

Decreasing Intraoperative Opioid Consumption In The Opioid Epidemic Era

MSQC/ASPIRE COLLABORATIVE
MEETING

APRIL 28TH 2017

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Disclosure

Funded Research

- Hemosonics
- Merck

Outline

- Opioid Epidemic in Numbers
- Epidemiology of Misuse, Abuse and Diversion
- The Perioperative Period-Priming Patients for Misuse, Abuse and Dependence?
- Perioperative Strategies:
 - Intravenous Lidocaine
 - Ketamine
 - Dexmedetomidine
 - Enhanced Recovery Programs
- Future Research
- Conclusion


Economic Impact of the Opioid Epidemic:


\$ 55 billion in health and social costs related to prescription opioid abuse each year¹


\$ 20 billion in emergency department and inpatient care for opioid poisonings²


Source: Pain Med. 2011;12(4):657-67.¹
2013;14(10):1534-47.²

On an average day in the U.S.:

 More than 650,000 opioid prescriptions
dispensed¹

 3,900 people initiate nonmedical use of
prescription opioids²

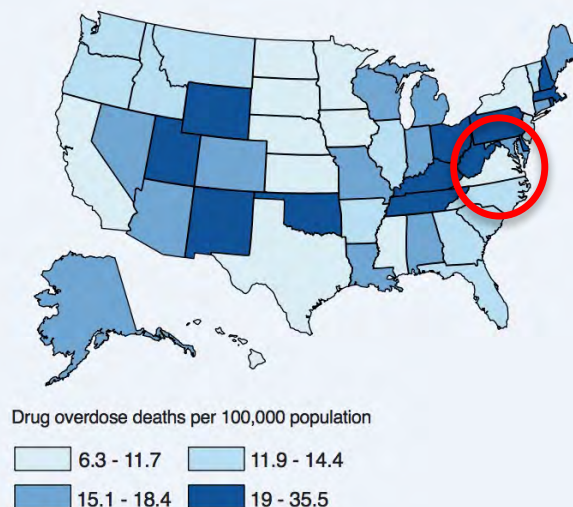
 580 people initiate heroin use²

 78 people die from an opioid-related overdose^{*3}

*Opioid-related overdoses include those involving prescription opioids and illicit opioids such as heroin

Source: IMS Health National Prescription Audit¹ / SAMHSA National
Survey on Drug Use and Health² / CDC National Vital Statistics System³

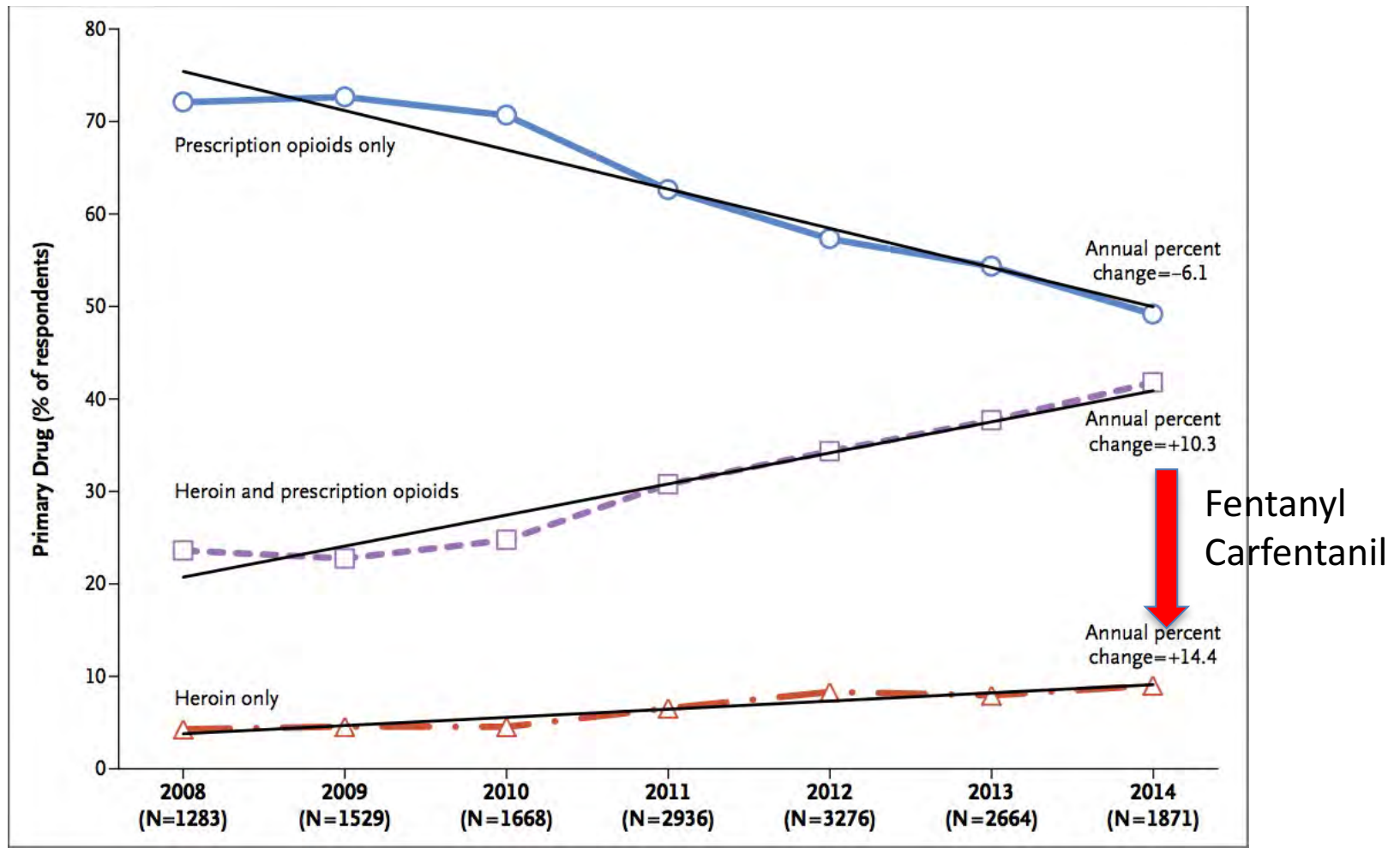
Drug overdose death rates, United States, 2014*



*Age-adjusted death rate per 100,000 population

Source: CDC National Vital Statistics System

Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States



NEJM 373;18, October 29, 2015

Deaths Involving Fentanyl Rise As Curbing Illicit Supply Proves Tough

November 18, 2016 · 3:27 PM ET

Heard on [All Things Considered](#)

MARTHA BEBINGER

FROM **90.9 wbur**
BOSTON'S NPR NEWS STATION

AROUND THE NATION

Fentanyl Contributes To Record Drug Overdoses In New York City

December 21, 2016 · 5:06 AM ET

Heard on [Morning Edition](#)

MARY HARRIS

FROM **WNYC** wnyc.org
93.9 fm
am 820

UNIVERSITY
of VIRGINIA
HEALTH SYSTEM

Heroin Epidemic Is Yielding to a Deadlier Cousin: Fentanyl

By KATHARINE Q. SEELYE MARCH 25, 2016



Two Pa. overdoses linked to use of elephant sedative; state issues warning

 **DEA** UNITED STATES
Drug Enforcement Administration

HOME ABOUT CAREERS OPERATIONS DRUG INFO PREVENTION

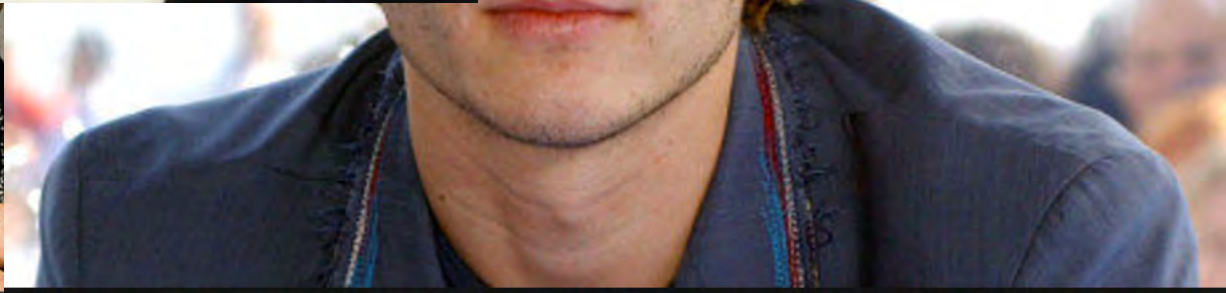
About » Office Locations » Headquarters » Headquarters News

HEADQUARTERS NEWS

September 22, 2016
Contact: DEA Public Affairs
(202) 307-7977

DEA Issues Carfentanil Warning to Police and Public
Dangerous opioid 10,000 times more potent than morphine and 100 times more potent than fentanyl





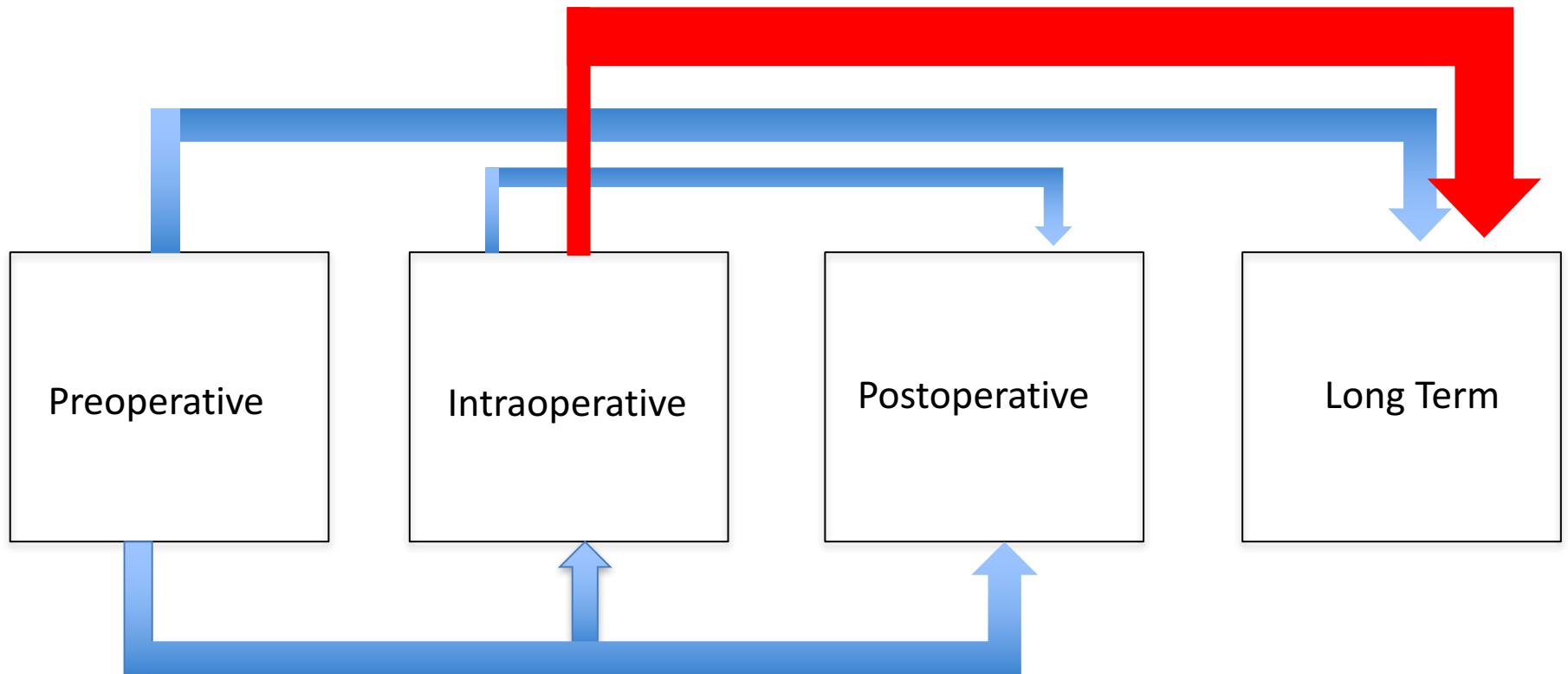
The New York Times

2 of a Farmer's 3 Children Overdosed. What of the Third — and the Land?

By JACK HEALY MARCH 12, 2017



Surgery and Opioid Use



Impact of Surgery On Chronic Opioid Dependence

- Increasing evidence that surgery can predispose to chronic opioid use
- This phenomena noted in opioid-naïve patients
- Patient and surgery-specific risk factors
- Approximately 3.1% of opioid-naïve patients continue to use opioids 90 days after major surgery

Sun et al. JAMA Intern Med. 2016;176(9):1286-1293
Clark et al. BMJ 2014;348:g1251

Impact of Surgery On Chronic Opioid Dependence

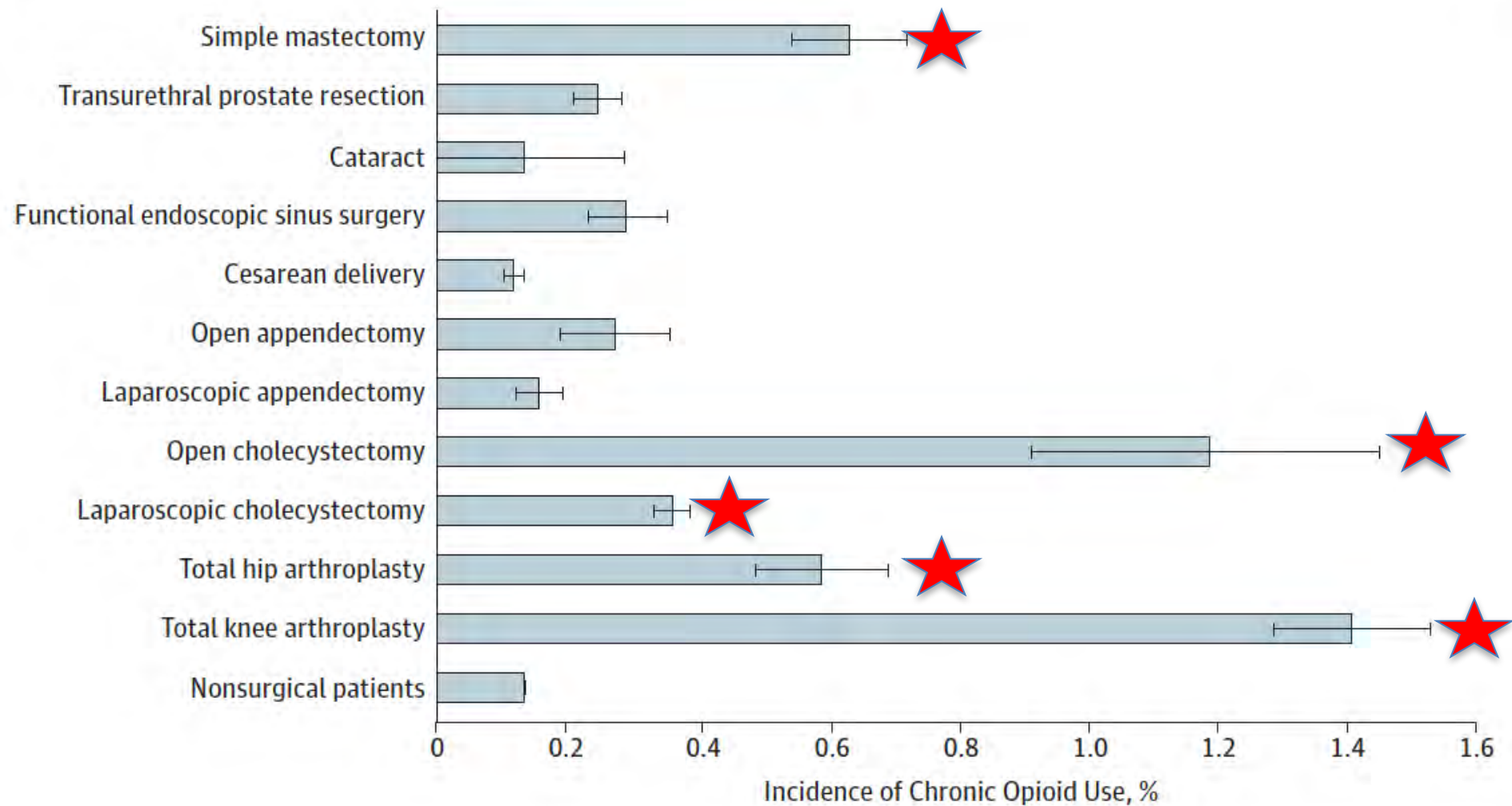
- Retrospective administrative health claims analysis
- January 1, 2001 to December 31, 2013
- 11 surgical procedures
- Multivariable logistic regression analysis to control for possible confounders
- Chronic opioid use: filled 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days
- Nonsurgical cohort: filled 10 or more prescriptions or more than 120 days' supply following a randomly assigned "surgery date."
- **641 941 opioid-naïve surgical patients**
- **18 011 137 opioid-naïve nonsurgical patients**

Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients

Risk Factor	Odds Ratio (SE) ^a	P Value
Demographics		
Male	1.34 (0.0648)	<.001
Age >50 y	1.74 (0.0942)	<.001
Preoperative drug use		
Benzodiazepines	1.82 (0.1049)	<.001
Antidepressants	1.65 (0.0928)	<.001
Antipsychotics	1.14 (0.1330)	.28
Medical comorbidities		
Depression	1.15 (0.0717)	.03
Psychosis	1.03 (0.2094)	.89
Alcohol abuse	1.83 (0.2834)	<.001
Drug abuse	3.15 (0.5385)	<.001

Sun et al. JAMA Intern Med. 2016;176(9):1286-1293.

Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients



Sun et al. JAMA Intern Med. 2016;176(9):1286-1293.

Impact of Surgery On Chronic Opioid Dependence

- Population based retrospective cohort study
- 1 April 2003 and 31 March 2010
- 39,140 opioid naïve patients aged 66 years or older who had major elective surgery, including cardiac, intrathoracic, intra-abdominal, and pelvic procedures
- Prolonged opioid use after discharge: ongoing outpatient prescriptions for opioids for more than 90 days after surgery

Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients

Factors	Odd ratio (95% CI)	P value
Age Group (66-75 years)	1.63 (1.08 to 2.46)	0.03
Open lung resection	2.58 (2.03 to 3.28)	< 0.001
Minimally invasive lung resection	1.95 (1.36 to 2.78)	< 0.001
Benzodiazepines (Preoperatively)	1.26 (1.07 to 1.48)	0.005
SSRIs (Preoperatively)	1.41 (1.10 to 1.80)	0.01

Clark et al. BMJ 2014; 348:g1251.

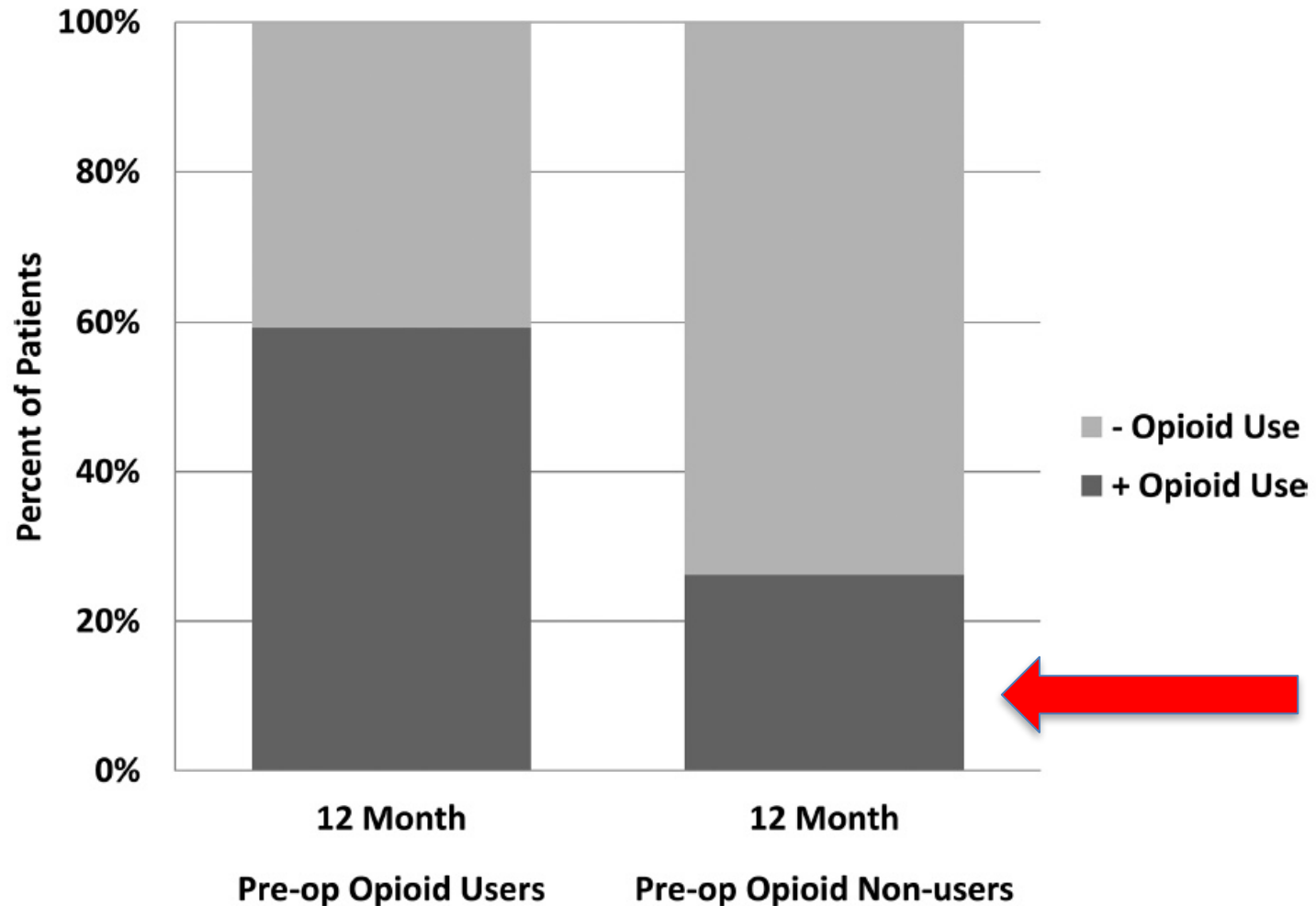
Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery

- Major spine surgery between 2011-2016
- Perioperative opioid/non-opioid use
- Determined opioid use 1, 6 and 12 months after surgery
- 1, 478 patients reviewed
 - 27.6% opioid-naïve preoperatively
 - 72.4 % required opioids preoperatively

Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery

- Mean preoperative opioid dose: 32.8 ± 46.3 mg
- Opioid naïve group
 - **21 %** of patients had a prescription for opioids 12 months after surgery
- Non opioid-naïve group
 - **39%** of patient had NO prescription for opioids 12 months after surgery
- Odds of being a chronic opioid user is higher for non-opioid naïve patients than opioid-naïve patients $\chi^2(1) = 164.01, p < 0.001$

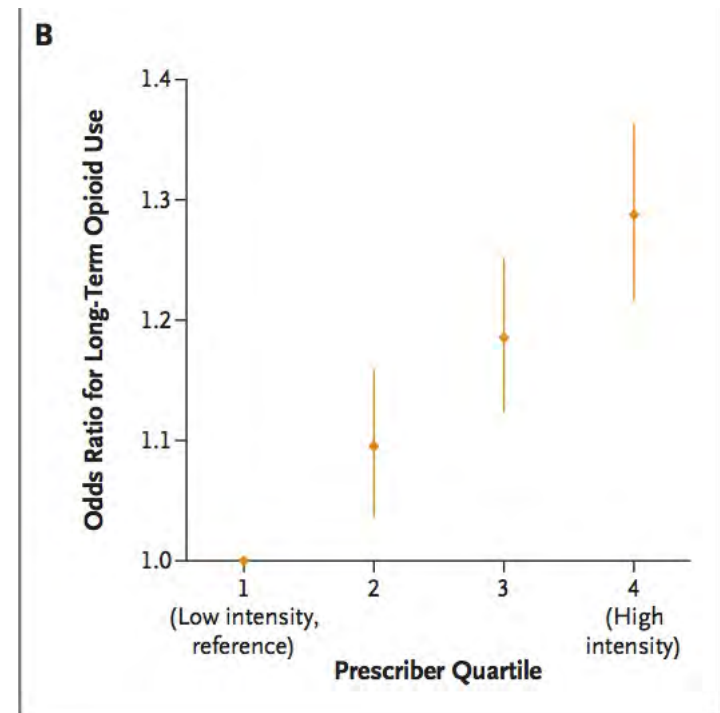
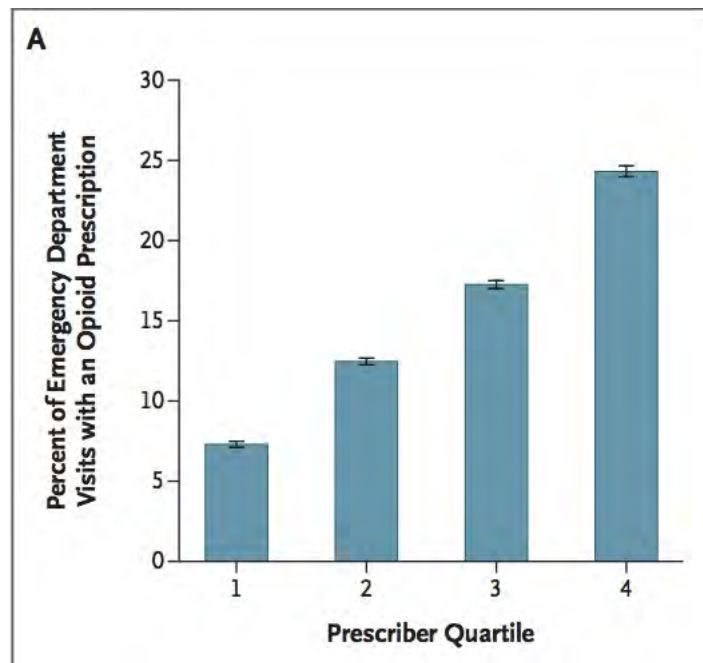
Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery



Armaghani et al. Spine 2014;39:E1524–E1530

Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use

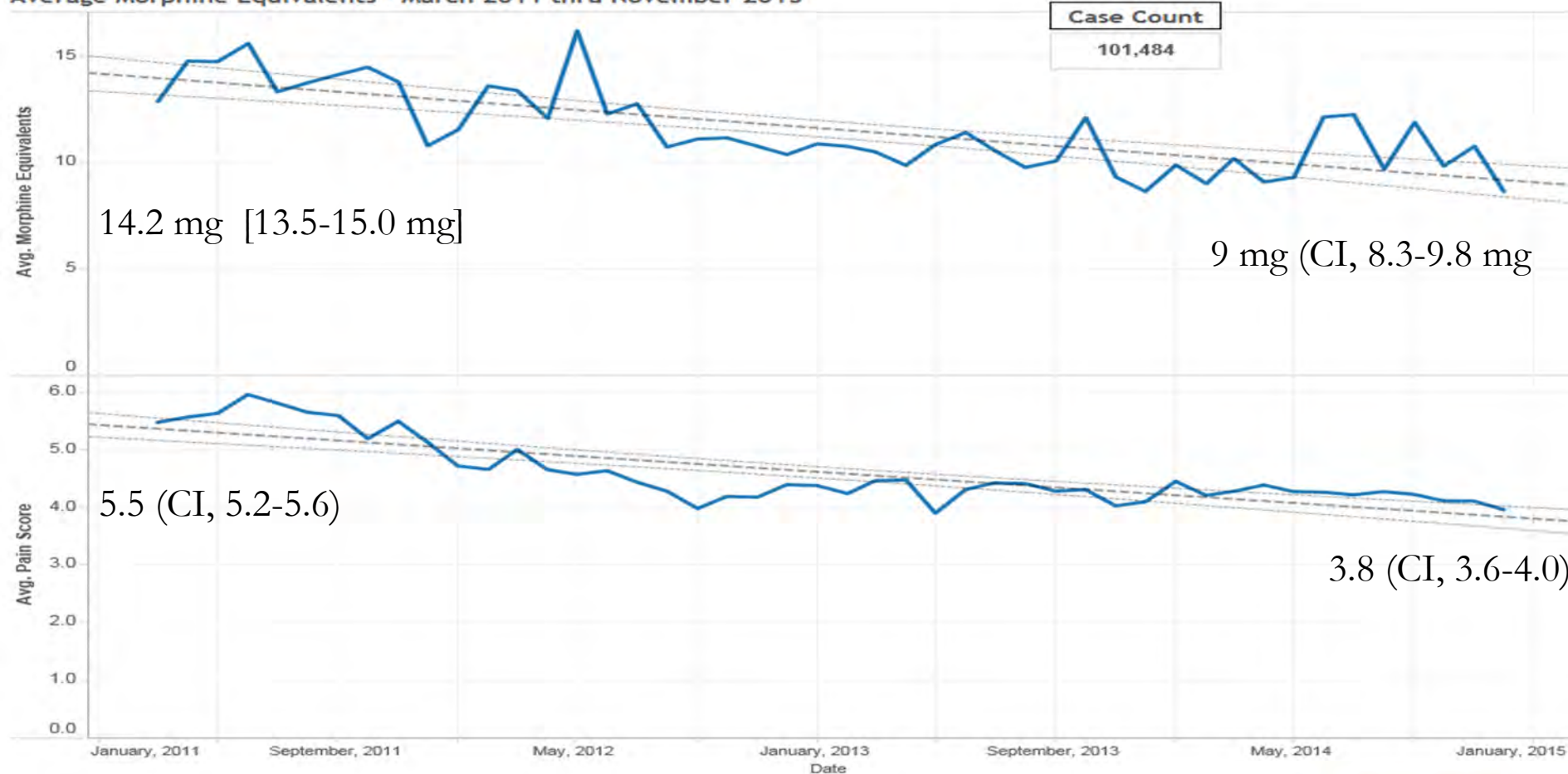
Michael L. Barnett, M.D., Andrew R. Olenski, B.S.,
and Anupam B. Jena, M.D., Ph.D.



N Engl J Med 2017;376:663-73

UVA Intraoperative Opioid Use and PACU Pain Scores

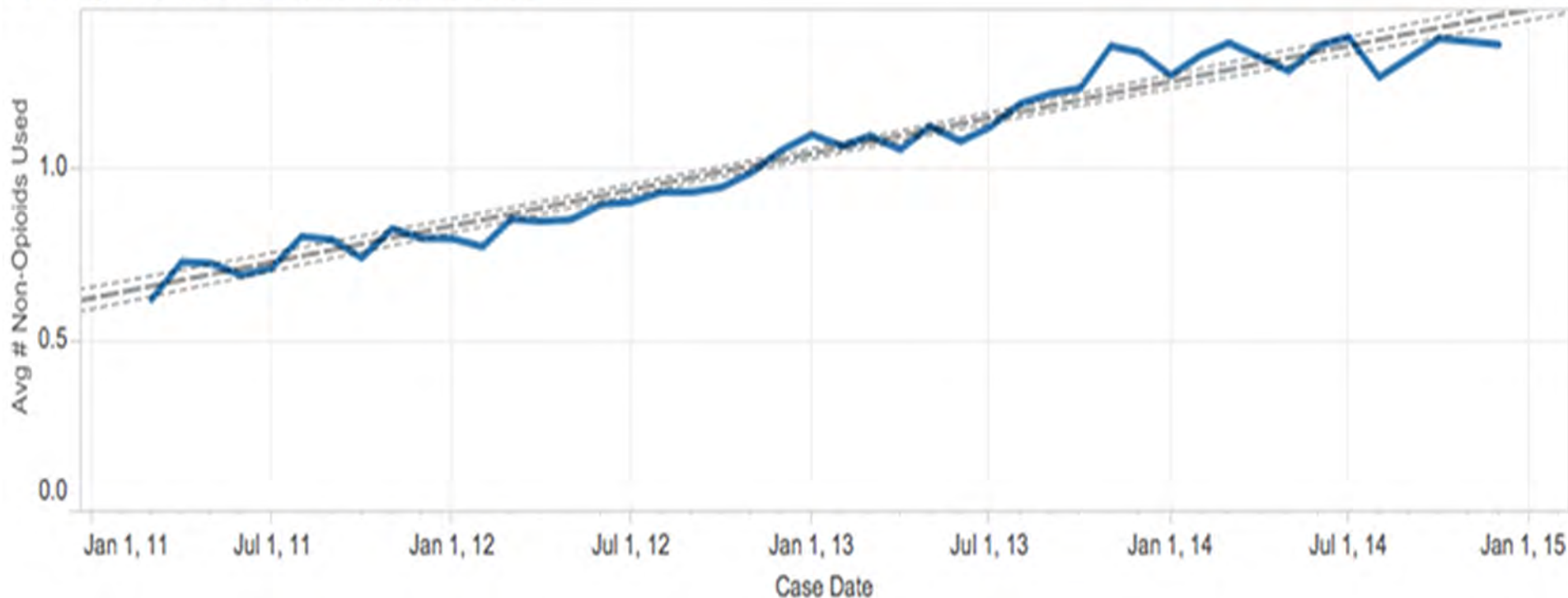
Average Morphine Equivalents - March 2011 thru November 2015



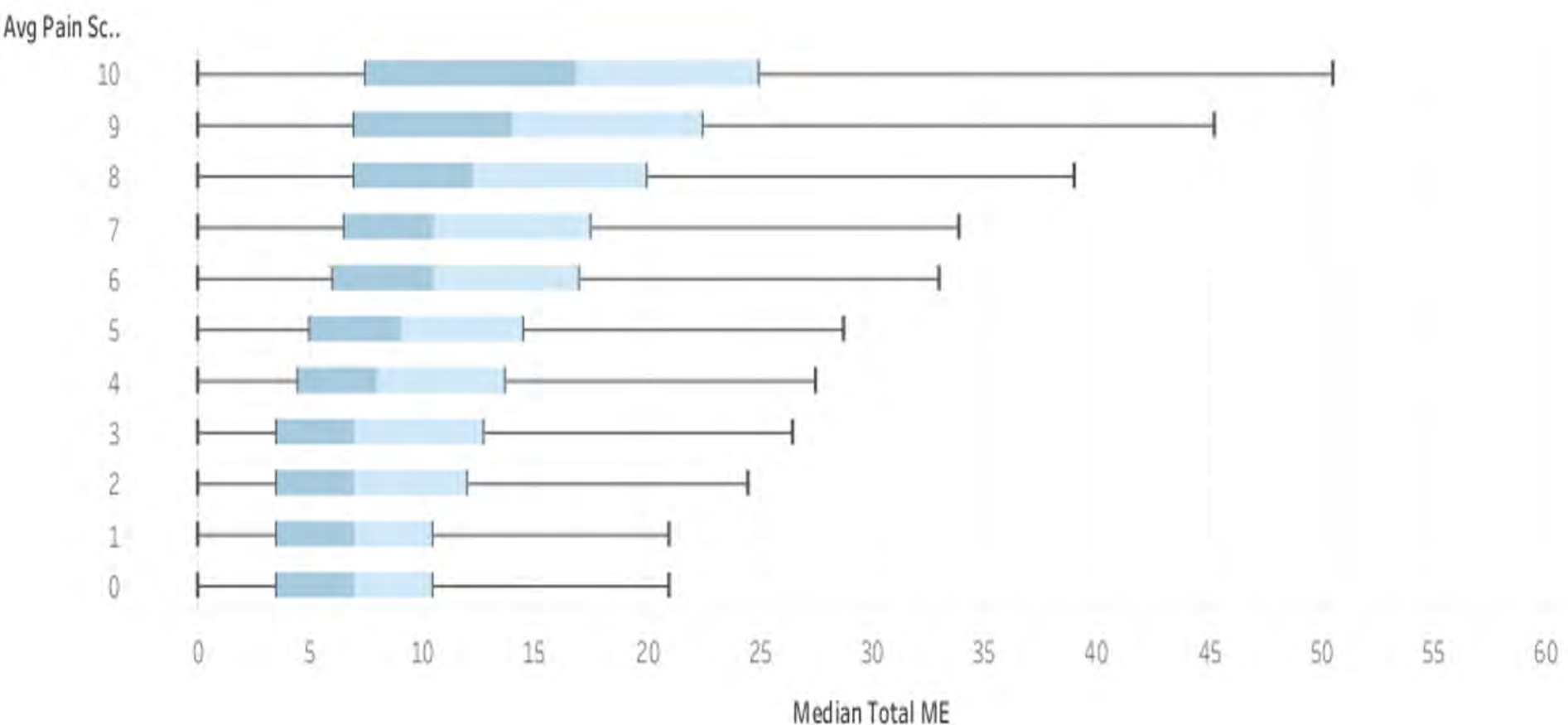
3/2011 to 11/2015

Non-Opioid Analgesic Use

Average Number of Non-Opioids Used



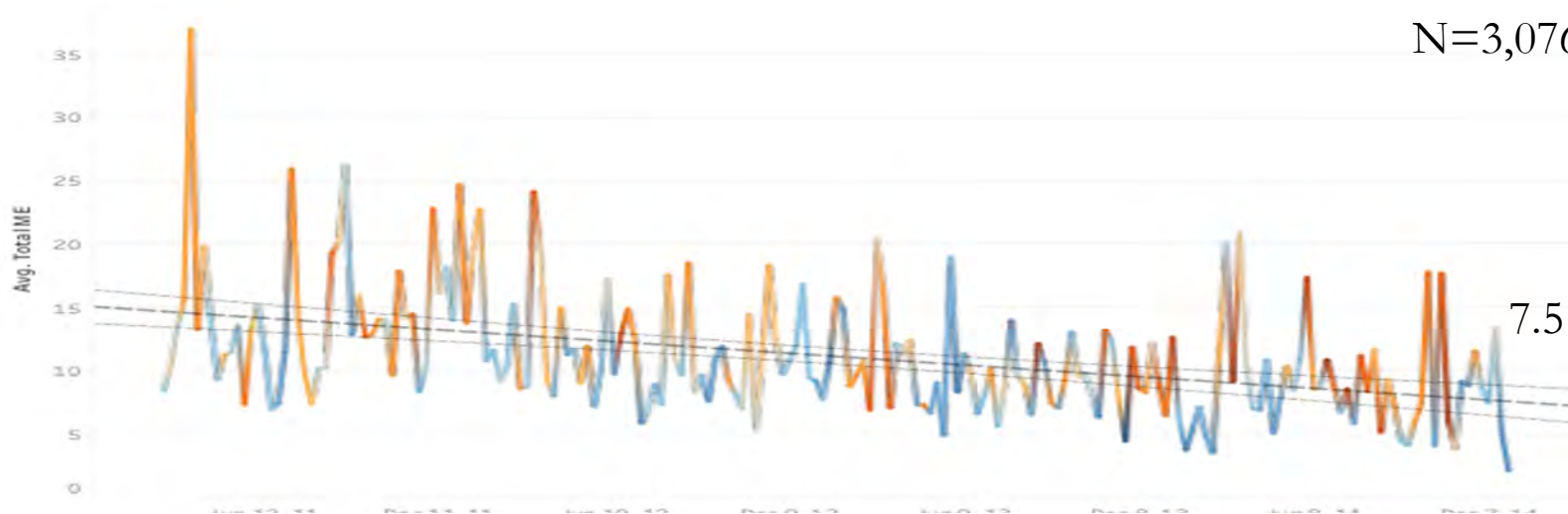
Intraoperative Opioid Use and Stratified PACU Pain Scores



Opioids Only Group

15 mg (13.5-16.5)

N=3,076



7.5 mg (6.0-9.0)

N=3,076



3.6 (3.2-4.0)

1.3 (0.9-1.7)

Perioperative Non-opioid Therapy

- Intravenous Lidocaine
- Ketamine
- Dexmedetomidine
- Enhanced Recovery Programs

Perioperative Lidocaine

- Anti-inflammatory
- Analgesic
- Anti-hyperalgesic properties
- Proposed mechanisms:
 - Na⁺ channel blockade
 - G-protein coupled receptors
 - NMDA receptor blockade

Mol Pharmacol. 2001 Feb;59(2):294-301

J Pain. 2006 May;7(5 Suppl 3):S1-29

Br J Anaesth. 2006 Jan;96(1):77-87. Epub 2005 Nov 18

Perioperative Lidocaine

CLINICAL CONCEPTS AND COMMENTARY

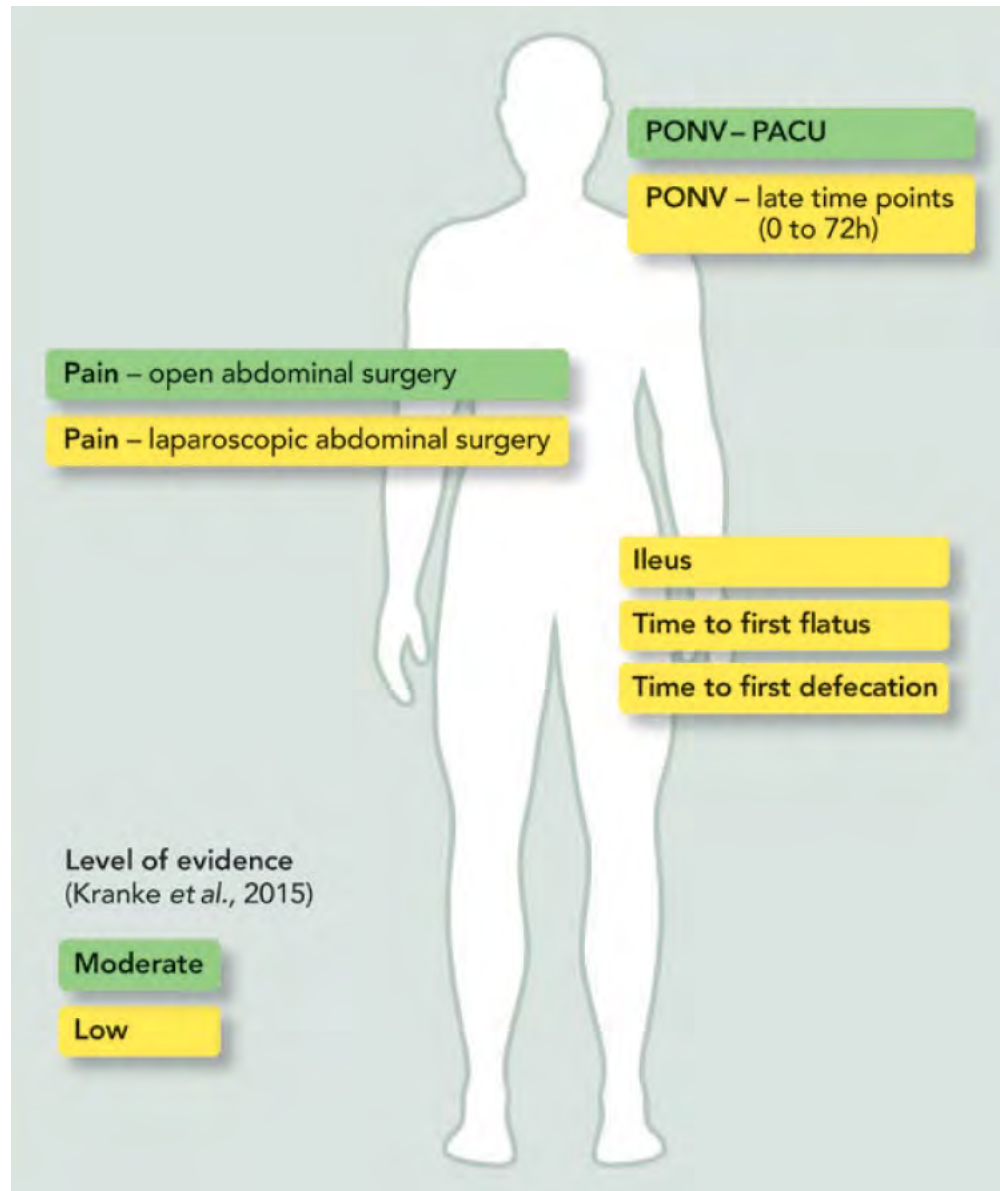
Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Perioperative Use of Intravenous Lidocaine

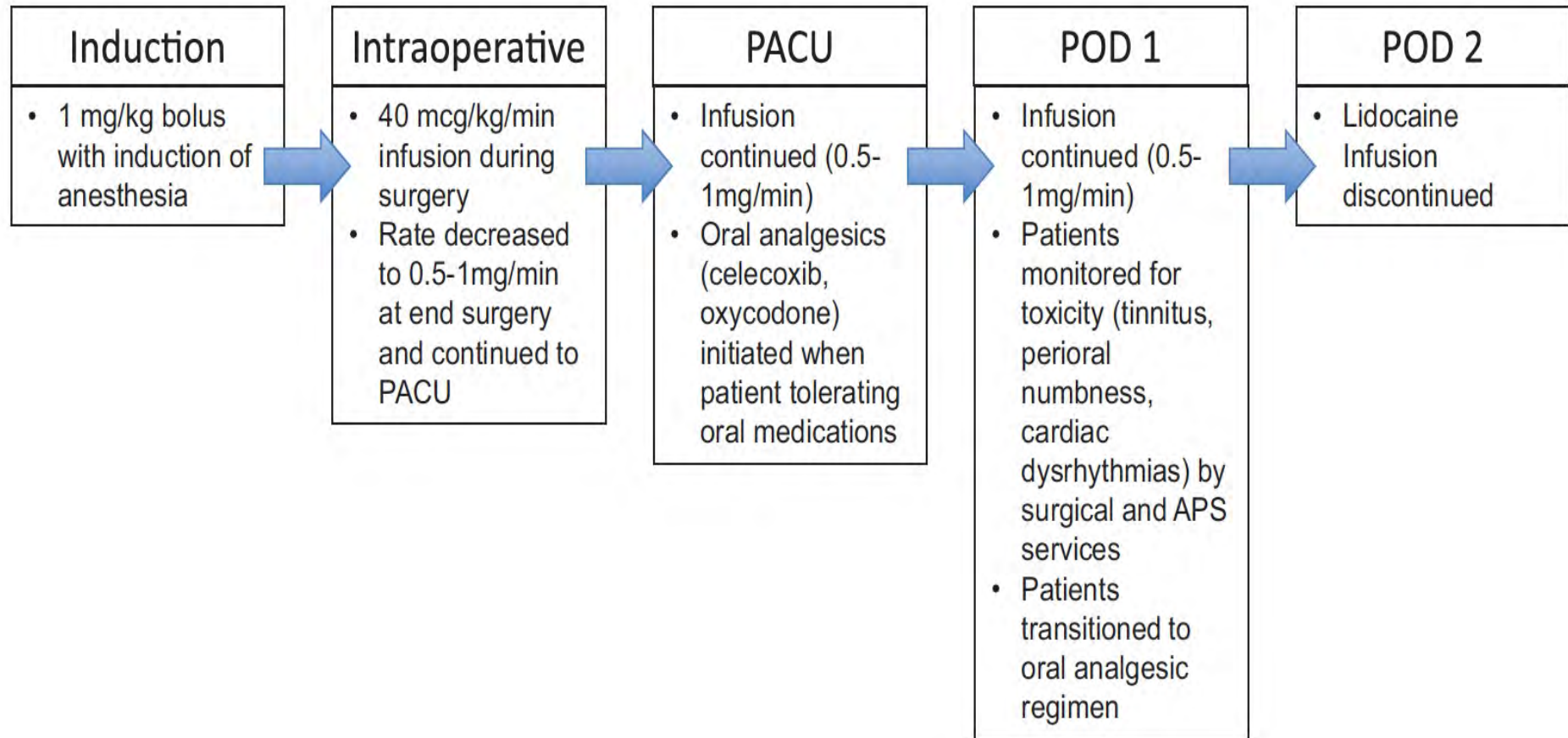
Lauren K. Dunn, M.D., Ph.D., Marcel E. Durieux, M.D., Ph.D.

Anesthesiology. 2017 Jan 23

Perioperative Lidocaine



Perioperative Lidocaine

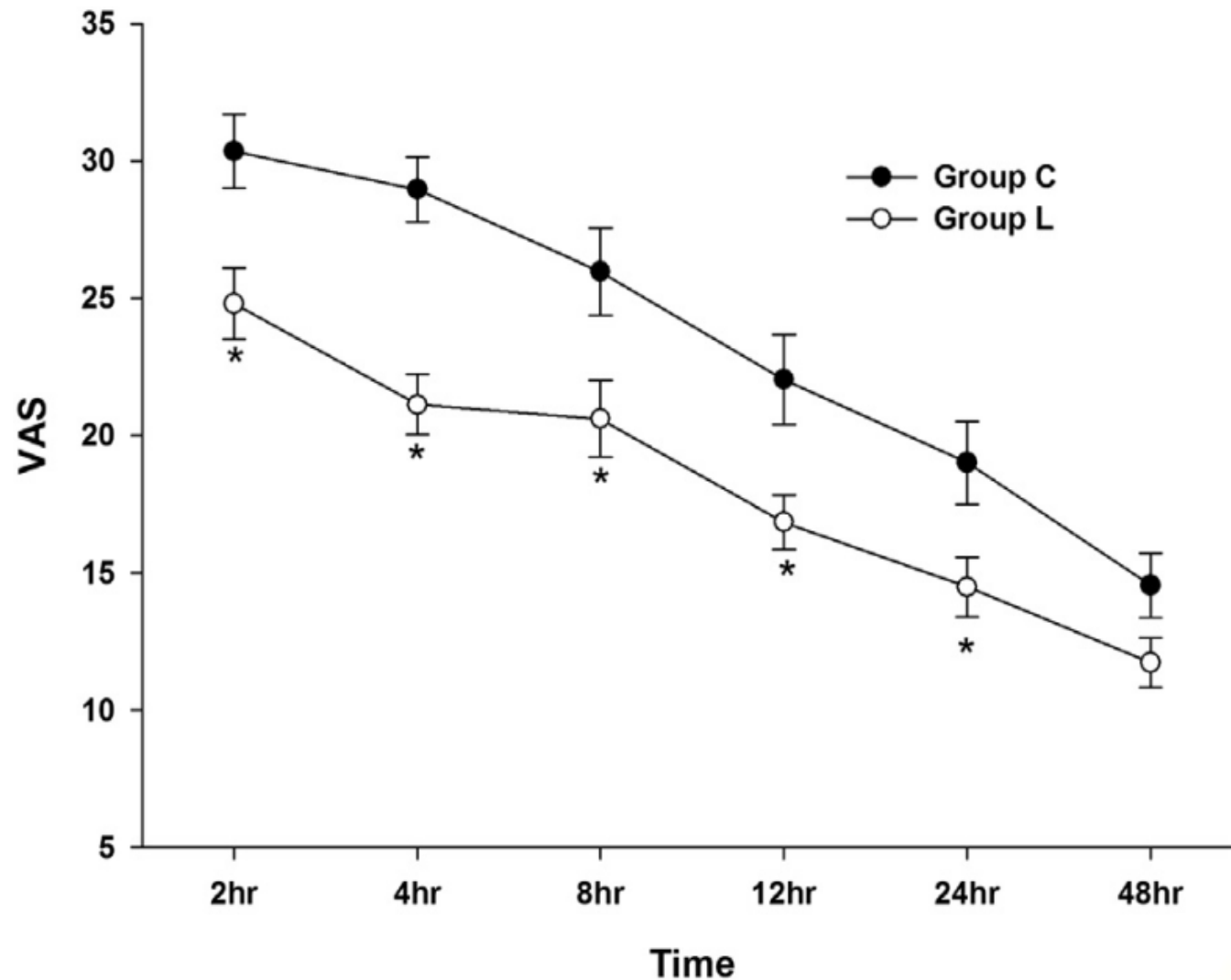


Lidocaine and Spine Surgery

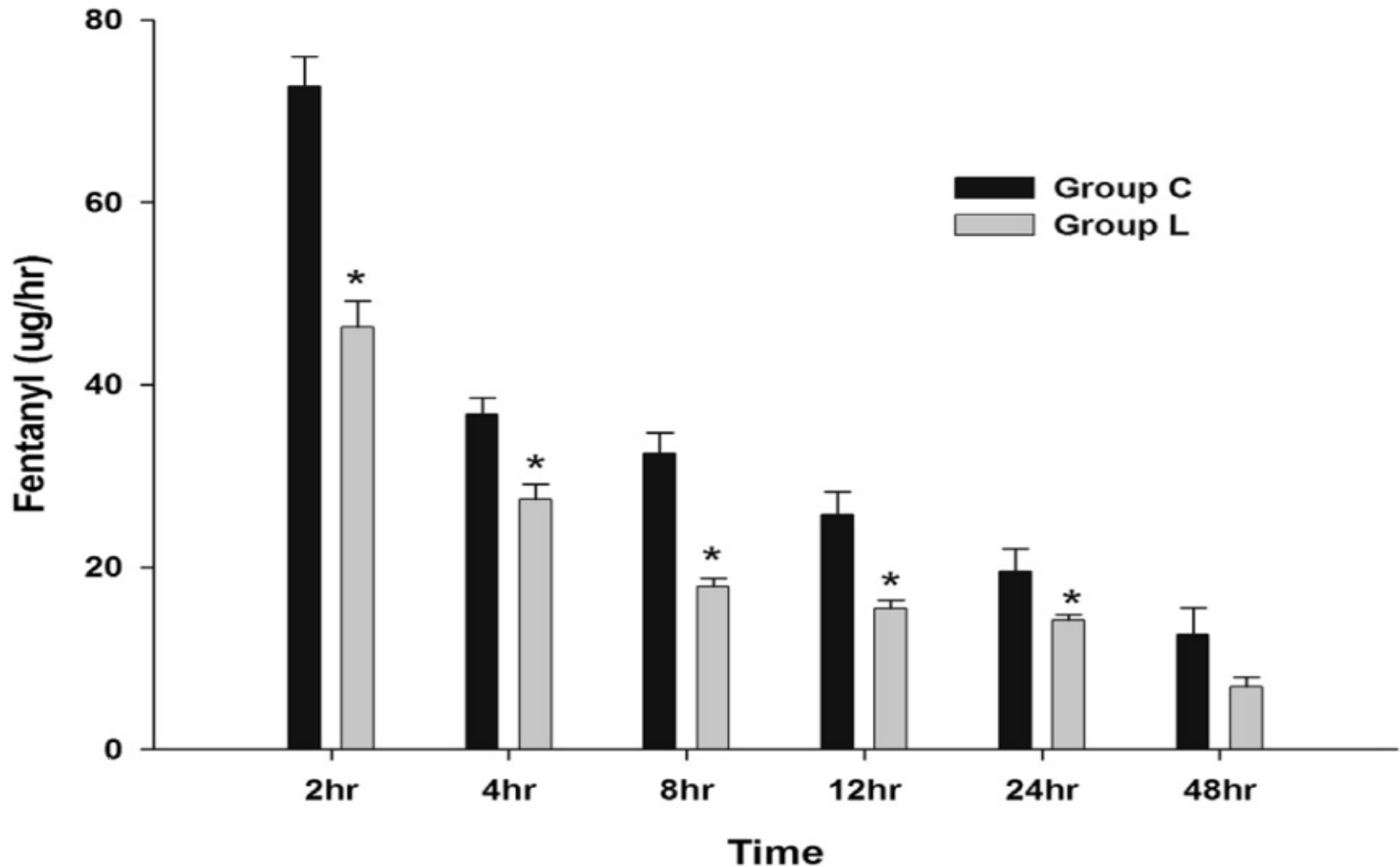
Intraoperative systemic infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded, randomized, placebo-controlled clinical trial

- 51 adults for one-level laminectomy and discectomy randomized to control or lidocaine groups
- Lidocaine group: 1.5-mg/kg bolus followed by 2-mg/kg/h infusion during procedure
- Primary outcome: visual analog score (VAS) 0 – 100mm at 4 hrs postop
- Secondary outcomes: VAS and Fentanyl consumption up to 48 hours, PCA, patient satisfaction, PONV, length of stay

Lidocaine and Spine Surgery



Lidocaine and Spine Surgery



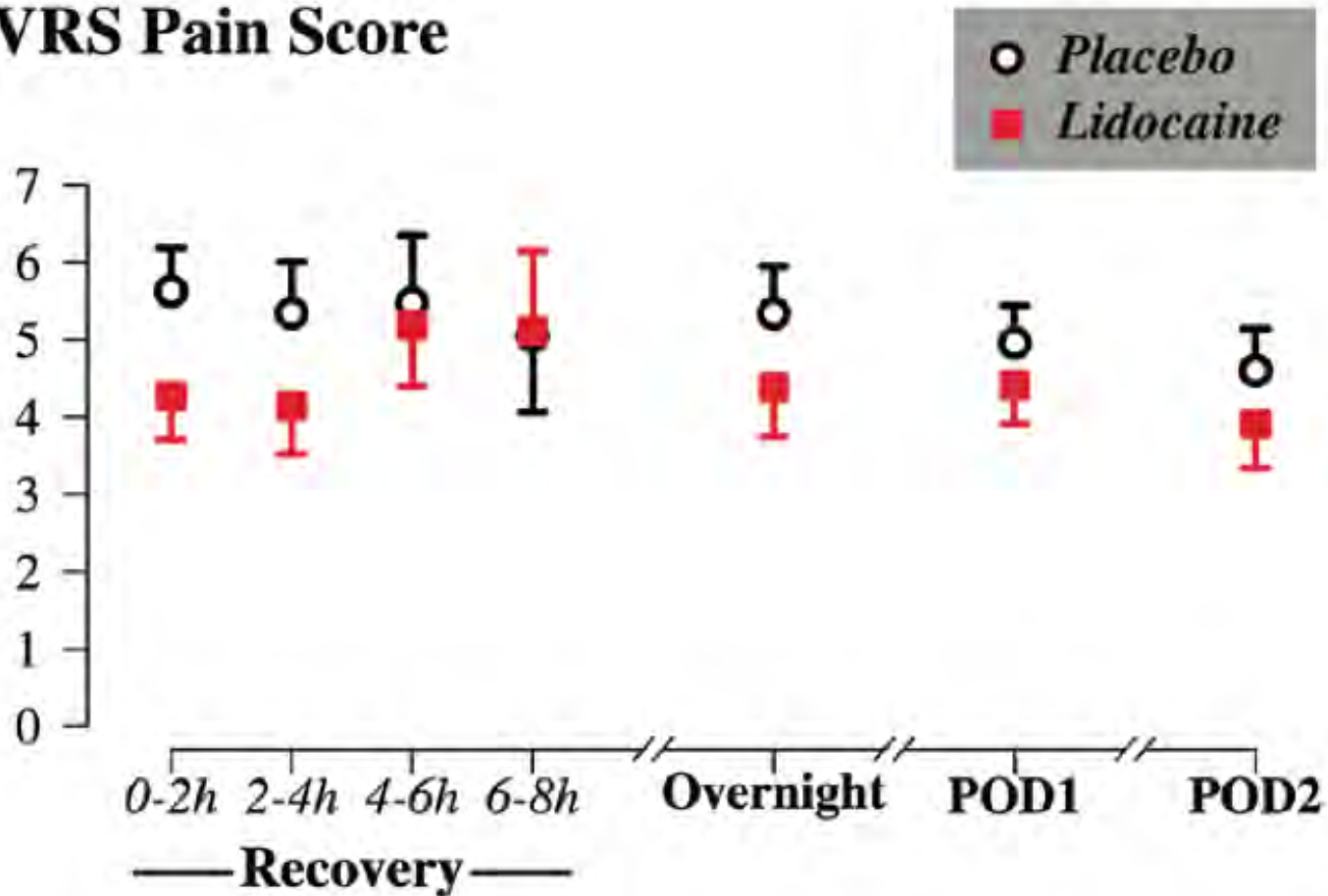
Lidocaine and Spine Surgery

Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

- 115 patients for multi-level spine surgery randomized to lidocaine or placebo
- Lidocaine group - 2mg/kg/hr infusion continued postoperatively for maximum 8 hours
- Primary outcomes: pain scores and opioid requirements in the first 48 hours postoperatively
- Secondary outcomes: 30 day postop complications, postop 24 hr PONV incidence, hospitalization duration, and postop quality of life.

Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

VRS Pain Score



Farag et al. Anesthesiology 2013

Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

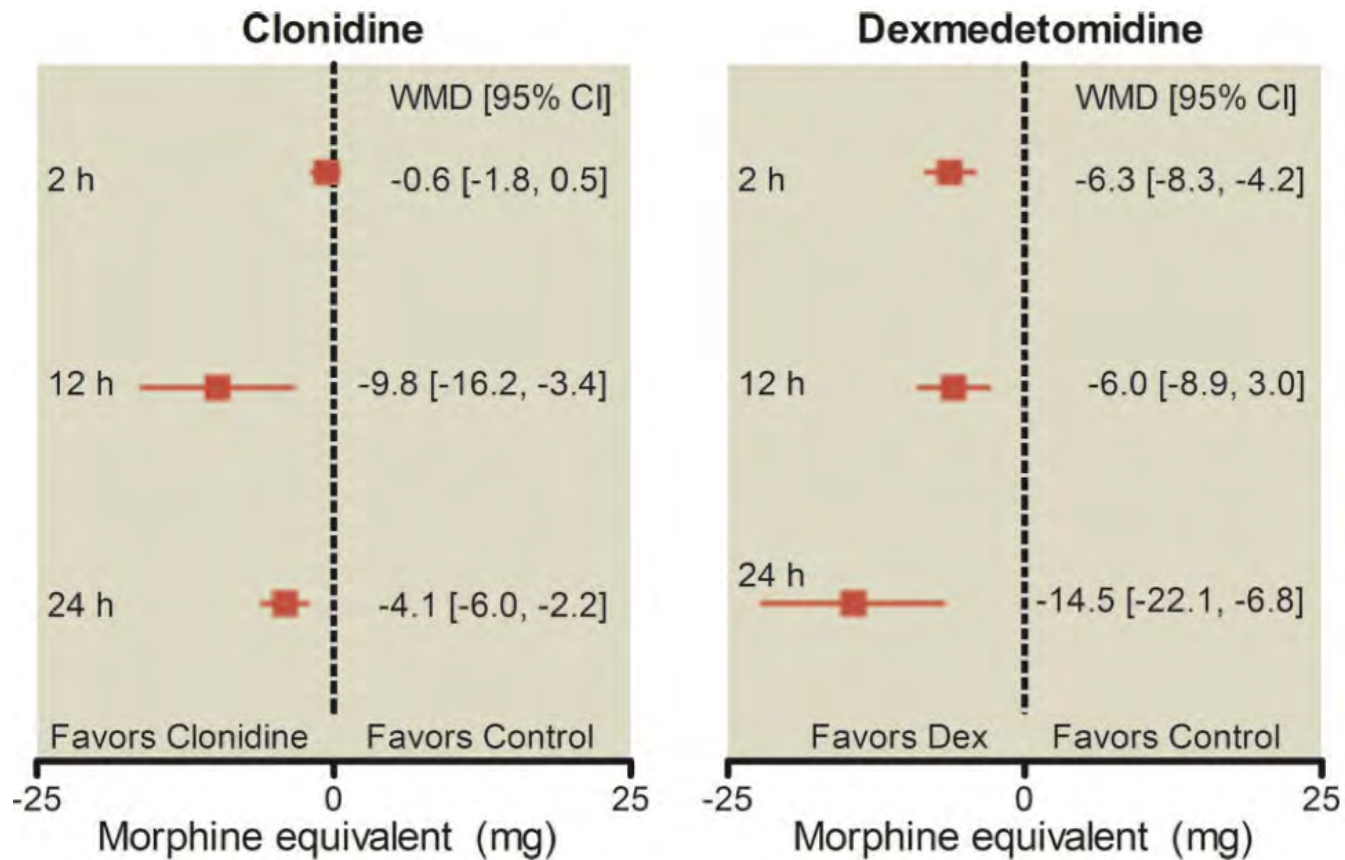
- Lidocaine group had significantly lower pain scores
- Morphine consumption was less in the lidocaine group
- Lidocaine group had significantly higher physical composite scores at 1 and 3 months
- No difference in PONV incidences or duration of hospital stay
- Lidocaine group had slightly fewer 30 day complication rates

α_2 Agonists

- Possible mechanisms for analgesia:
 - Peripheral nerve blockade, especially in conjunction with local anesthetics
 - Interdependence between α_2 receptors and mu receptors
 - Acts centrally on dorsal horn
 - Potentially acts supra-spinal on locus ceruleus and nucleus raphe magnus.
- Clonidine: $\alpha_2:\alpha_1$ selectivity of 200: 1
- Dexmedetomidine: $\alpha_2:\alpha_1$ selectivity of 1620:1

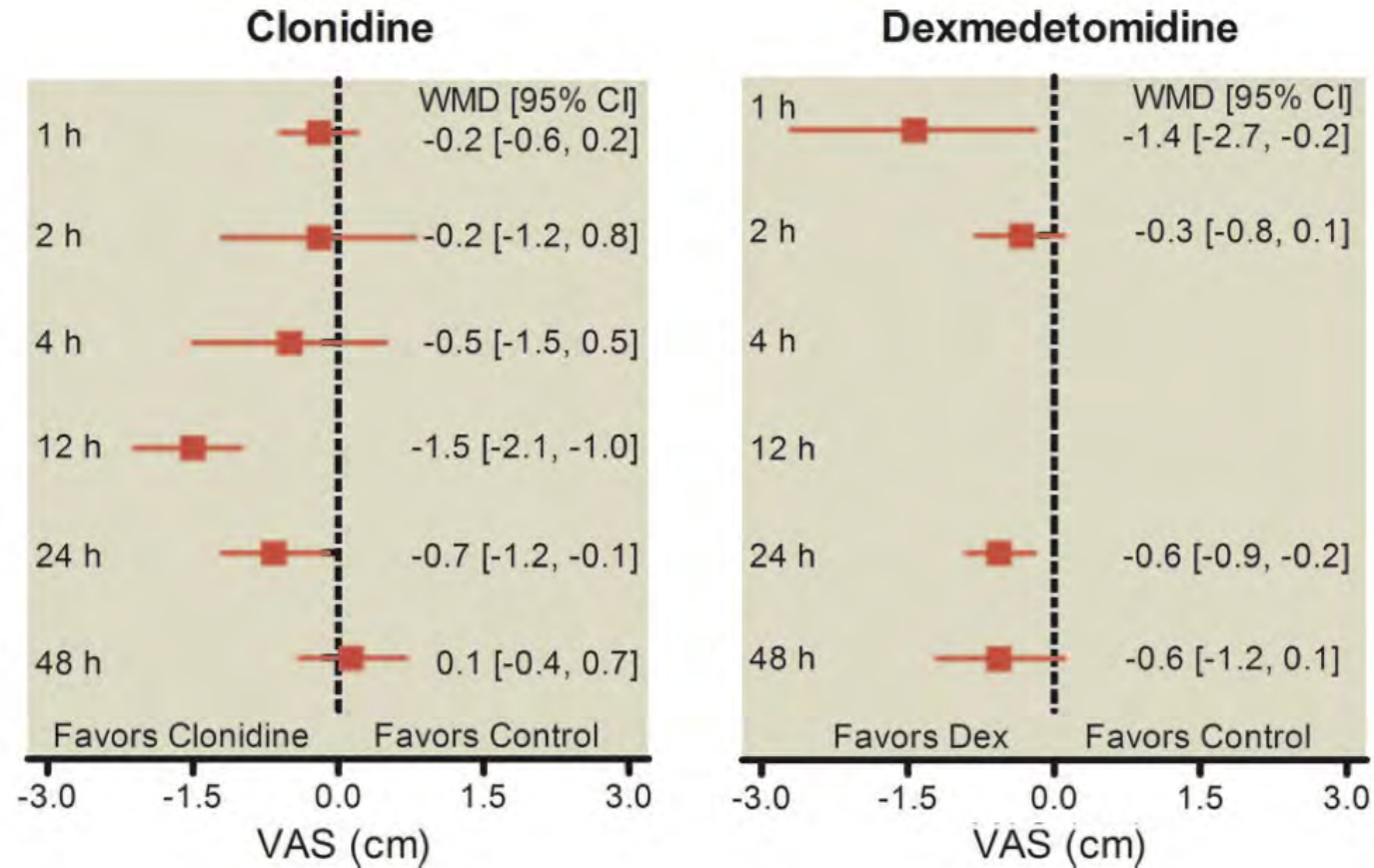
Effect of Perioperative Systemic α_2 Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials



Effect of Perioperative Systemic α_2 Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials



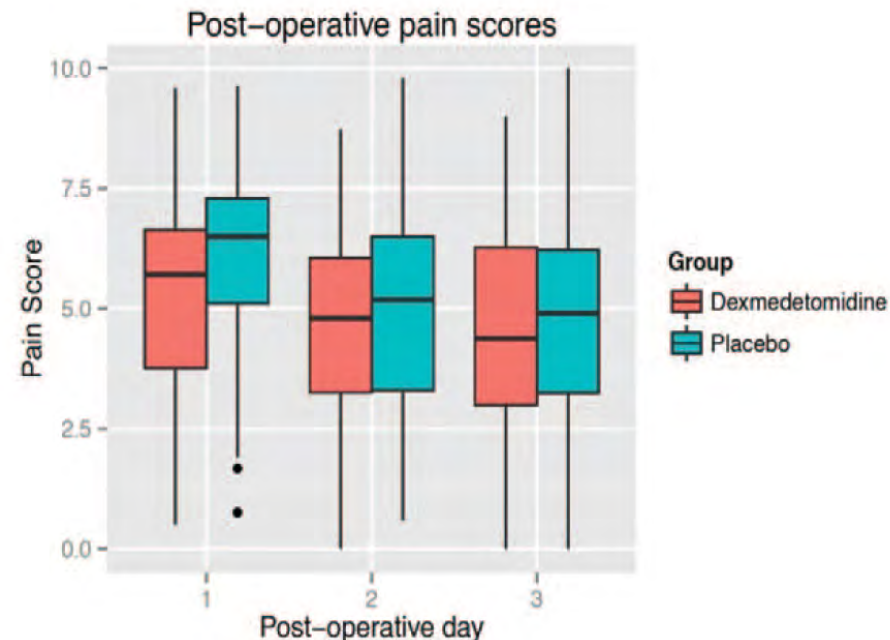
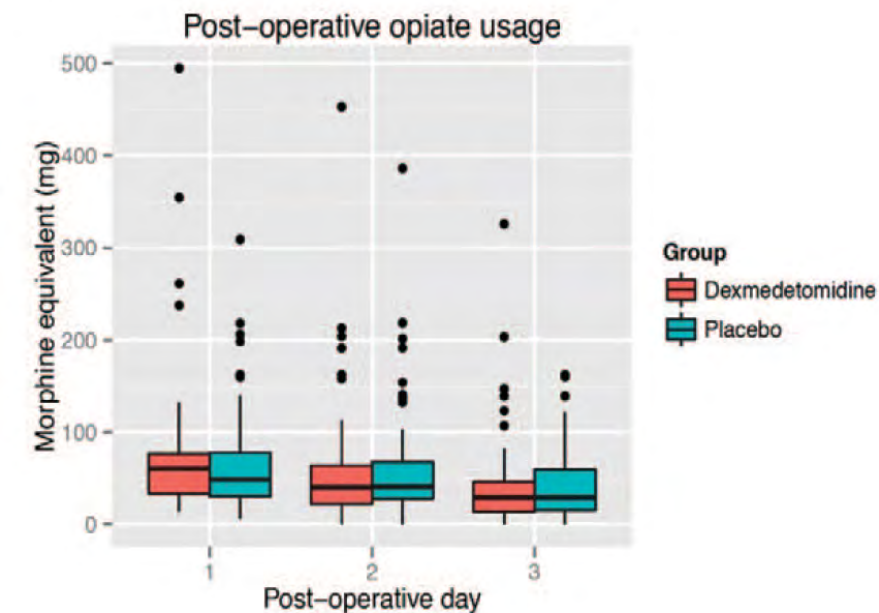
The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery

Bhiken I. Naik, MBBCh,*† Edward C. Nemergut, MD,*† Ali Kazemi, MD,* Lucas Fernández, MD, DSc,* Sarah K. Cederholm, MD,* Timothy L. McMurry, PhD,‡ and Marcel E. Durieux, MD, PhD*†

- Prospective Double Blind Study
- Evaluating intraoperative dexmedetomidine vs. placebo
- Major spine surgery
- N = 131
 - Dexmedetomidine = 63 patients
 - Placebo = 68 patients
- Primary outcome
 - Postoperative opioid consumption
 - Postoperative pain scores

The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery

Bhiken I. Naik, MBBCh,*† Edward C. Nemergut, MD,*† Ali Kazemi, MD,* Lucas Fernández, MD, DSc,* Sarah K. Cederholm, MD,* Timothy L. McMurry, PhD,‡ and Marcel E. Durieux, MD, PhD*†





Ketamine and Spine Surgery

- Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery
 - Loftus et al. Anesthesiology 2010
- Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery
 - Yamauchi et al. Anesthesia & Analgesia 2008
- Intra- and Postoperative Very Low Dose Intravenous Ketamine Infusion Does Not Increase Pain Relief after Major Spine Surgery in Patients with Preoperative Narcotic Analgesic Intake
 - Subramaniam et al. Pain Medicine 2011

Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

- 101 adult patients with daily opiate use > 6 weeks for lumbar back surgery randomized to ketamine or control
- Ketamine group: 0.5mg/kg of ketamine at induction; 10ug.kg⁻¹.min⁻¹ infusion during case
- Primary outcomes: 48 hour morphine consumption
- Secondary outcomes: postop complications, side effects related to opioid and ketamine, PACU stay, hospital stay, pain scores up to 6 weeks, opiate consumption up to 6 weeks

Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

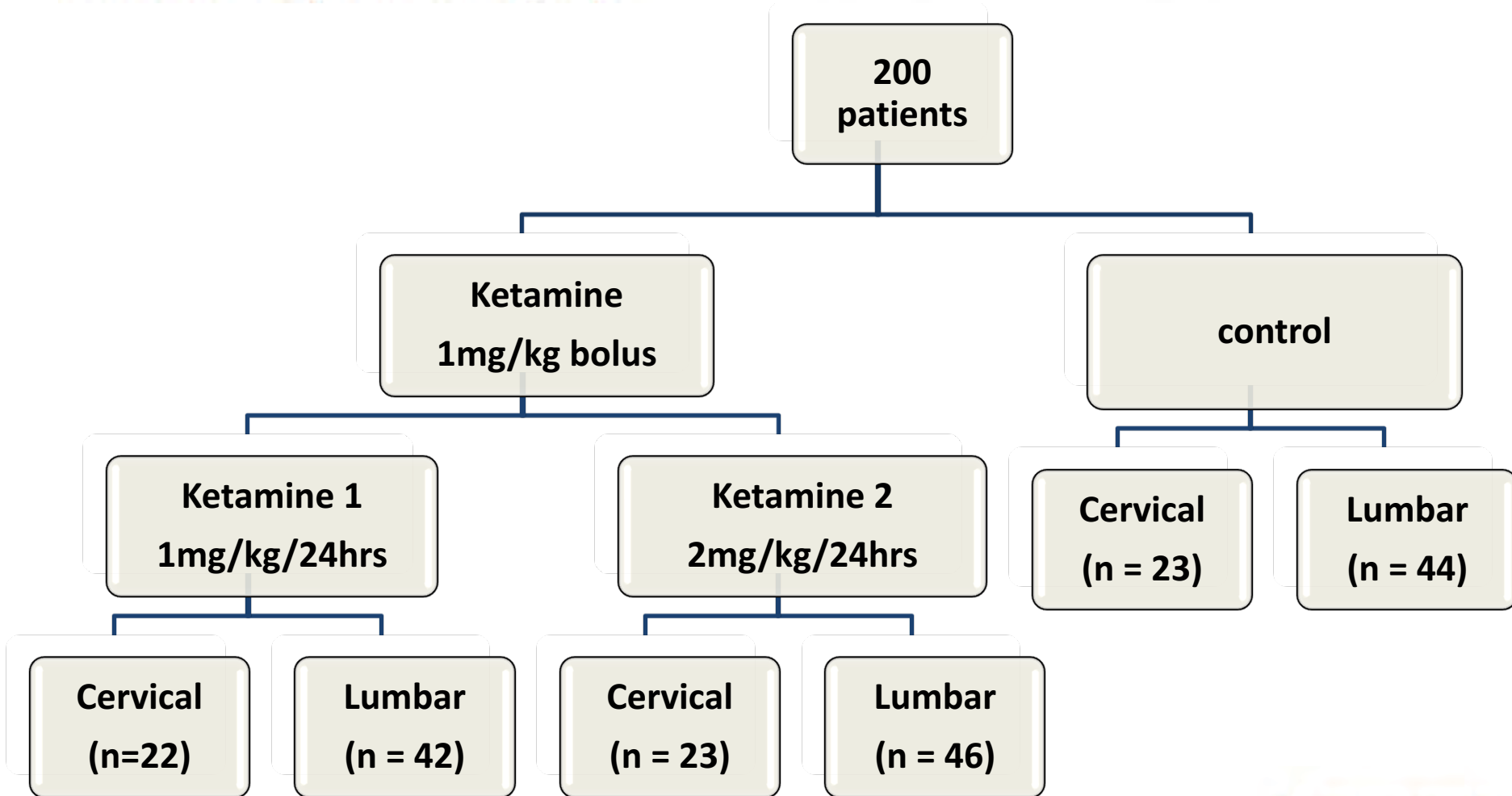
	Placebo	Ketamine	P-value
24-hr total ME	202 \pm 176	142 \pm 82	0.03
48-hr total ME	309 \pm 341	195 \pm 111	0.03
6 week ME (mg/h)	2.8 \pm 6.9	0.8 \pm 1	0.04 
6-week VAS	4.2 \pm 2.4	3.1 \pm 2.4	0.03 

Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

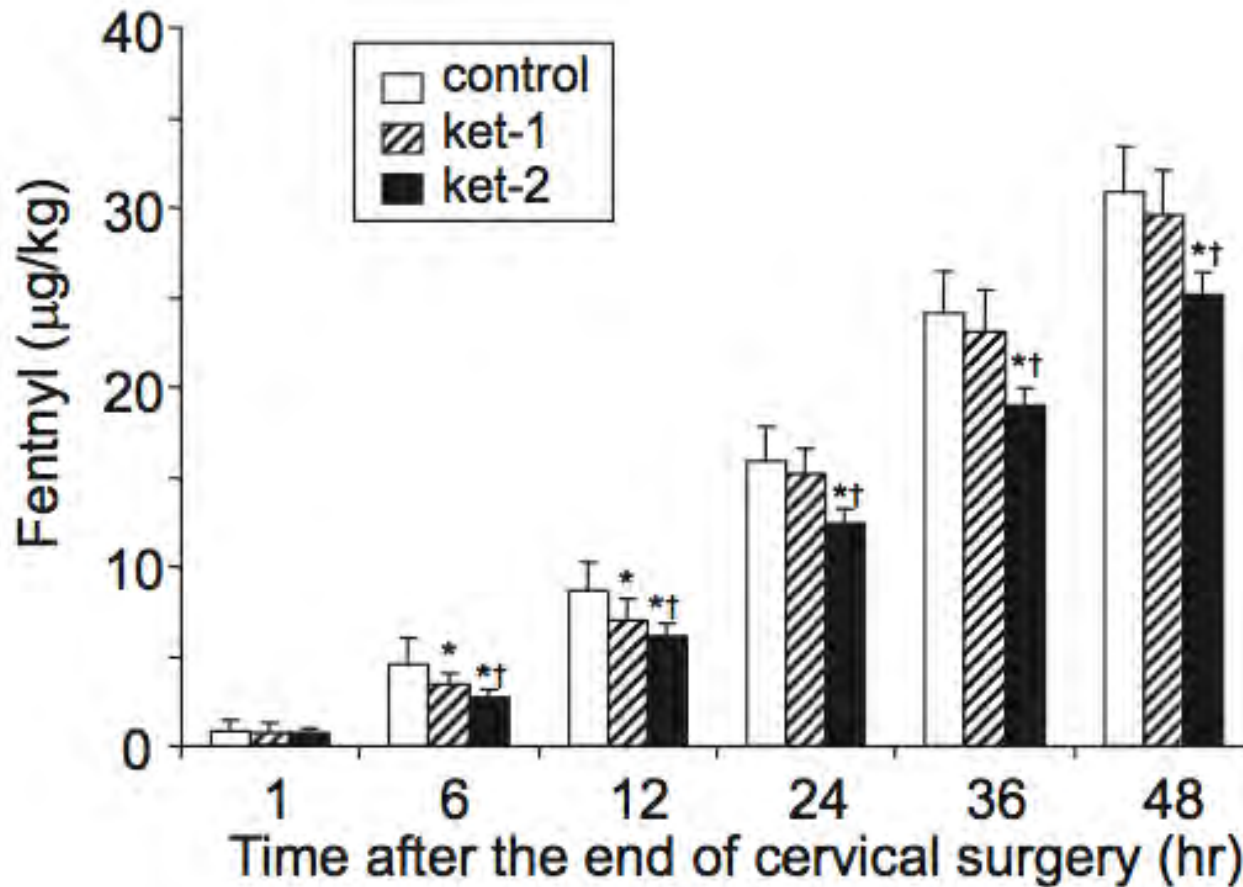
Ketamine Effect Stratified According to Preoperative Morphine Use

	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

Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery



Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery

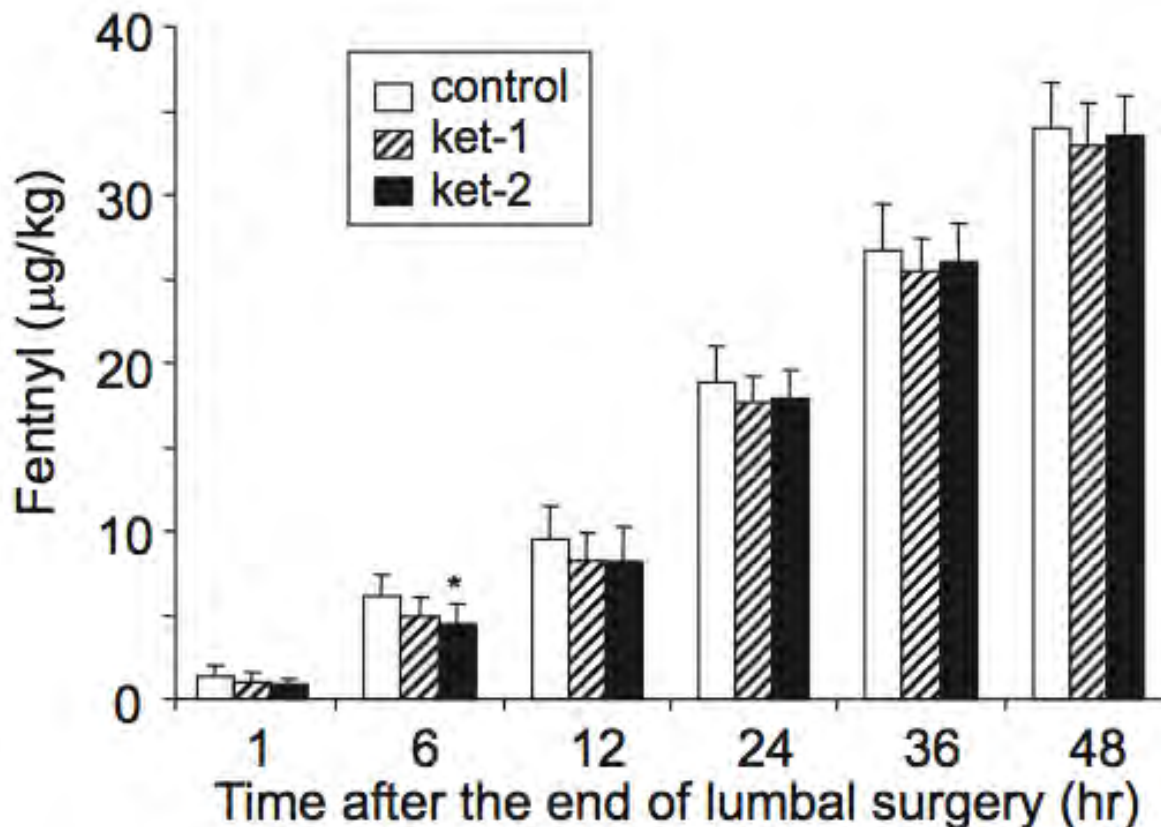


* $P < 0.05$ versus control

† $P < 0.05$ versus ket-1

Anesth Analg 2008;107:1041-4

Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery



* $P < 0.05$ versus control

$\tau P < 0.05$ versus ket-1

Anesth Analg 2008;107:1041-4

British Journal of Anaesthesia 1997; 78: 606–617

Multimodal approach to control postoperative pathophysiology and rehabilitation

H. KEHLET

ERAS Colorectal Surgery

Day before operation

Regular diet until 6 PM; bowel preparation (mechanical and oral antibiotics); chlorohexidine shower night before and morning of surgery

Day of operation, preoperative holding area

Identify enhanced recovery patients and initiate protocol; allow patients to have clears up until 2 hours before operation; Gatorade 20 oz, must be completed 2 hours before operation

Medications:

acetaminophen 1000 mg po

Intraoperative

Duramorph (100 µg) spinal preinduction; no intraoperative opioids without attending approval

Induction: propofol, ketamine 0.5 mg/kg, magnesium 30 mg/kg (over 10 min), dexamethasone 4 mg

IV analgesia: lidocaine 40 µg/kg/min (continued into PACU), ketamine 0.6 mg/kg/h (10 µg/kg/min, stop approximately 45 minutes before waking in laparoscopic, drop to 5 µg/kg/min for open cases)

“Goal-directed” fluids guided by Pleth Variability Index; tidal volumes 6–8 mL/kg using 100% FiO₂

Diet: Clears begins night of surgery, solid food postoperative day 1

Pain:

1 g IV acetaminophen 6 hours after initial dose and every 6 hours

Lidocaine infusion (0.5–1 mg/min) until postoperative day 2

Oxycodone 5 mg po q4h prn mild pain, 10 mg q4h prn moderate pain, oxycodone 15 mg po q4h prn severe pain

Celecoxib 100 mg po bid in patients without coronary artery disease

Activity: Ambulation begins night of surgery, head of bed at 30 degrees at all times

Medications:

Alvimopan 12 mg bid for 7 days

Magnesium oxide 400 mg po daily

Fluids:

LR at 40 mL/h for 24 h

Discharge

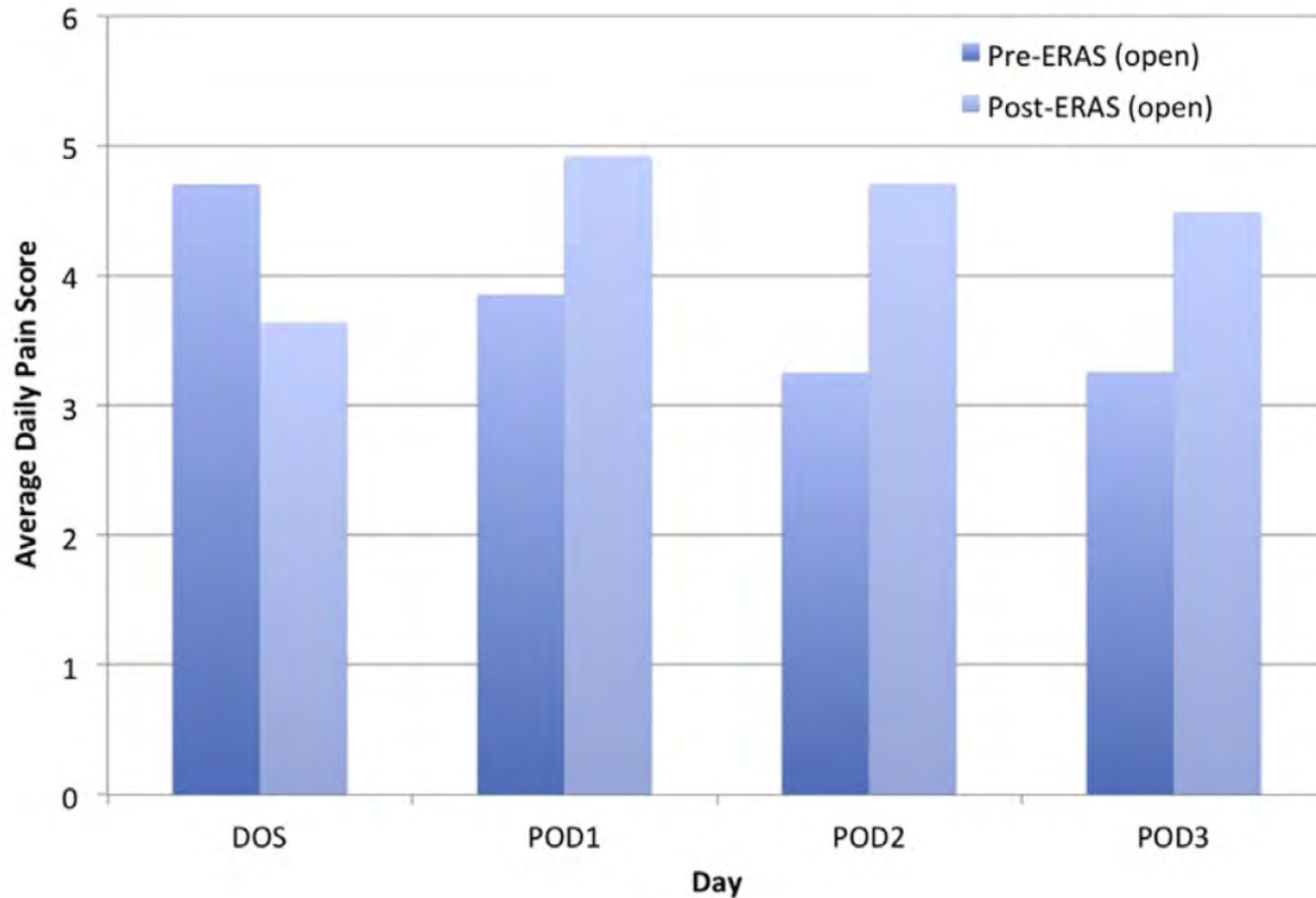
Medications: acetaminophen 1 g q8h for 1 week, oxycodone 5 mg q4h prn

Arrange for early follow-up in high-risk patients with surgeon or primary care; follow-up phone call within 48 hours of discharge

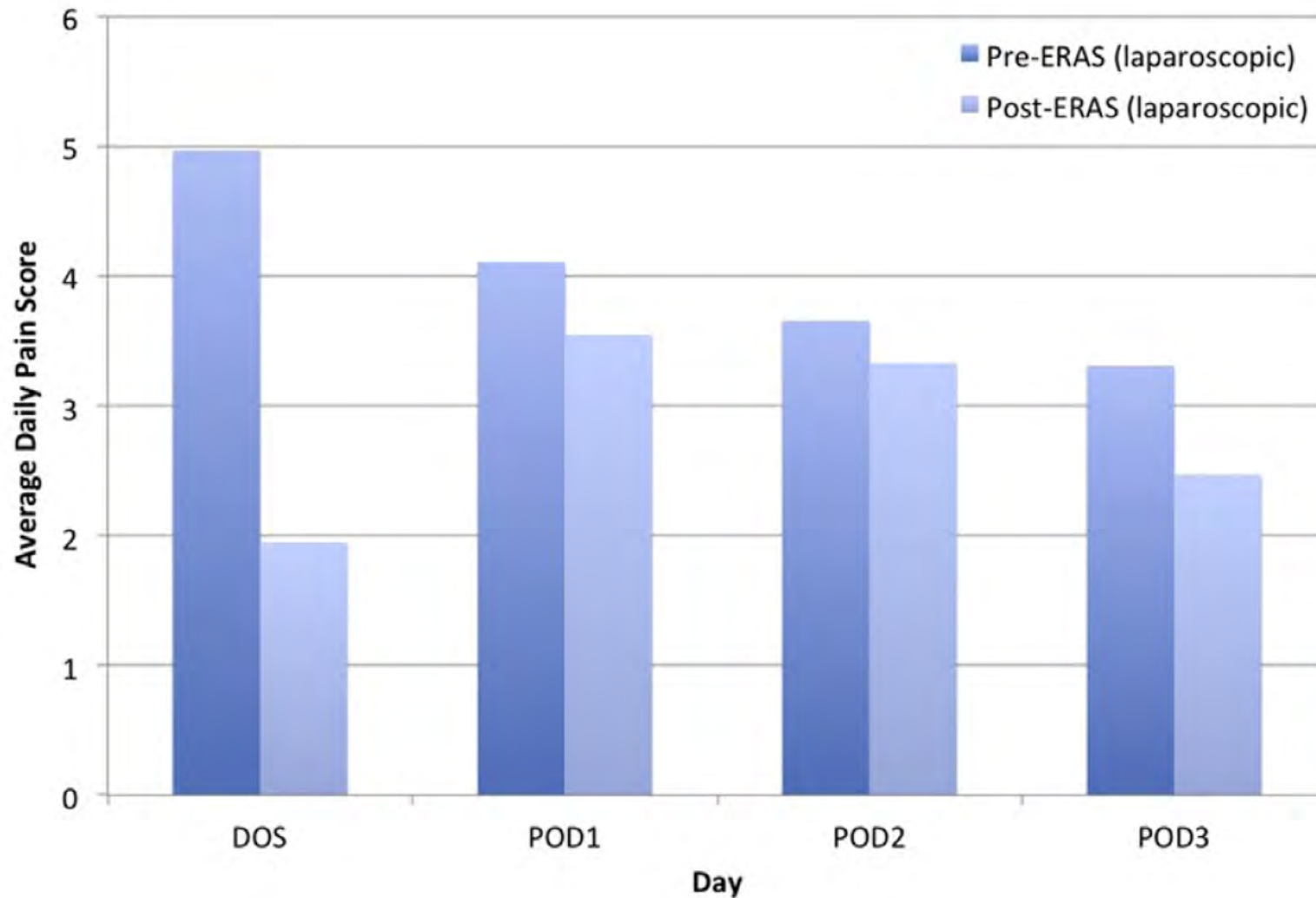
ERAS Colorectal Surgery

Protocol elements	Before ER protocol (n = 98)	After ER protocol (n = 109)	p Value
Intraoperative morphine equivalents, mg, mean \pm SD	21.7 \pm 10.7	0.5 \pm 1.1	0.0001
Total morphine equivalents, mg, mean \pm SD	280.9 \pm 395.7	63.7 \pm 130.0	0.0001
Intraoperative net fluid balance, mL, mean \pm SD	2,733 \pm 1,464	848 \pm 953	0.0001
Total net fluid balance, mL, mean \pm SD	4,409 \pm 5,496	-182 \pm 3,933	0.0001
Gatorade, n (%)	—	90 (83)	NA
Ambulate DOS, n (%)	0	84 (77)	0.0001
Ambulate by POD 1, n (%)	79 (81)	96 (88)	0.178

ERAS Pain Scores-Open Procedures

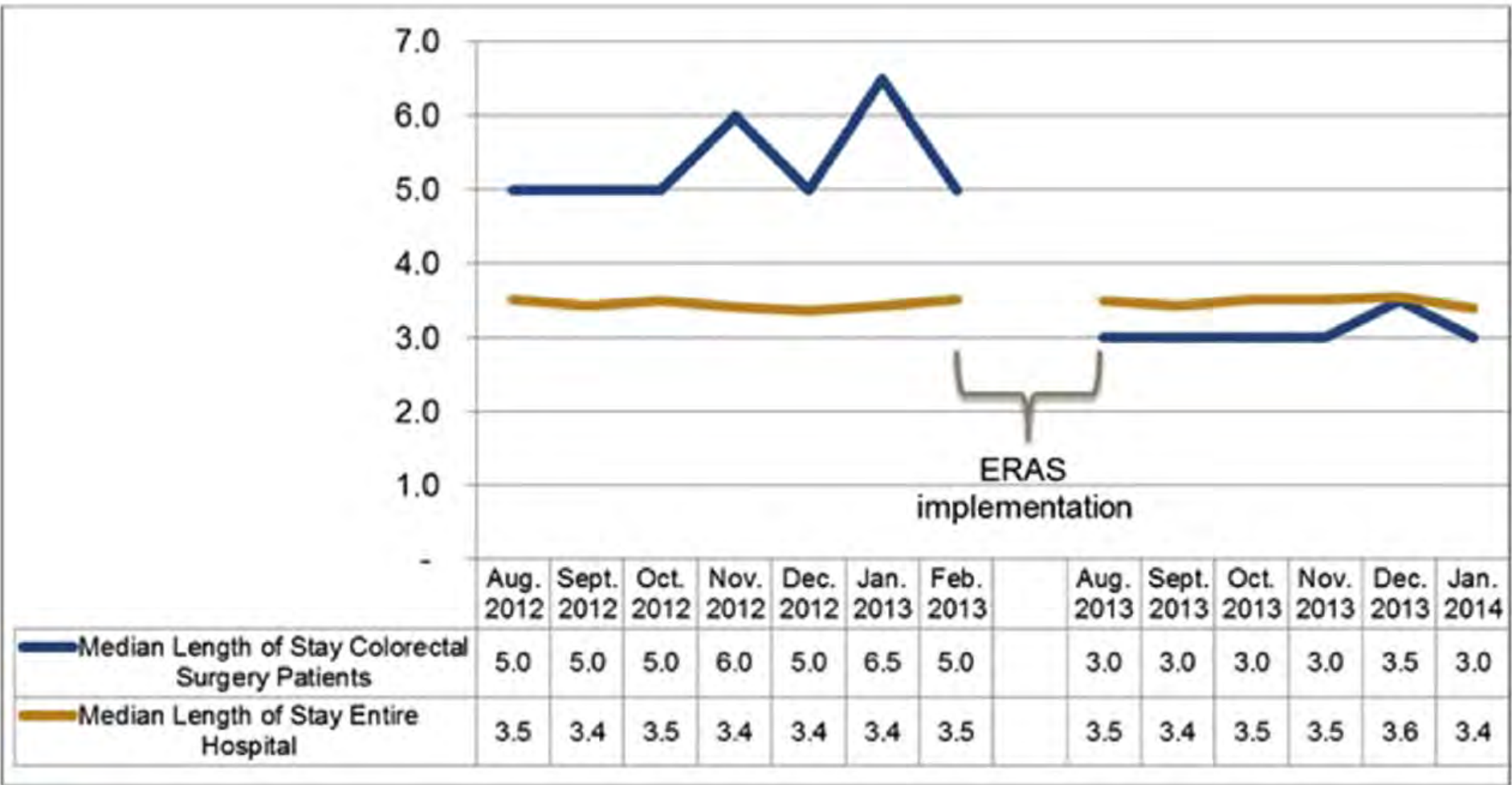


ERAS Pain Scores-Laparoscopic Procedures

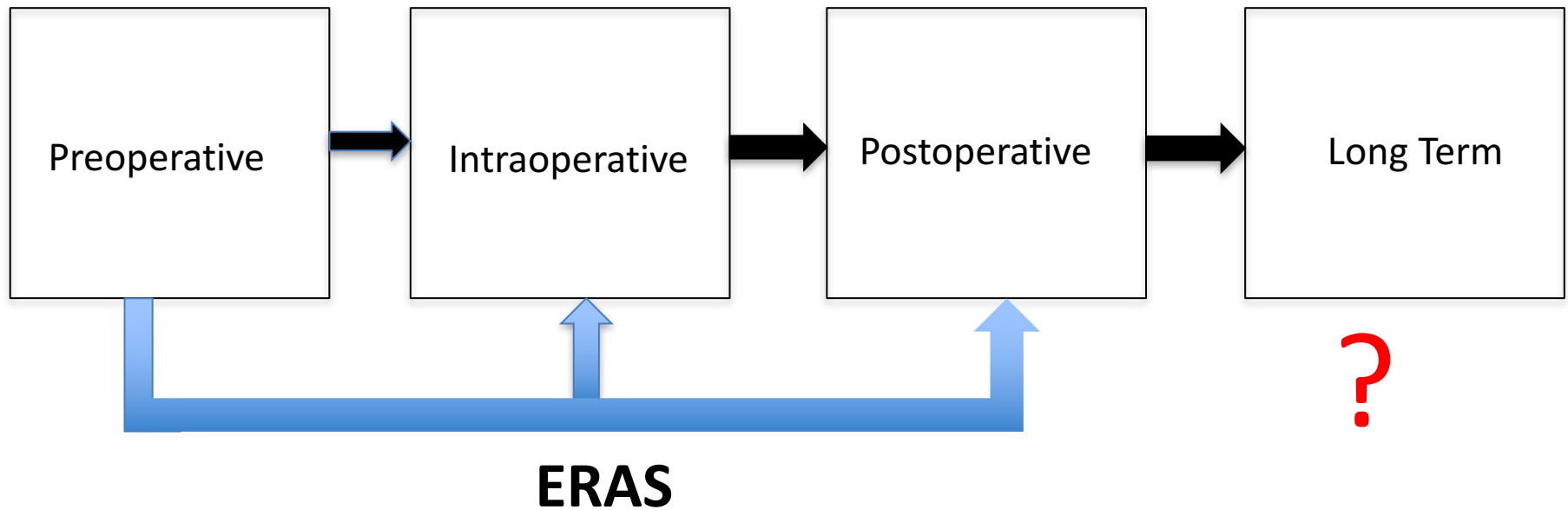


Thiele et al. J Am Coll Surg 2015;220:430e 443

How Effective Are ERAS Programs Without Epidurals ?



Surgery and Opioid Use



Enhanced Observational Study

Postoperative Pain Profiles, Analgesic Use,
and Transition to Chronic Pain and
Excessive and Prolonged Opioid Use
Patterns



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- The Perioperative Period-Priming Patients for Misuse, Abuse and Dependence?
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