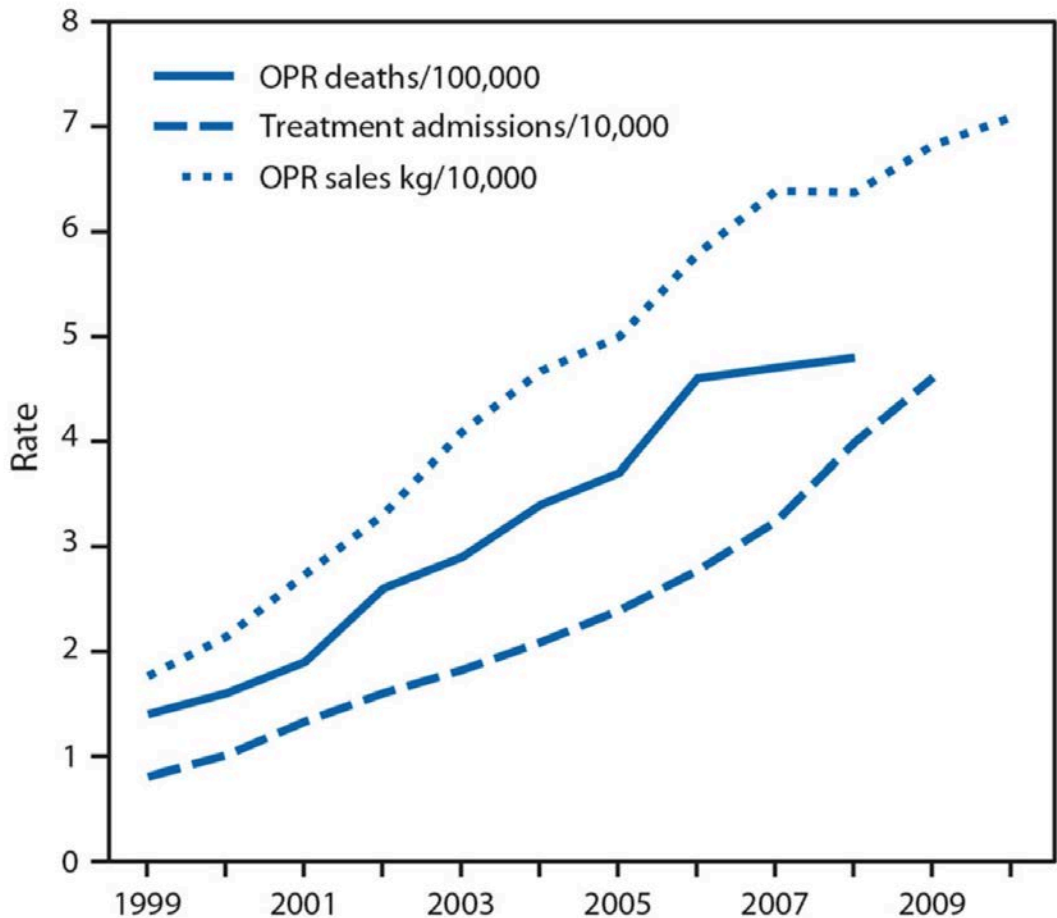
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Disclosures

- No relevant financial disclosures
- Some medications are off-label when used for analgesic indications, but have been extensively studied.
 - Gabapentin, pregabalin, dexamethasone, ketamine, magnesium, lidocaine, esmolol, dexmedetomidine

Perioperative Pain Management?





Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: The role of the anesthesiologist. *Periop Med.* 2018; 7(16).

The Evolving Approach to Analgesia



Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: The role of the anesthesiologist. *Periop Med.* 2018; 7(16).

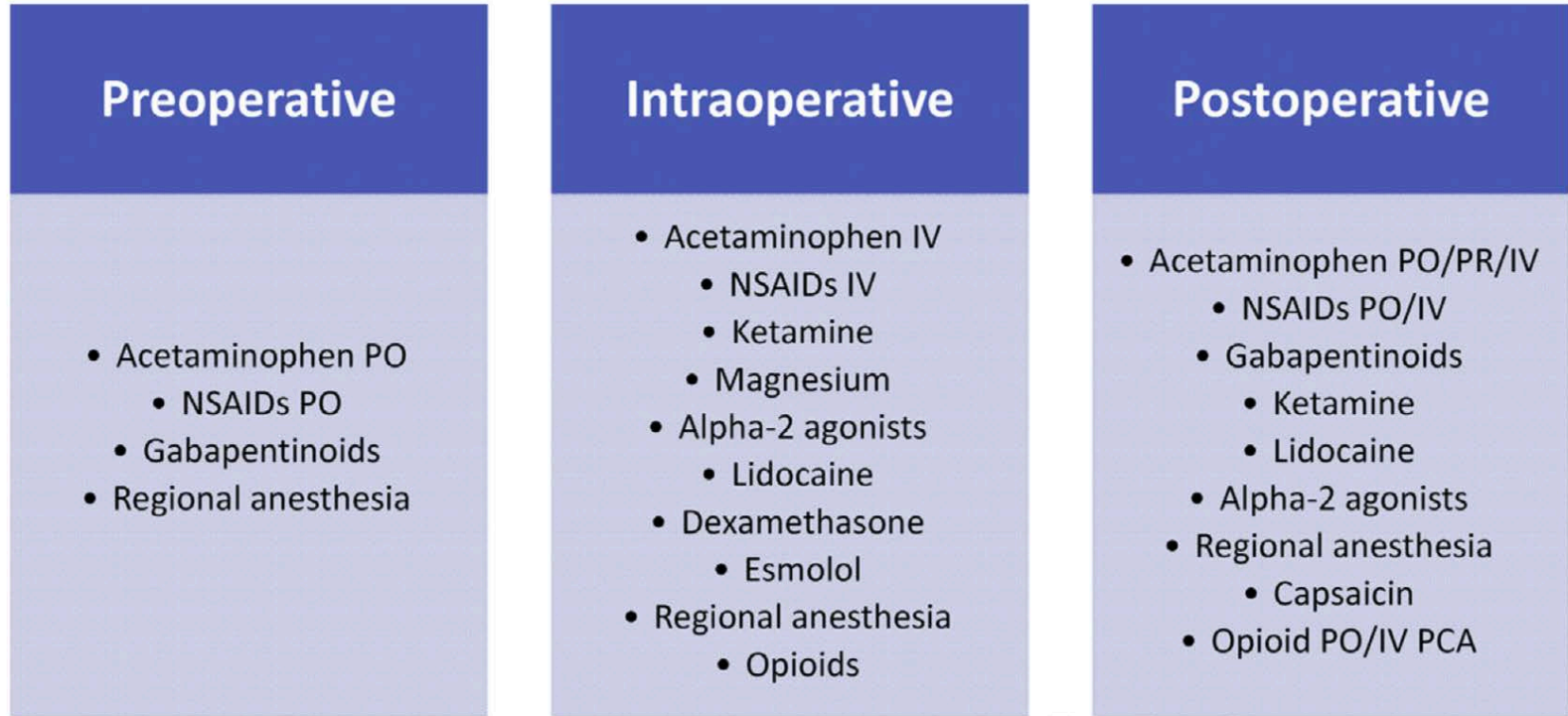
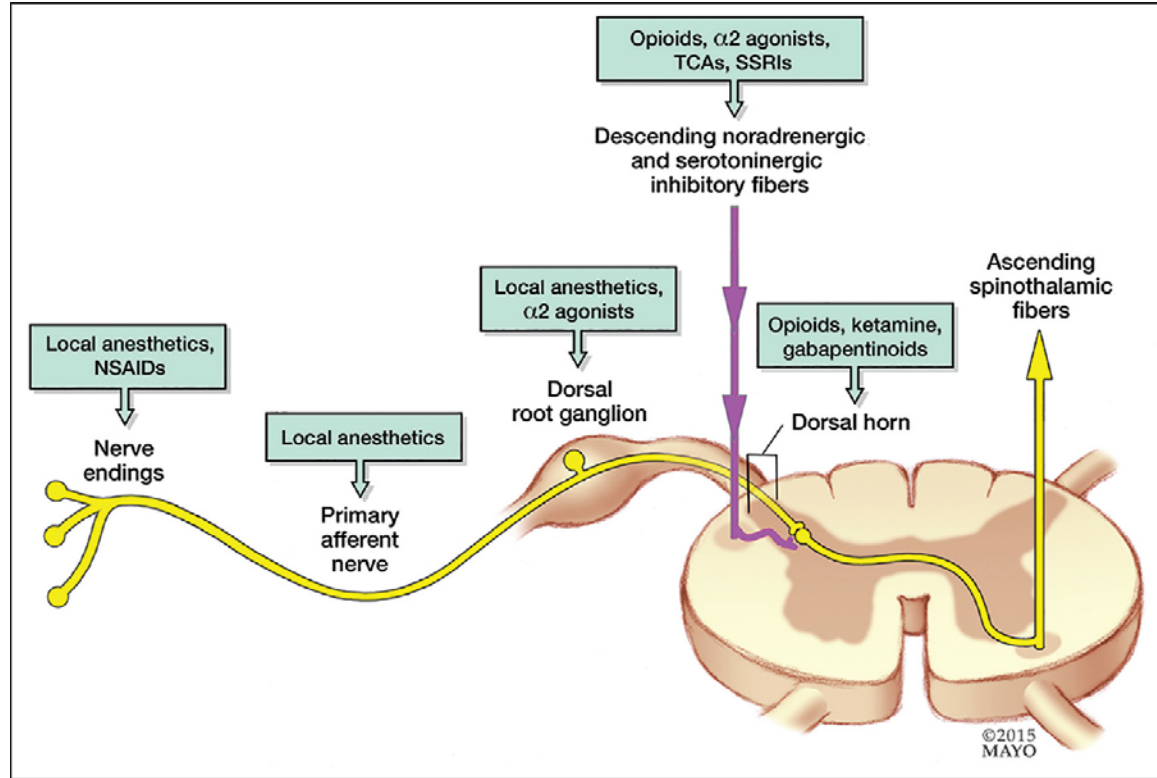


Fig. 3. Pharmacologic approaches to perioperative management of the patient with medication-assisted treatment for substance abuse disorders. IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally; PR, per rectum.

Table 2. Common Regional Analgesic Techniques

Techniques	Advantages	Disadvantages
Neuraxial		
Epidural	Less pain (vs systemic opioids); reduced cardiac/pulmonary morbidity; earlier return of GI tract function; catheter use can continue into the postoperative period	Epidural LA: hypotension; sensory deficits; motor weakness; urinary retention Epidural opioids: nausea; vomiting; pruritus; respiratory depression Technique related: backache; PDPH (spinal); neurologic injury; epidural hematoma
Spinal/intrathecal	Less pain; reduced systemic opioid requirements	Nausea; vomiting; pruritus; respiratory depression
Peripheral		
TAP block	Less pain; reduced systemic opioid requirements in the immediate postoperative period; typically performed under ultrasonographic guidance	Visceral pain; LA toxicity; perforation of the peritoneum with possible damage to visceral structures
Paravertebral block	Less pain; reduced systemic opioid requirements; lower risk of pulmonary complications for patients undergoing thoracotomy; catheter use can continue into the postoperative period; comparable levels of analgesia as epidural analgesia; less hypotension	Possible hypotension; vascular or pleural puncture; possible pneumothorax
Brachial plexus, sciatic/femoral nerve block	Less pain (vs systemic opioids); reduced systemic opioid requirements; catheter use can continue into the postoperative period	Not useful for abdominal or thoracic surgery; LA toxicity
Wound infiltration	Less pain and morphine consumption within the first few hours after surgery; easily administered by the surgeon	Uncertain long-term (≥ 24 h) analgesic efficacy

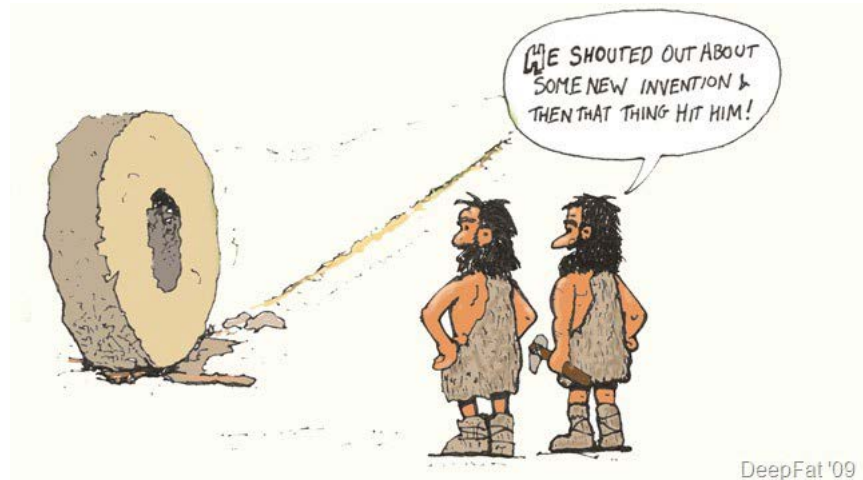
Wick, EC, Grant, MC, Wu, CL. Postoperative multimodal analgesic pain management with nonopioid analgesics and techniques: A review. *JAMA Surgery*. 2017; 152(7): 691-697.



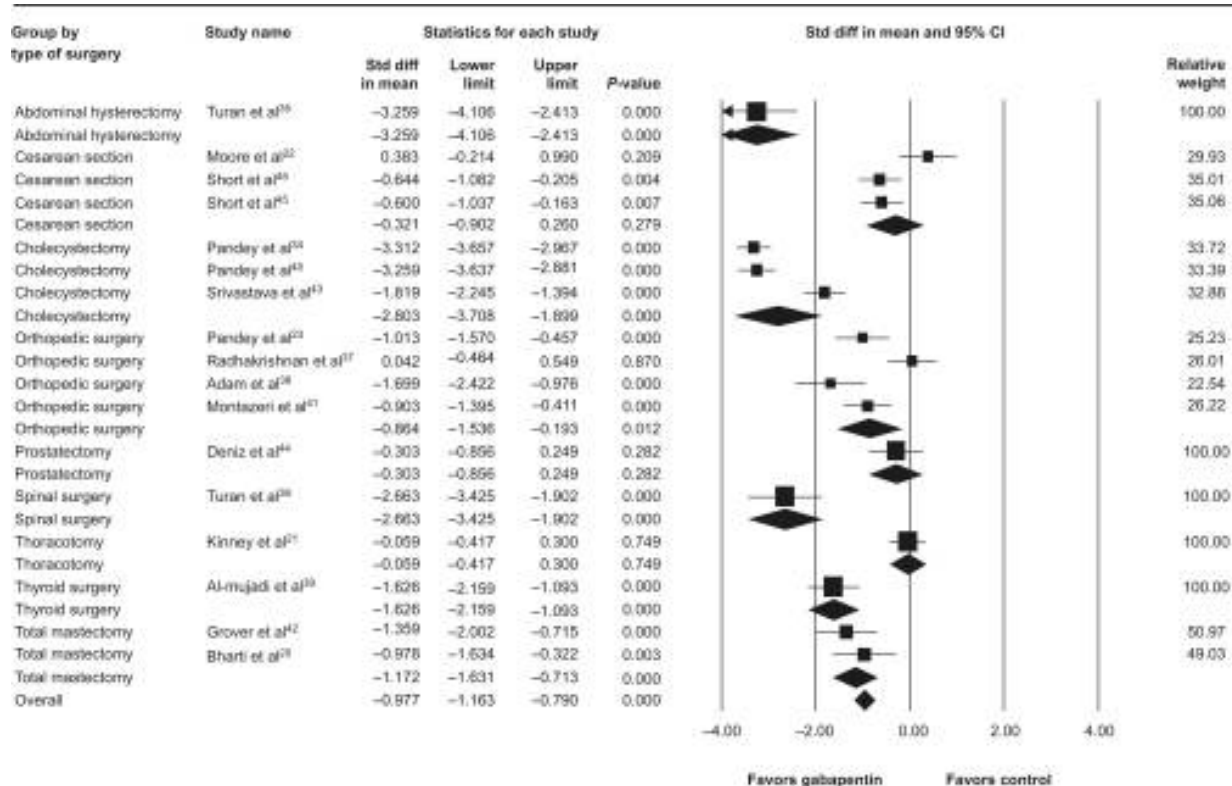
Gorlin AW, Rosenfeld DM, Ramakrishna, H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol.* 2016; 32(2): 160-167.

Preoperative Analgesics

- NSAIDs
 - Selective: celecoxib
 - Nonselective: ibuprofen, ketorolac, indomethacin, naproxen, diclofenac, nabumetone
- Acetaminophen
- Gabapentanoids
 - Gabapentin, pregabalin
- Dexamethasone



Gabapentin



Arumugam S, Lau CSM, Chamberlain RS. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. *J Pain Res.* 2016; 9: 631-640.

Pregabalin

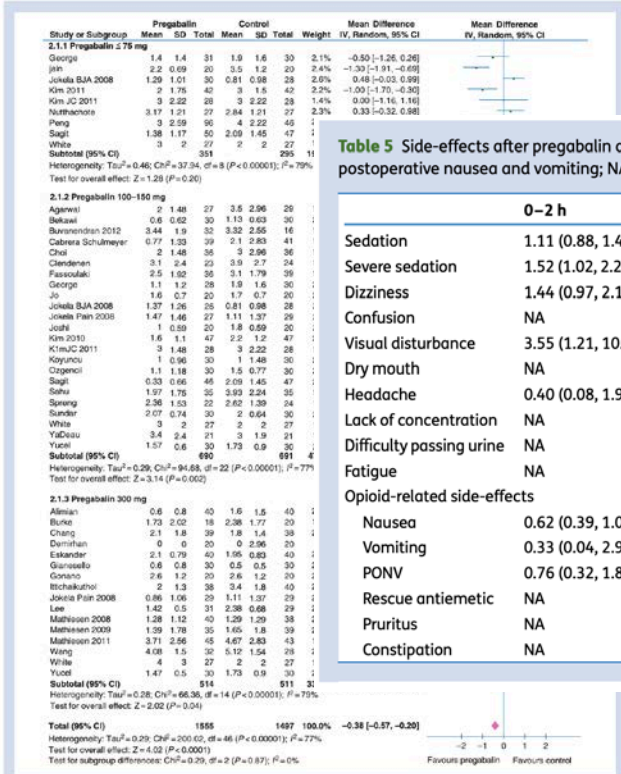


Fig 3 Forest plot for pain scores at 24 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

Mishriky BM, Waldron NH, Habib AS. 2015. Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. *Br J Anaesth*; 114(1): 10-31.

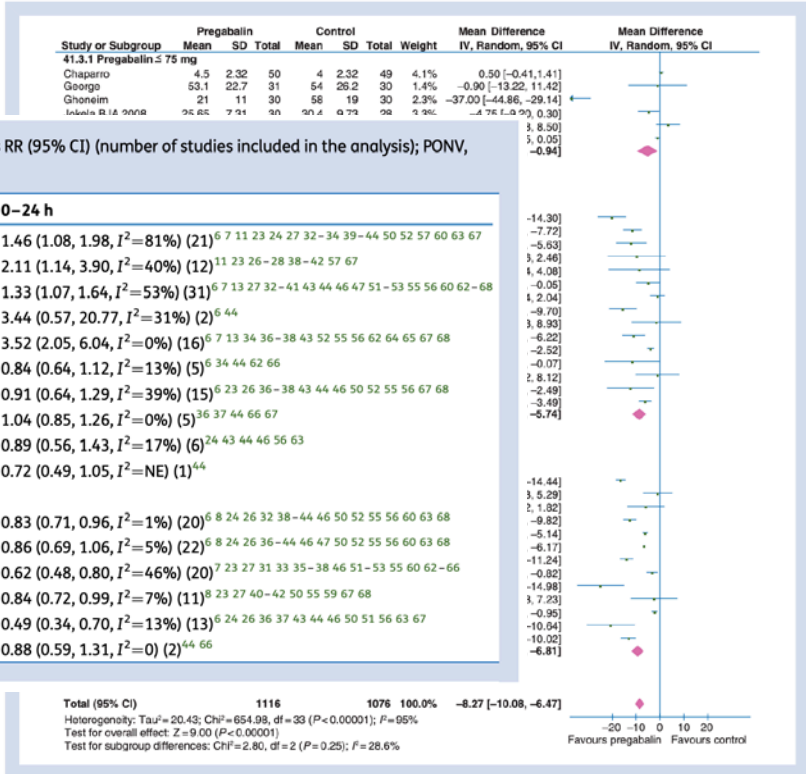
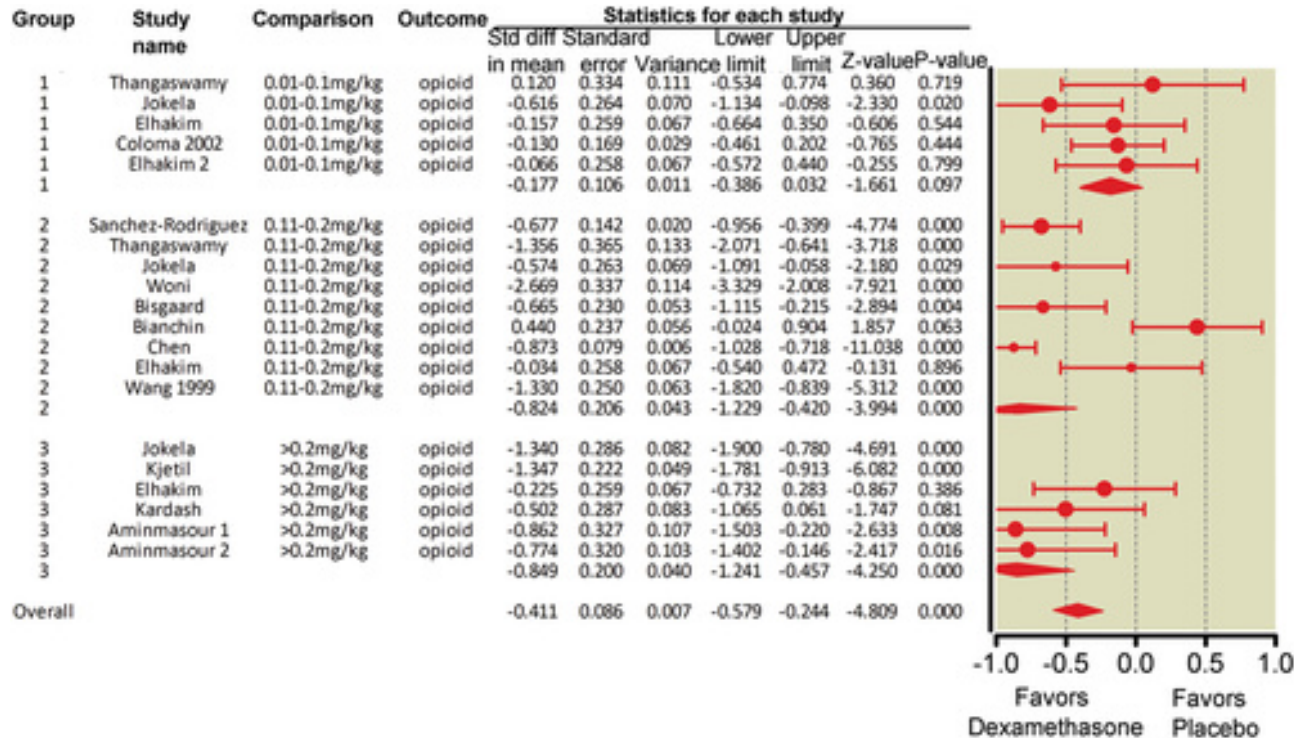


Fig 5 Forest plot for opioid consumption at 24 h. SD, standard deviation; CI, confidence interval; IV, inverse variance.

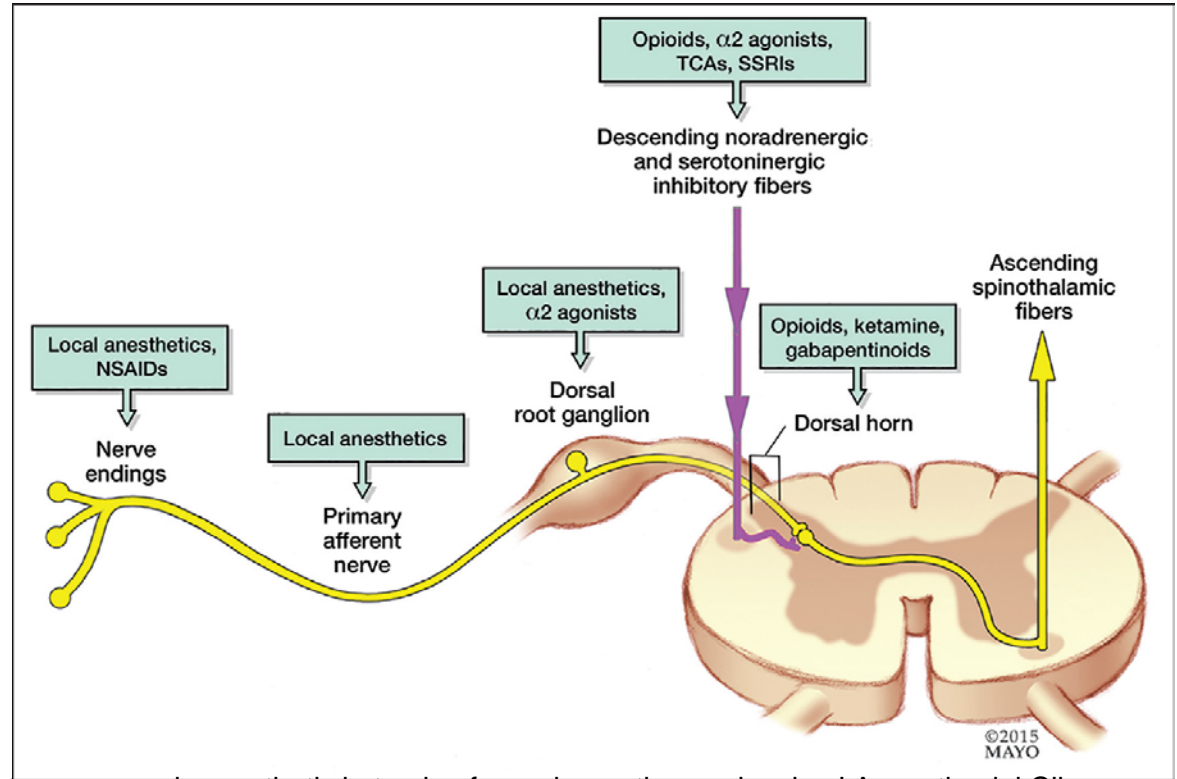
Dexamethasone



DeOliveira GS, Almeida M, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. *Anesthesiology*. 2011; 115(3): 575-588.

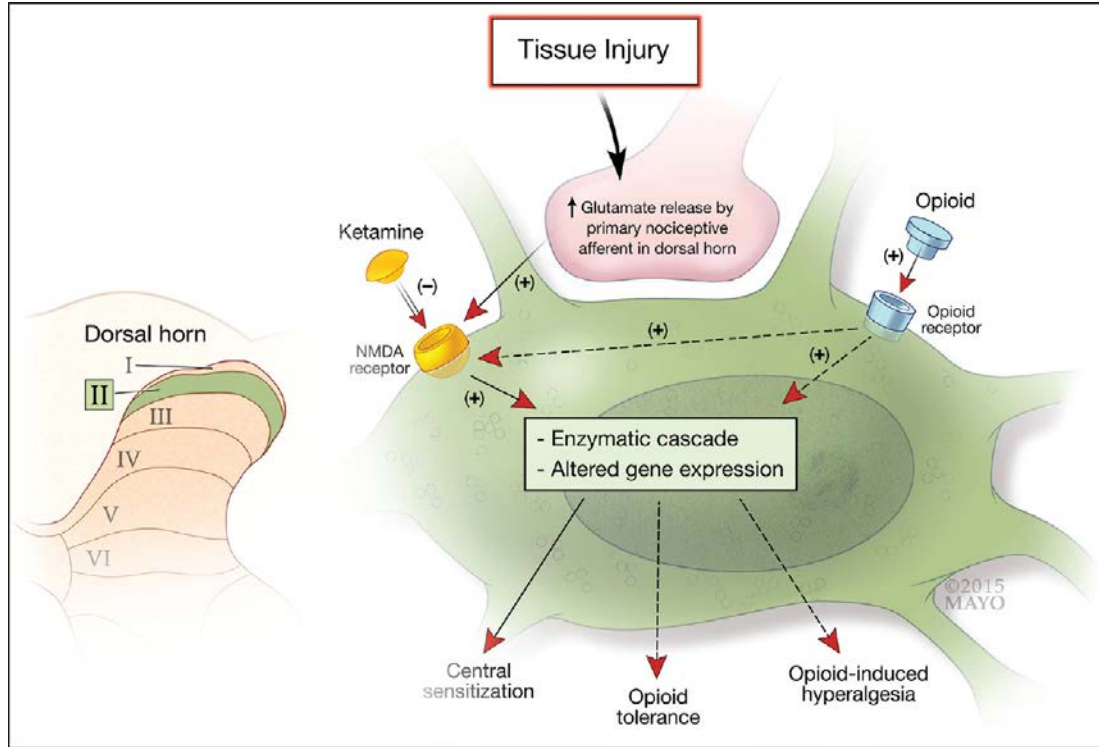
Nonopioid Analgesic Infusions

- Ketamine
- Magnesium
- Lidocaine
- Esmolol
- Dexmedetomidine
- Naloxone



Gorlin AW, Rosenfeld DM, Ramakrishna, H. Intravenous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin Pharmacol. 2016; 32(2): 160-167.

Ketamine



DeOliveira GS Jr, Benzon HT, White PF. The role of nonopioid analgesic infusions in the management of postoperative pain. In Hadzic A, ed. *Hadzic's Textbook of Regional Anesthesia and Acute Pain Management*. New York: McGraw-Hill Education; 2017:1226-1234.

Gorlin AW, Rosenfeld DM, Ramakrishna, H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin*

ASRA/AAPM/ASA Consensus Guidelines

TABLE 4. A Summary of Results of Systematic Reviews and Meta-Analyses on the Role of Ketamine as an Adjunct for Perioperative Analgesia

Authors and Year	No. RCTs Included	Goal of Study	Conclusions	Comments
Laskowski et al ² (2011)	70	Determine the effect of IV ketamine on postoperative analgesia	Ketamine reduced pain scores and opioid consumption; greatest efficacy in thoracic, upper abdominal, major orthopedic surgeries	Effect independent of type of intraoperative opioid, dose, or timing of ketamine Hallucinations and nightmares more common with ketamine
Jouguelet-Lacoste et al ⁴¹ (2015)*	39	Determine the effect of an IV single dose or infusion of ketamine on postoperative analgesia	Ketamine reduced pain scores and opioid consumption for the first 48 postoperative hours	Evaluated a low-dose infusion rate of less than 1.2 mg/kg per hour with or without bolus dose of 1 mg/kg
Wang et al ⁴² (2016)	36	Determine the effect of IV ketamine added to opioid IV-PCA	Ketamine reduced pain scores, opioid consumption, and PONV in the first 72 postoperative hours	Adverse events of ketamine were probably underreported
Assouline et al. ⁴³ (2016)	19	Determine the effect of ketamine added to an opioid IV-PCA in surgical patients	Ketamine reduced pain scores, opioid consumption and PONV at 24 hours.	No significant change in the incidence of hallucinations. Data insufficient to draw conclusions on respiratory adverse events or a dose-response relationship.
Pendi et al ³⁵ (2018)	14	Determine the effect of ketamine on analgesia after spine surgery	Ketamine reduced pain scores and opioid consumption for the first 24 postoperative hours	No increase in adverse effects with ketamine

*Evidence-based review.

PONV indicates postoperative nausea and vomiting.

Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med.* 2018; 43(5): 456-466.

ASRA/AAPM/ASA Consensus Guidelines

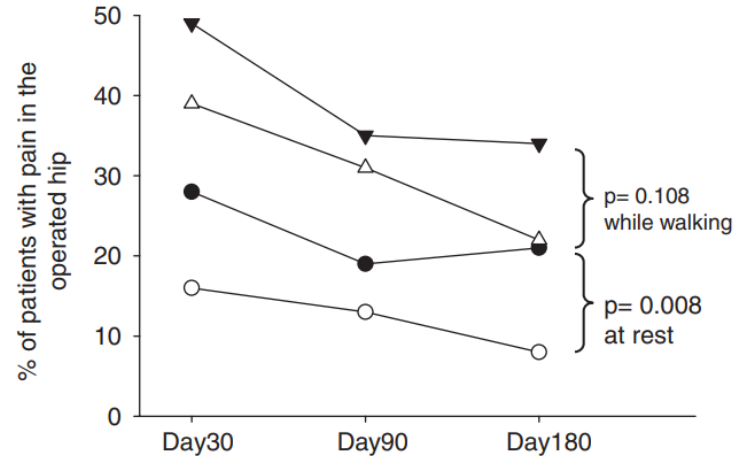
- Who benefits?
 - Pts undergoing surgery with severe postoperative pain expected
 - Pts already opioid tolerant/dependent or with an acute exacerbation of chronic condition
 - Pts at risk for opioid-induced respiratory depression
- How much?
 - 0.3-0.5mg/kg +/- 0.1-0.5mg/kg/hour infusion per guidelines (Grade C level rec)
- When to avoid?
 - Poorly controlled CV disease, hepatic dysfunction, elevated IOP or ICP, hx psychosis, pregnancy

Ketamine Beyond the OR

- Decreased opioid consumption when compared to placebo when continued postoperatively with no significant change in side effects.

Table 4. Postoperative Side Effects Between Day 0 and Day 7

	Placebo (N = 75)	Ketamine (N = 79)	P*
Risk for PONV according to Apfel score ^{19,20} (%)	47 ± 13	48 ± 14	0.58
Patients receiving ondansetron at Day1 (%)	33	41	0.36
Patients receiving ondansetron at Day 7 (%)	39	48	0.24
PONV described by patients at Day 7 (%)	53	42	0.15
Nausea from Day 0 to Day 7 (%)	48	34	0.08
Vomiting from Day 0 to Day 7 (%)	24	25	0.99
Pruritus (%)	17	23	0.40
Trouble with vision (%)	9	17	0.13
Urinary retention (%) ^a	10	9	0.99
Nightmares (%)	17	19	0.79
Pleasant dreams (%)	13	9	0.38
Hallucinations (%)	11	8	0.51



Remerand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg*. 2009; 109(6): 1963-1971.

Ketamine in Opioid Tolerant Patients

Table 6. Ketamine Effect Stratified According to Preoperative Morphine Use

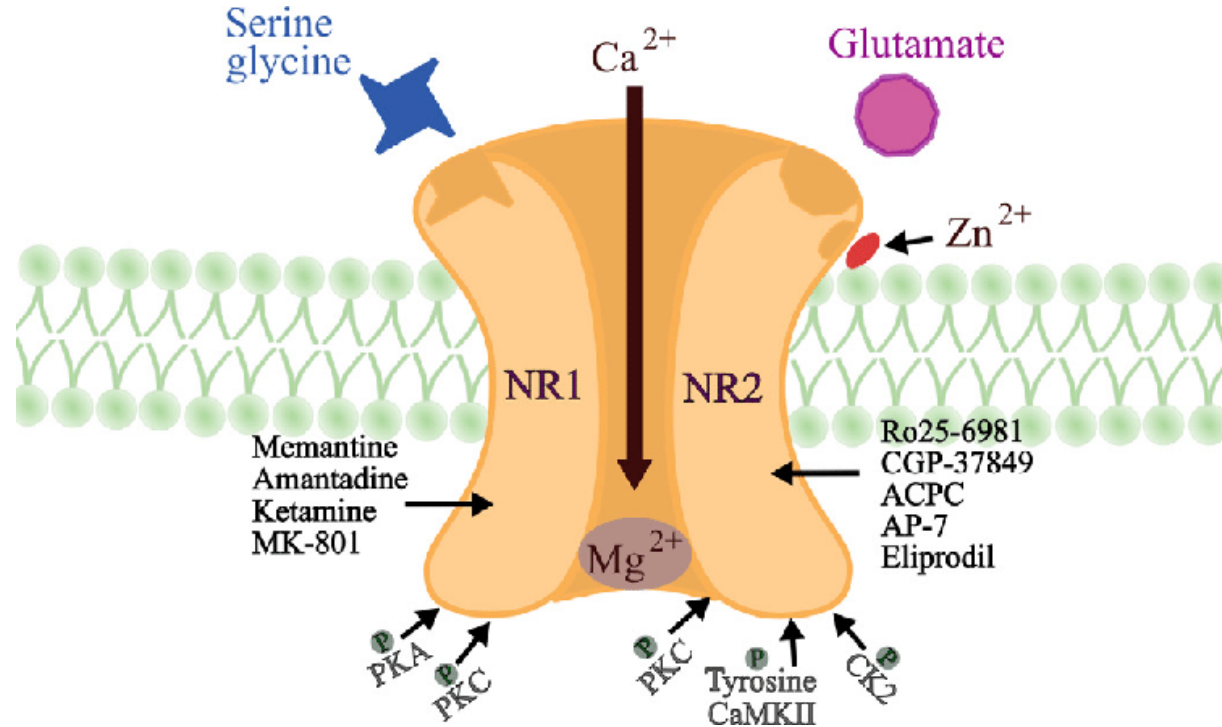
Stratified by Preoperative Morphine Equivalent	Treatment			Placebo			P Value
	N	Mean (mg)	SD	N	Mean (mg)	SD	
≥0.556 mg/hr intravenously							
24-hr ME	17	168.8	94.4	22	302.5	216.8	0.014
48-hr ME	16	241.3	145.7	22	471.3	441.3	0.031
<0.556 mg/hr intravenously							
24-hr ME	34	129.3	73.8	27	119.9	59	0.58
48-hr ME	33	172.7	83.2	25	166.3	86.8	0.78

ME = morphine equivalent.

Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*. 2010; 113(3): 639-646.

Magnesium

- 2nd most common intracellular ion
- NMDA antagonism is mechanism of analgesia

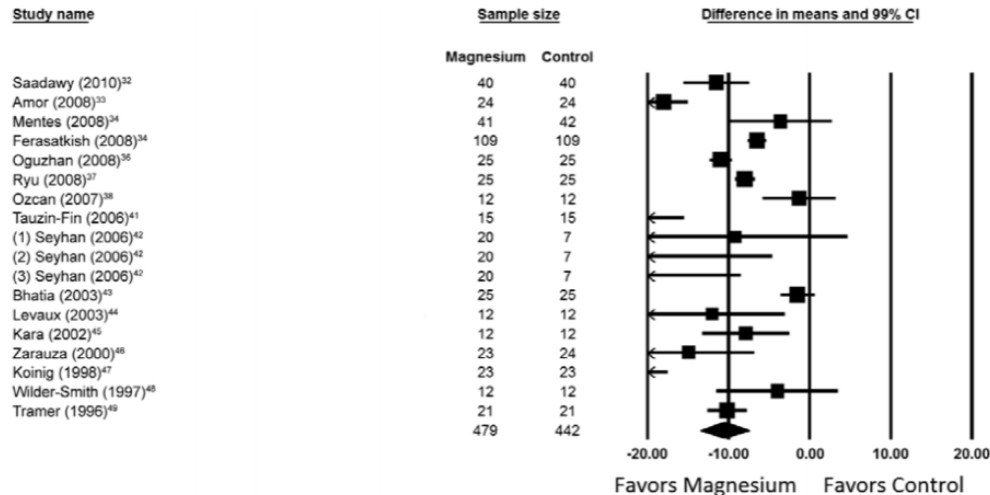


DeOliveira GS Jr, Benzon HT, White PF. The role of nonopioid analgesic infusions in the management of postoperative pain. In Hadzic A, ed. *Hadzic's Textbook of Regional Anesthesia and Acute Pain Management*. New York: McGraw-Hill Education; 2017:1226-1234.

Réus G, Abelaira H, Tuon, T, et al. Glutamatergic NMDA Receptor as Therapeutic Target for Depression. 2015. doi: 10.1016/bs.apcsb.2015.10.003.

DeOliveira et al Meta-analysis

- 30-50mg/kg bolus followed by 10-25mg/kg/hr
- 20 studies, 1257 patients
 - Cases included cardiothoracic, open abdominal, orthopedic/spine and endocrine

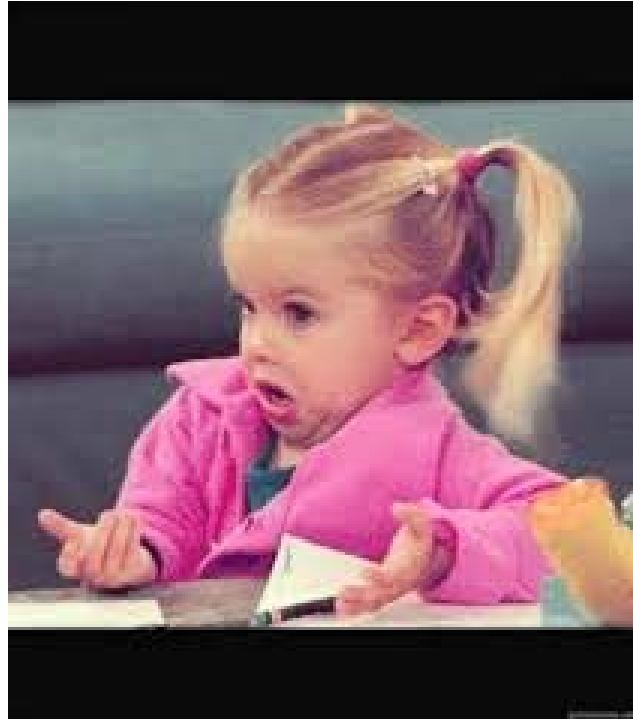


De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: A meta-analysis of randomized controlled trials. *Anesthesiology*. 2013; 119(1): 178-190.

Albrecht et al Meta-analysis

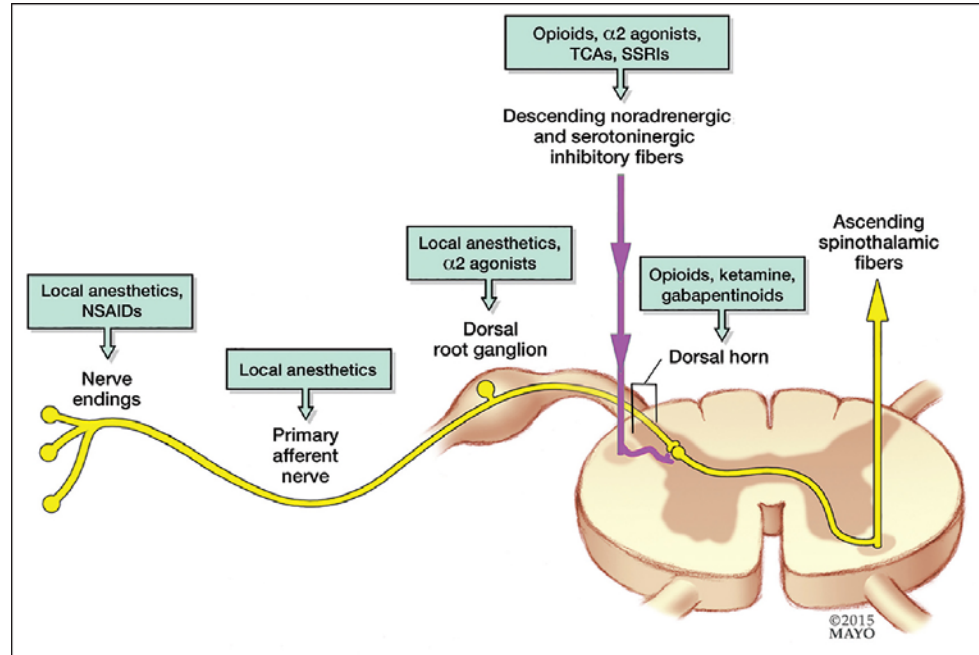
- 25 trials, 1461 patients
 - Cases included abdominal, gynecologic, and orthopedic surgeries
 - Various protocols including bolus (30-50 mg/kg), bolus + infusion (6-25 mg/kg/hr), or infusion alone
- No correlation with total dose or protocol followed and cumulative opioid use
- Decreased morphine consumption occurred within the first 24 hours, but not beyond
- Very small decreases in postoperative pain scores (4-9/100)

Is Mg²⁺ supplementation all that is necessary?



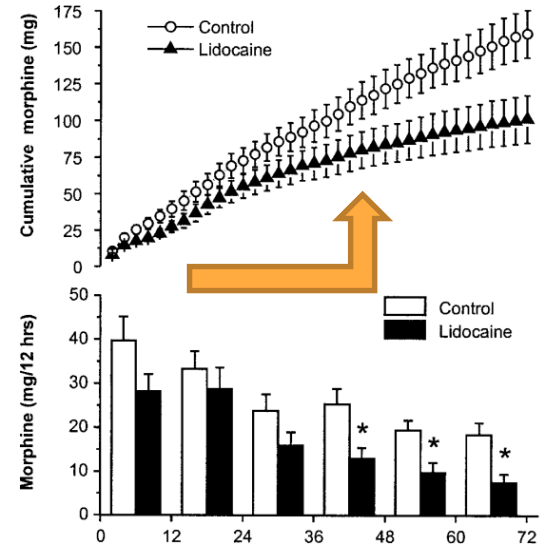
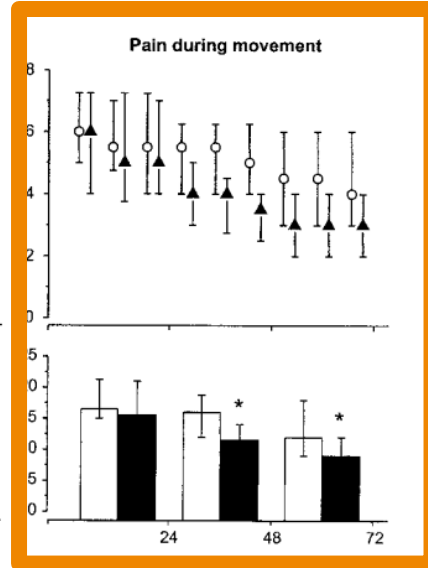
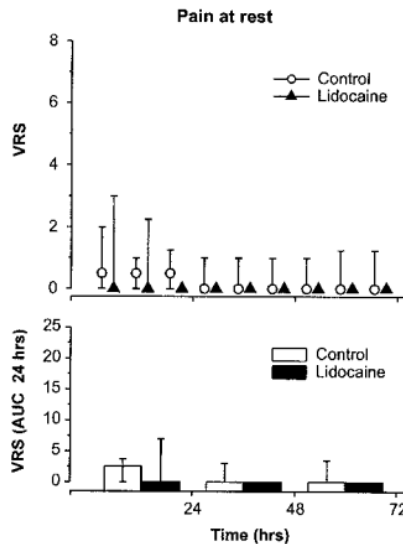
Lidocaine

- Short-acting, amino-amide local anesthetic with analgesic, antihyperalgesic and anti-inflammatory properties



Koppert et al RCT in Major Abdominal Surgeries

- 40 patients without chronic pain history undergoing major abdominal surgery
 - Study arm received 1.5mg/kg bolus post-induction, 1.5mg/kg/hr infusion pre-incision, and continued until 60 minutes after closure.



Koppert W, Weigand M, Neumann F, et al. Perioperative intravenous lidocaine has preventative effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth Analg*. 2004; 98(4): 1050-1055.

Cochrane Review on Continuous IV Lidocaine

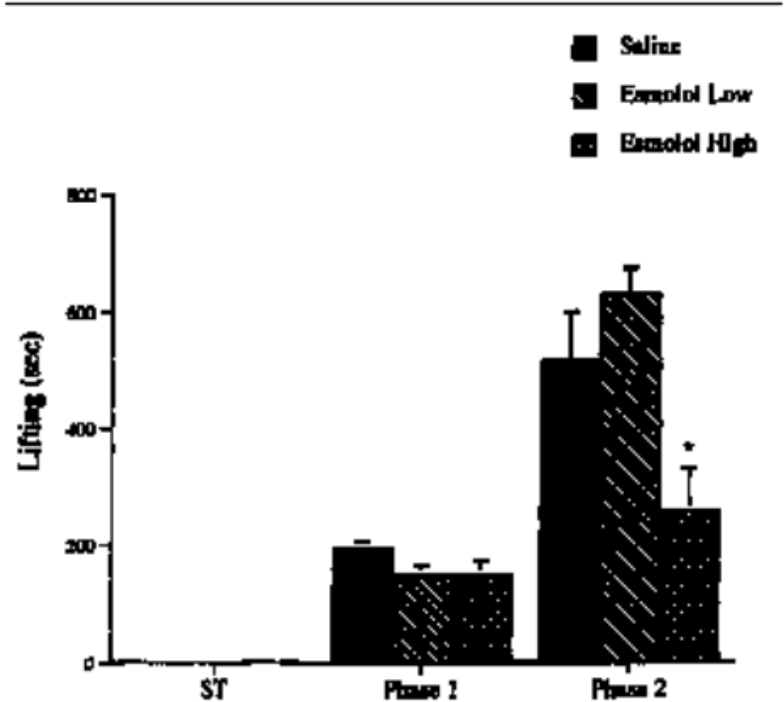
- 68 trials in 2017 update
 - Open abdominal, lap abdominal, and other surgeries; Most included 1.5 mg/kg bolus followed by 1-5mg/kg/hr started before incision with termination at end of surgery up to several days
- Small decrease in pain scores at rest with IV lidocaine in early postop (1-4 hrs) and intermediate period (24 hrs), but not late (48 hrs)
- Decreased intraoperative, early postop and overall opioid consumption
- Small decrease in incidence of ileus and time to first flatus and first bowel movement
- Shortened length of stay, higher patient satisfaction, decreased nausea (no difference in vomiting)

Limitations

- Ideal versus actual body weight?
- Route of administration? Thoracic epidural analgesia still preferable to IV lidocaine infusion if possible.

Esmolol

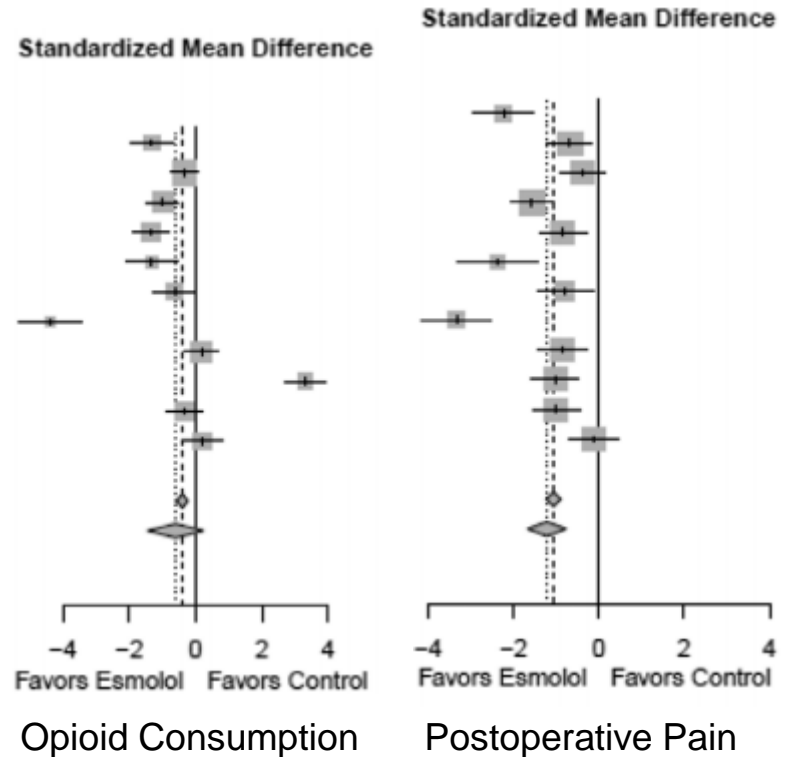
- Short-acting β_1 -receptor antagonist that is rapidly metabolized by plasma esterases
- Rat models suggest that the sympathetic blockade from esmolol may attenuate the inflammatory response to pain



Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. *Can J Anaesth.* 2001; 48(1): 59-64.

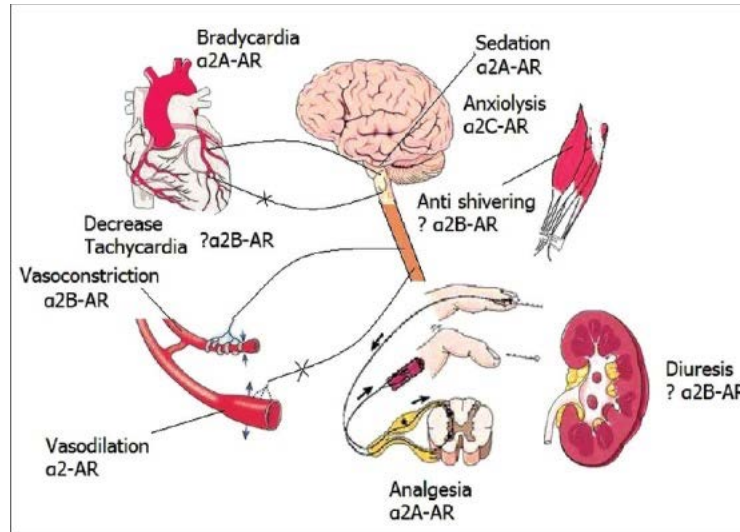
Gelineau et al Systematic Review and Meta-Analysis

- 23 RCTs including 1339 patients
 - 6 laparoscopic gynecologic, 8 laparoscopic abdominal, 2 unspecified abdominal, 3 orthopedic, 2 hernia repair, 2 septorhinoplasty and 1 total abdominal hysterectomy studies
- Esmolol regimen: 0.5-1mg/kg bolus followed by 0.5-50 mcg/kg/min infusion



Dexmedetomidine

- Alpha-2 adrenergic agonist, more selective than clonidine
- Sedative, sympatholytic and analgesic activity with minimal respiratory depressant effects



Bielka et al RCT

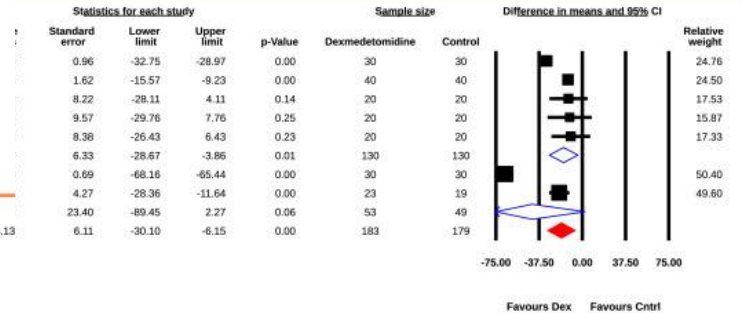
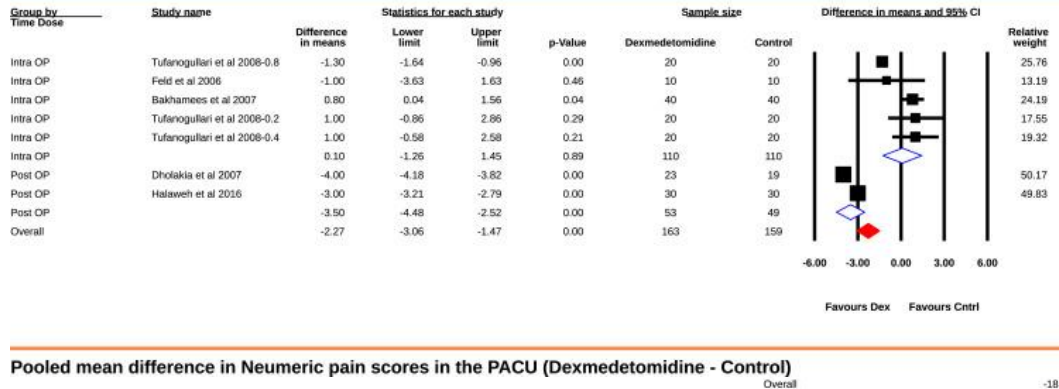
- 60 patients undergoing laparoscopic cholecystectomy
- Study arm received dexmed 0.5 mcg/kg/hr infusion from induction to emergence

Outcome	Group D	Group C	p-value
Postoperative morphine consumption in 24 h (mg)	5 (0–10)	15 (10–20)	0.001 ²
Cumulative morphine consumption (mg)	15 (10–25)	30 (20–30)	0.001 ²
Severe pain incidence; n (%)	1 (3)	7 (23)	0.04 ¹
Time to first use of rescue analgesia (min)	180 (130–210)	80 (60–120)	0.001 ²
Time to extubation (min)	10 (5–10)	20 (15–20)	0.001 ²
Postoperative pain level (VRS score)			
3 h	3 (3–4)	4 (4–5)	0.067 ²
6 h	4 (4–5)	5 (4–5)	0.08 ²
12 h	3 (3–3)	4 (4–5)	0.33 ²
24 h	4 (4–4)	4 (4–4)	0.72 ²
Intraoperative fentanyl consumption (mg)	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.03 ²
Persistent postsurgical pain incidence; n (%)	1 (3)	10 (33)	0.005 ¹

Bielka K, Kuchyn I, Babych V, Martycshenko K, Inozemtsev O. Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic cholecystectomy: A randomized controlled trial. *BMC Anesthesiol.* 2018; 18(1): 44.

Singh et al Meta-Analysis

- 6 trials with 362 patients undergoing bariatric surgery
 - Protocols ranged from no bolus to 1 mcg/kg and infusions from 0.2 to 0.8 mcg/kg/hr, some occurring intraoperatively, some only postoperative



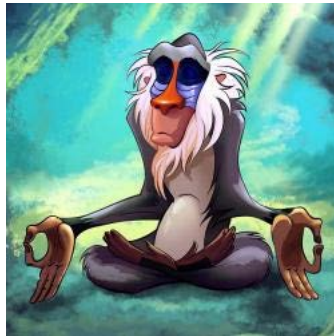
Singh PM, Panwar R, Borle A, Mulier JP, Sinha A, Goudra B. Perioperative analgesic profile of dexmedetomidine infusions in morbidly obese undergoing bariatric surgery: a meta-analysis and trial sequential analysis. *Surg Obes Relat Dis.* 2017; 13(8): 1434-1446.

Cochrane Review

- 7 trials including 492 patients all undergoing abdominal surgery
 - 0.5-1 mcg/kg bolus followed by 0.2-0.8 mcg/kg/hr
- Modest reduction in 3 and 24 hour morphine consumption in dexmedetomidine group
- Clinically insignificant decrease in pain scores

Postoperative

- Continue Acetaminophen, NSAIDs, Gabapentinoids?
- Can continue some perioperative infusions (ketamine, lidocaine, dexmedetomidine)
- Consider alternative modalities
 - TENS units, massage, acupuncture, capsaicin, hot/cold packs, pet therapy, aromatherapy, distraction, meditation



Scheduled Medications

Medication	Preop Dose	Postop Schedule
Acetaminophen	650-1000mg	650-1000mg q6-8h
Ibuprofen	400-800mg	400-800mg q6-8h
Celecoxib	400mg	200mg BID
Ketorolac	15-30mg IV	15mg q6h IV
Gabapentin	300-600mg	300-1200mg q8h
Pregabalin	100-300mg	150mg BID
Dexamethasone	7-10mg intraoperatively	

Intraoperative/Postoperative Infusions

Medication	Bolus Dose	Infusion Rate
Ketamine	0.3-0.5 mg/kg post-induction	0.1-0.5 mg/kg/hr intraoperatively 10-12 mg/hr postoperatively
Magnesium	30-50 mg/kg bolus	10-25 mg/kg/hr *Limited evidence for benefit of infusion
Lidocaine	1.5 mg/kg bolus post-induction	1-2 mg/kg/hr *Based on ideal body weight
Esmolol	0.5-1 mg/kg post-induction	0.5-50 mcg/kg/min *Limited evidence for benefit
Dexmedetomidine	0.5-1 mcg/kg bolus *Infuse over 10 minutes	0.2-0.8 mcg/kg/hr *Can continue into early PACU stay
Naloxone	No bolus	0.25 mcg/kg/hr

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