Drugs and Procedures in Acute Pain Management: An Update for better Outcomes

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Disclosures: Current ASRA President - Elect 2015-2017

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Objectives and Outline

1. Pharmacological methods for acute pain with multimodal analgesia & outcomes (25 min)

2. Procedures for acute pain management (5 min)

3. The importance of pain scores after discharge from hospitals and payment (5 min)

Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century

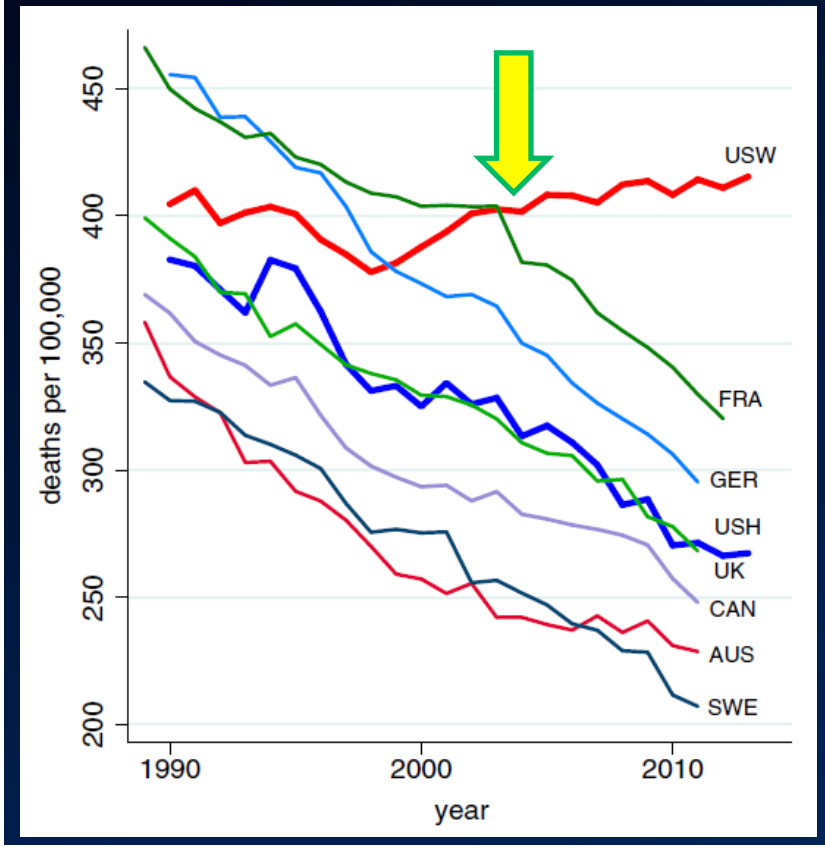
Anne Case[1] and Angus Deaton[1]

Woodrow Wilson School of Public and International Affairs and Department of Economics, Princeton University, Princeton, NJ 08544

PNAS 2016

Contributed by Angus Deaton, September 17, 2015 (sent for review August 22, 2015; reviewed by David Cutler, Jon Skinner, and David Weir)

- Data from 1999-2013 comparisons



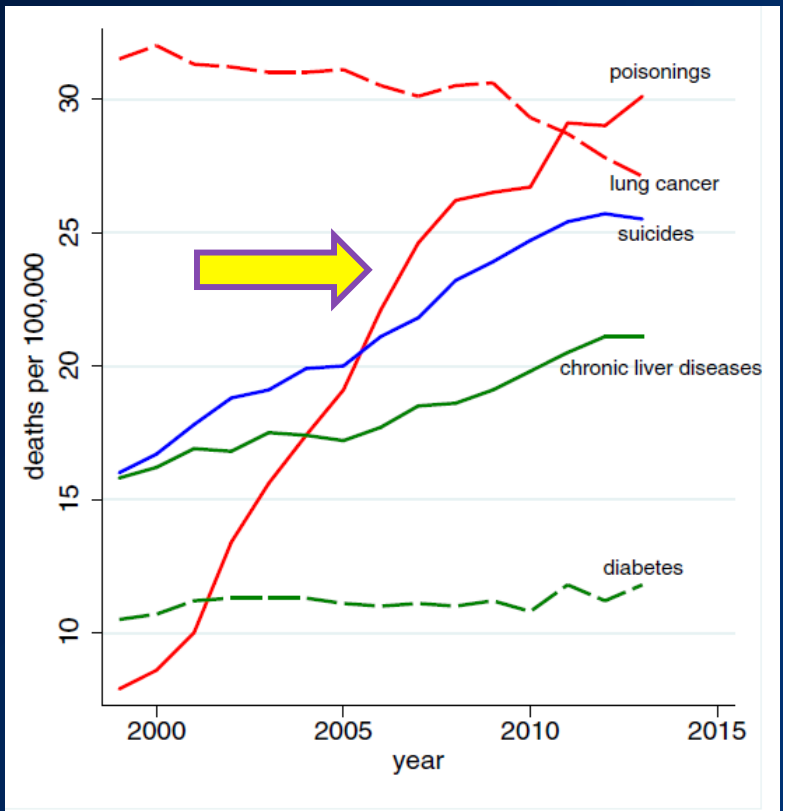


Fig. 2. Mortality by cause, white non-Hispanics ages 45–54.

Opioids and Pain (data from CDC)

- Estimated 20% of patients presenting to physician offices with non-cancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription.

- In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, *enough for every adult in the United States to have a bottle of pills*

Opioids and Pain (data from CDC)

- The Drug Abuse Warning Network estimated that > 420,000 ER visits were related to the misuse or abuse of narcotic pain relievers in 2011.

- In 2013, estimated 1.9 million persons abused or were dependent on prescription opioid pain medication with more than 16,000 deaths, four times the number of overdose deaths related to these drugs in 1999. In 2014 this number is 19,000 deaths

2016 Feb

The NEW ENGLAND JOURNAL of MEDICINE

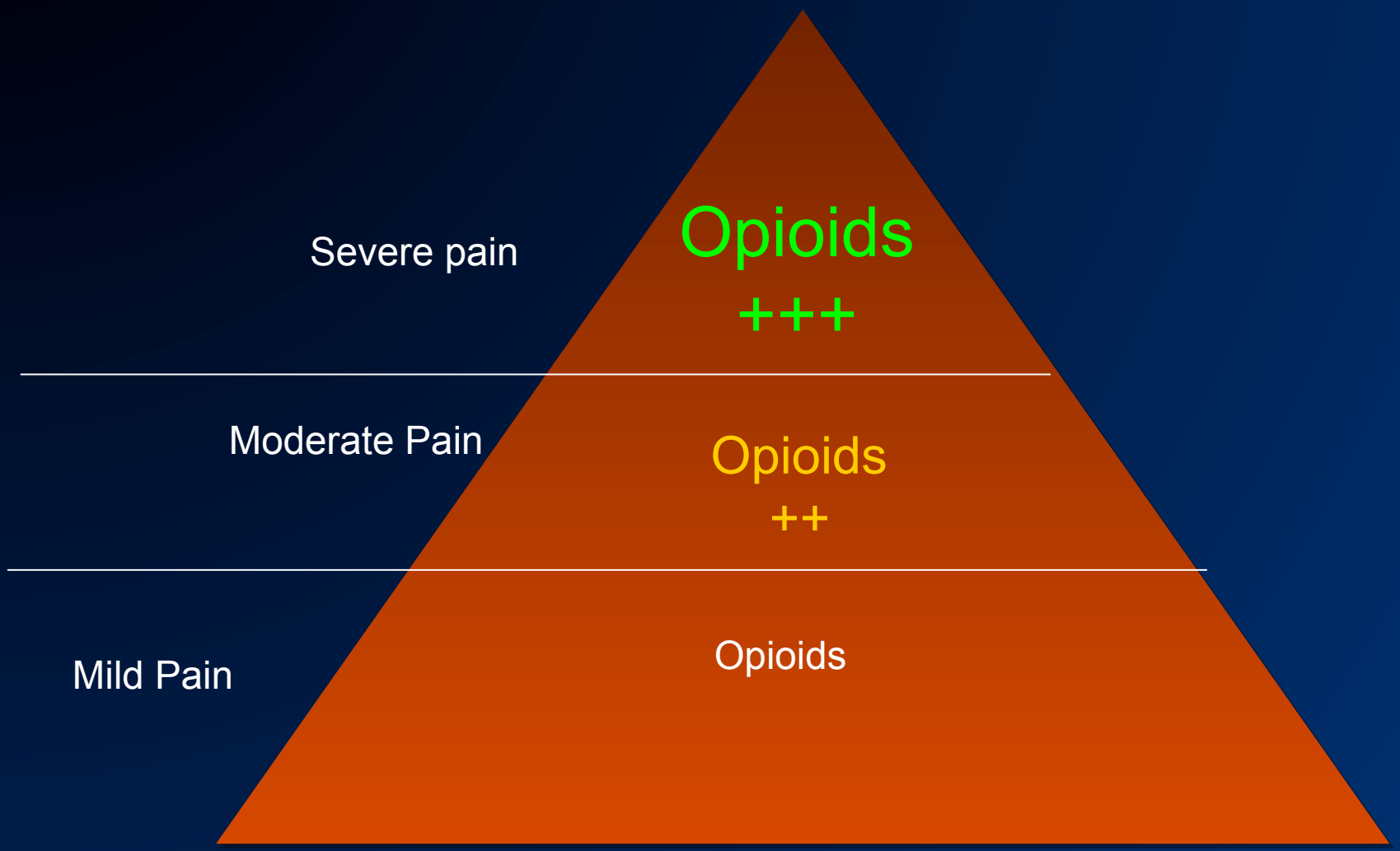
SPECIAL REPORT FDA

A Proactive Response to Prescription Opioid Abuse

Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D.

- Nationally, the annual number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents.
- Regardless of whether we view these issues from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable.

Management of Acute Pain



Opioids and Acute Pain

- In 2008, 20.8% of reported using at least one prescribed opioid medication during the preceding 12 months.

- Of those who reported being prescribed an opioid:
  - **71.0%** said they were prescribed the drug for short-term pain
  - 14.7% said they were prescribed the drug for long-term pain
  - 14.4% said they were prescribed the drug for both short-term and long-term pain.

Opioids and Acute Pain

- Of respondents prescribed at least one opioid during the preceding 12 months:
  - *72.0% had leftover medication from their most recently filled prescription*.
- Of those with **left over medication**:
  - 71.0% reported that they had kept the medication
  - 25.2% had disposed of the medication,
  - 2.3% had given the medication to someone else.
- Among respondents, 3.2% of those who had received a prescription opioid reported using the medication more frequently or in higher doses than directed by their doctor.

Proposed CDC Guidelines & Acute Pain

- **# 6.**
- Long-term opioid use often begins with treatment of acute pain.
- When opioids are used for acute pain, providers should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
- Three or fewer days usually will be sufficient for most nontraumatic pain not related to major surgery (recommendation category: A, evidence type: 4).

Ohio | Med Bd E-News

med.ohio.gov

January 22, 2016 SPECIAL EDITION

Ohio's New Opioid Prescribing Guidelines for Acute Pain Expand Fight Against Prescription Drug Abuse

- In 2014, more than 262 million opioid doses were dispensed in Ohio for the management of acute pain —35% of the state's 750 million dispensed opioid doses.
- Prescription opioids remain a significant contributor to unintentional drug overdose deaths in Ohio, contributing to nearly one-half of all deaths in 2014.

Definition of Multimodal Analgesia

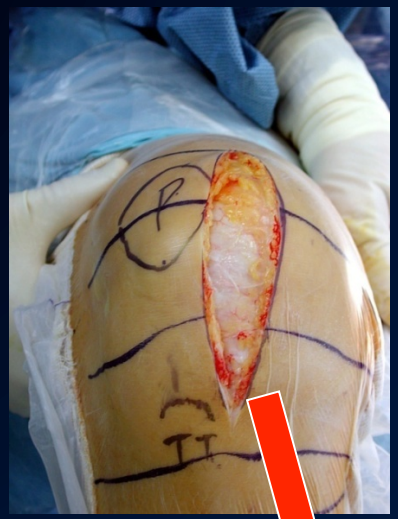
- Multimodal analgesia is the combination of different analgesics **that act by different mechanism**, resulting in additive or synergistic analgesia with lowered adverse effects; compared to sole administration of an individual pharmacological agent

- Goal: Decrease use of Postoperative Opioids

Kehlet H et al: *Anesth Analg* 1993; 77: 1048

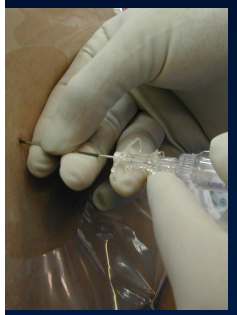
Surgery and Pain Mediators

Tissue Injury



Arachidonic acid

Inflammatory Mediators



Neuronal Pathway

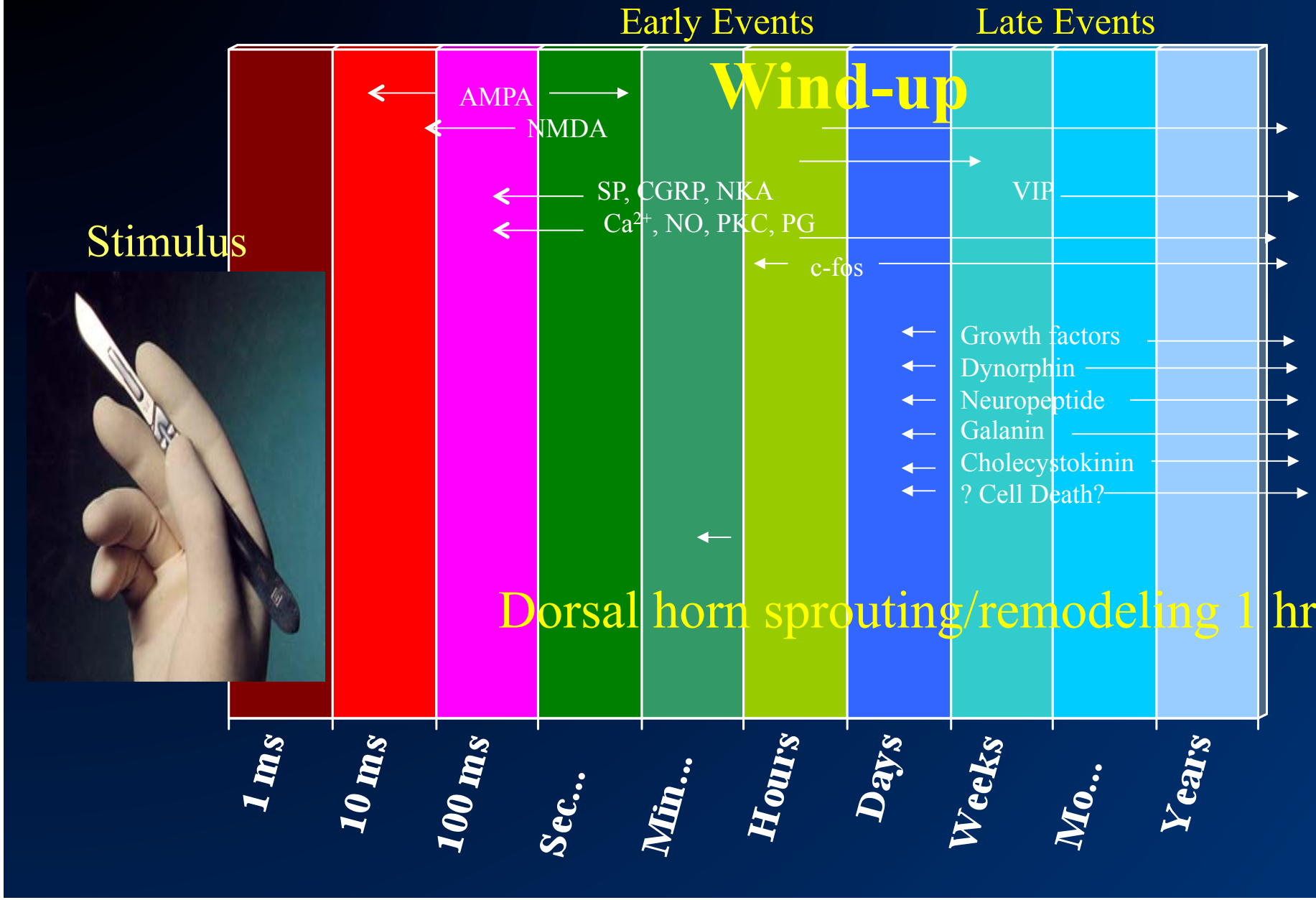
Multimodal Pharmacological

X

Regional Anesthesia
& Analgesia

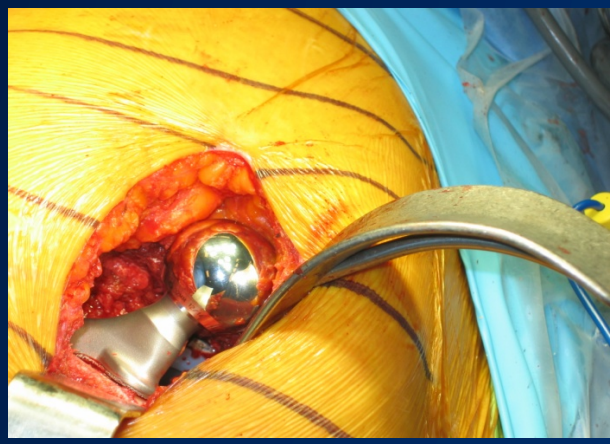
Spinal Cord

Biochemical Response to Surgery



Inflammatory Mediators with Spinal Anesthesia & Analgesia

- Prospective, controlled trial
- Patients had:
  - Standard hip replacement
  - Intrathecal catheter
  - Hip drain
- PGE_2 and ILs measured



■ 2005 JOURNAL SYMPOSIUM PLASTICITY AND POSTOP PAIN

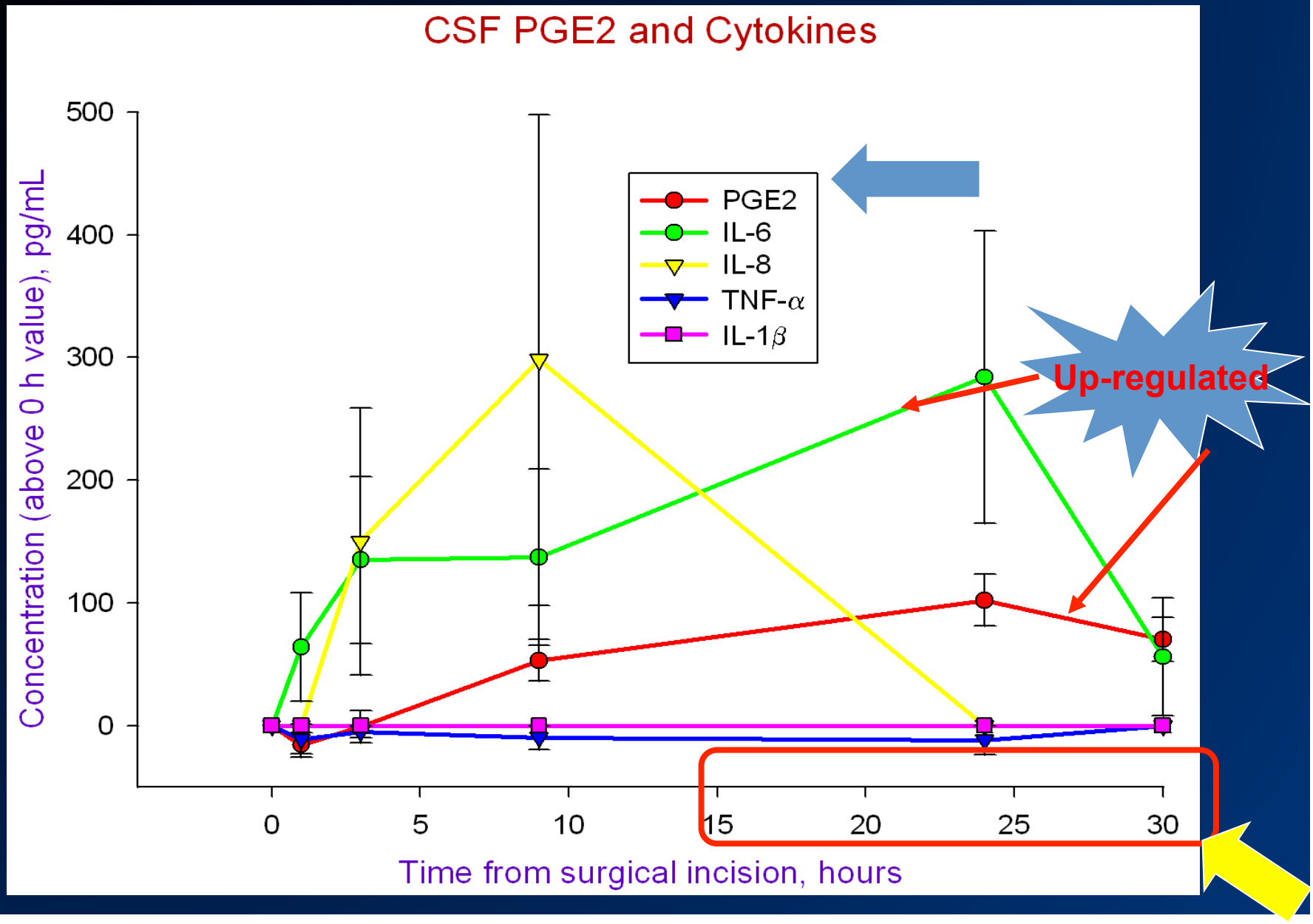
Anesthesiology 2006; 104:403–10

Upregulation of Prostaglandin E_2 and Interleukins in the Central Nervous System and Peripheral Tissue during and after Surgery in Humans

Asokumar Buvanendran, M.D., Jeffrey S. Kroin, Ph.D.,† Richard A. Berger, M.D.,‡ Nadim J. Hallab, Ph.D.,‡ Chiranjeev Saha, M.D.,§ Corina Negrescu, M.D.,‖ Mario Moric, Ph.D.,# Marco S. Caicedo, M.S.,** Kenneth J. Tuman, M.D.†*

CSF measurements

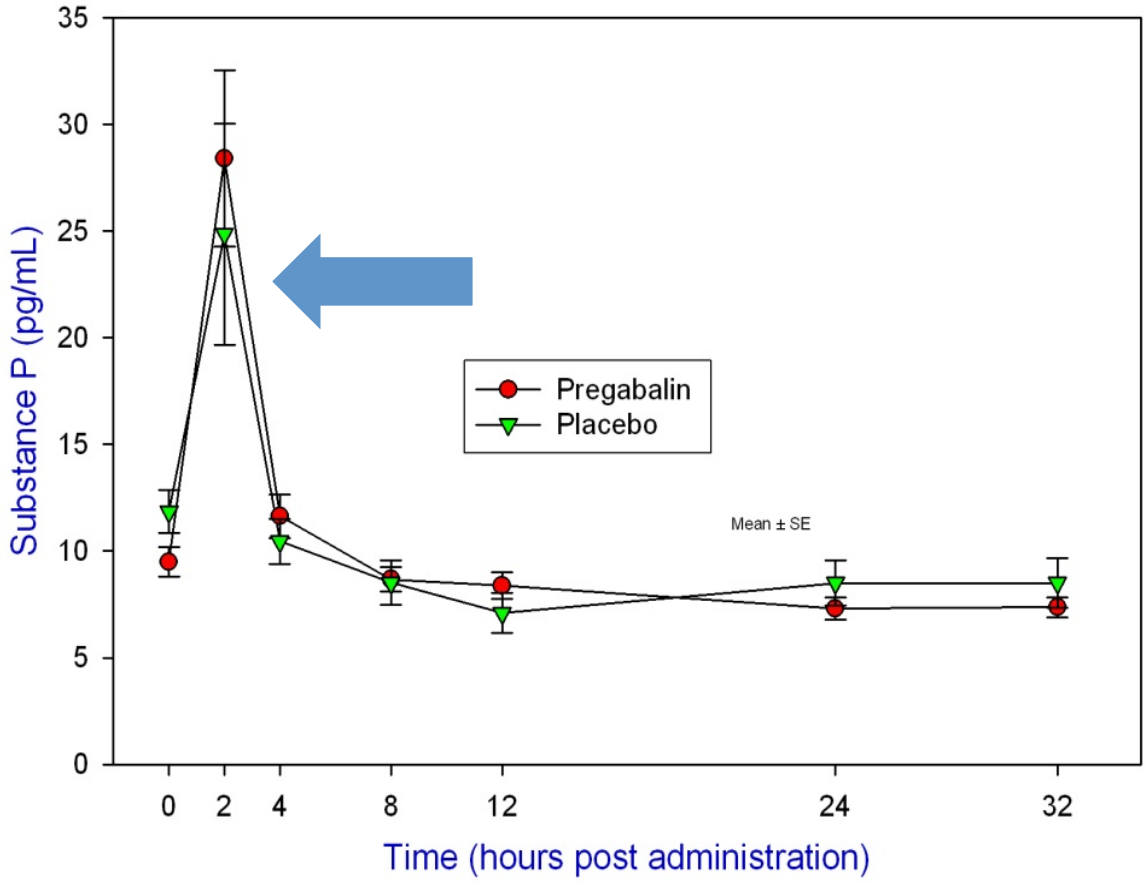
Buvanendran et al:Anesthsiology 2006



Cerebrospinal Fluid Neurotransmitter Changes During the Perioperative Period in Patients Undergoing Total Knee Replacement: A Randomized Trial

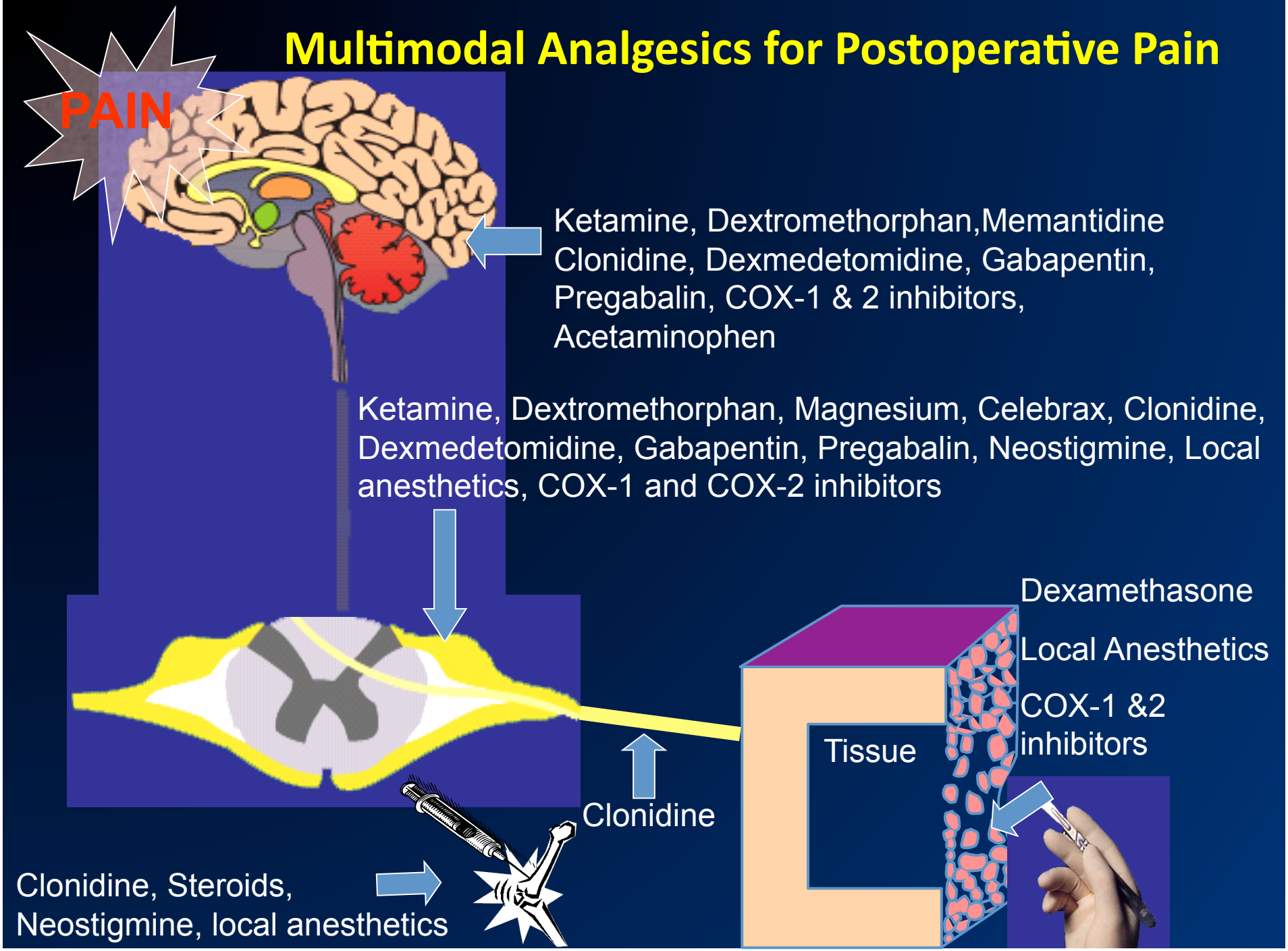
Asokumar Buvanendran, MD,* Jeffrey S. Kroin, PhD,* Craig J. Della Valle, MD,† Mario Moric, MS,* and Kenneth J. Tuman, MD*

2012; Feb



Glutamate
Substance P
Norepinephrine
Epinephrine

Multimodal Analgesics for Postoperative Pain



Meta-analyses: NSAIDs, COX-2 inhibitors & Acetaminophen

- 52 RCT were included:

Results:

- 24 h morphine consumption: ↓ 20 - 40 %
- Postoperative VAS: ↓ 10-15 %
- Opioid related AE: ↓ 15 – 25 %

Adverse events:

- Severe bleeding: 0 to 1.7%
- Renal insufficiency in *cardiac patients:* 0 % to 1.4%

Elia N et al: *Anesthesiology* 2005; 103: 1296-1304

Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review

E. Maund*, C. McDaid, S. Rice, K. Wright, B. Jenkins and N. Woolacott

BJA 2011

- 60 trials were included
- All patients received PCA morphine
- All surgical procedures were considered
- Primary outcome:
  - 24 hour morphine consumption
- Adverse effects:
  - 2.4% of NSAIDs had surgical bleeding vs 0.4% for placebo

NSAIDs, COX-2 inhibitor & Paracetamol

	Morphine consumption	PONV (odds ratio)
Paracetamol vs Placebo	- 8.68 mg	1.0
NSAIDs vs Placebo	- 9.45 mg	0.7
COX-2 vs Placebo	- 10.67 mg	0.8
NSAIDs vs Paracetamol	- 0.77 mg	0.7
COX-2 vs Paracetamol	- 1.99 mg	0.9
COX-2 vs NSAIDs	- 1.22 mg	1.2

Negative for morphine consumption means study drug better than control
Odds ratio < 1 intervention better than control

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

- July 2015: FDA strengthens warning that *non-aspirin NSAIDs can cause heart attacks or strokes*
- Based on our comprehensive review of new safety information, we are requiring updates to the drug labels of all prescription NSAIDs. As is the case with current prescription NSAID labels, the Drug Facts labels of over-the-counter (OTC) non-aspirin NSAIDs already contain information on heart attack and stroke risk. We will also request updates to the OTC non-aspirin NSAID Drug Facts labels.

Acetaminophen: Mechanisms of Action

- Exact mechanism of action still unclear[1]
- Analgesic effect
  - Inhibits the synthesis of prostaglandins in the CNS (central acting) and peripherally blocks pain impulse generation[2]
  - Unlike NSAIDs, not a strong peripheral COX inhibitor[1]
  - Proposed serotonergic (5-HT) mechanism[3]
- Antipyretic effect[2]
  - Inhibition of hypothalmic heat-regulating center
  - No anti-inflammatory effects

1. Aronoff DF, et al. *Clin Pharmacol Ther*. 2006;79:9-19.
2. Malaise et al. *Future Neurol* 2007;2:673-688.
3. Bonnefont J, et al. *Mol Pharacol*. 2007;71:407-415.

Single-dose Intravenous Acetaminophen for treatment of postoperative pain: Meta-Analysis

- 36 studies, n≈ 3,000
- ↓ 16-30% in opioid consumption in the acetaminophen group compared to placebo
- Patient satisfaction (VAS) was 1.6 better in the acetaminophen group compared to placebo

McNicol ED et al: *Br J Anaesth* 2011; 106: 764-75

- Prophylactically administered ↓ PONV, mainly mediated through superior pain control.

Apfel CC et al: Pain 2013

High Dose Preop Methylprednisolone for TKA

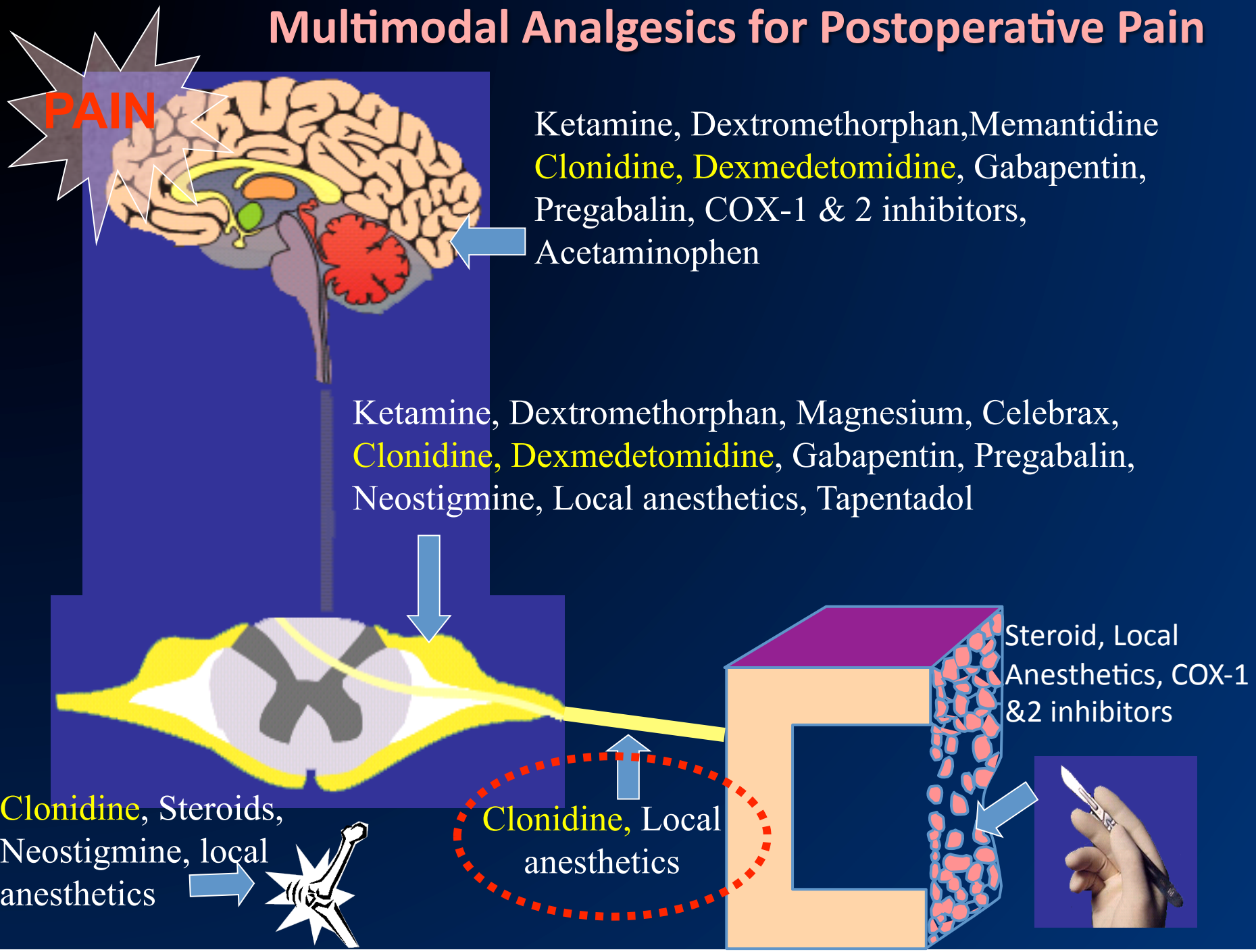
- RCT, n=48: Lunn TH et al: *Br J Anaesth* 2011; 106: 230-8
  - Study group: IV methyprednisolone 125 mg (2 ml)
- Standard TKA and spinal anesthetic
- Outcome in favor of high dose methyprednisolone:
  - ↓ 48 hour pain scores with walking and rest
  - ↓ postop opioid use & ↓ PONV
- Conclusion: safety of this needs to be determined

Similar results of ↓ 24 h pain scores obtained in THA after 125 mg of steroid administered preop

Lunn TH Br J Anaesth 2012; October

Alpha – 2 Agonist

Multimodal Analgesics for Postoperative Pain



Effect of systemic alpha 2 agonist on postoperative pain intensity

- 13 RCT with clonidine and dexmedetomidine (n=1792 patients)

	↓ Morphine consumption	↓ Pain Scores
Clonidine	4.1 mg	0.7
dexmedetomidine	14.5 mg	0.6

- Side effects: Hypotension and bradycardia

Blaudszun G et al: Anesthesiology 2012 July

Clonidine as an Adjuvant to Local Anesthetics for Peripheral Nerve and Plexus Blocks

Anesthesiology 2009

A Meta-analysis of Randomized Trials

Daniel M. Pöpping, M.D., Nadia Elia, M.D., M.Sc.,† Emmanuel Marret, M.D.,‡ Manuel Wenk, M.D.,* Martin R. Tramèr, M.D., D.Phil.§*

- 20 RCT, n=1054
- Intermediate (n=12) and long (n=13) acting LA were included
- Doses used for clonidine: 90-150 μg
- Peripheral and plexus blocks examined

Clonidine as an Adjuvant to Local Anesthetics for Peripheral Nerve and Plexus Blocks

A Meta-analysis of Randomized Trials

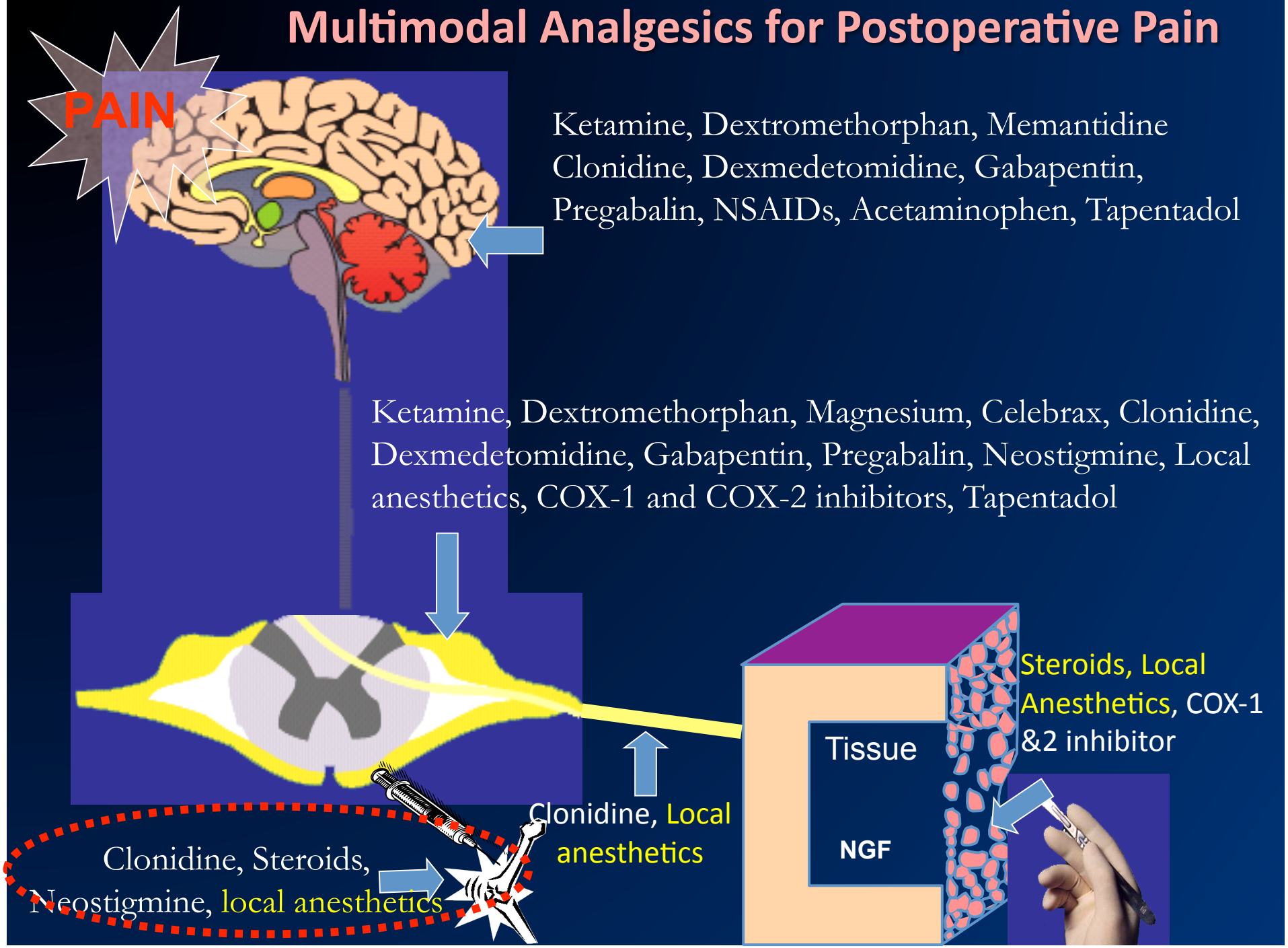
Anesthesiology 2009

Daniel M. Pöpping, M.D., Nadia Elia, M.D., M.Sc.,† Emmanuel Marret, M.D.,‡ Manuel Wenk, M.D.,* Martin R. Tramèr, M.D., D.Phil.§*

- Results:
  - ↑ Duration of analgesia by 123 min. No evidence for dose response
  - ↓ onset time of block by 2.2 min
  - ↑ duration of Sensory block by 74 min
  - ↑ duration of motor block by 141 min
- When split by type of LA, the ↑ was more pronounced in the long acting compared to intermediate acting LA
- Adverse events: ↑ of hypotension (4.1 vs 13.1) & bradycardia (4.1 vs 8.5%) in the clonidine group

Administration of local Anesthetics, Adjuvant to surgical site

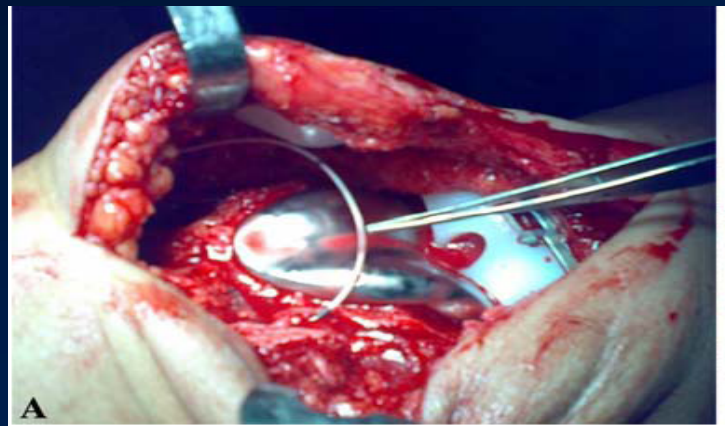
Multimodal Analgesics for Postoperative Pain

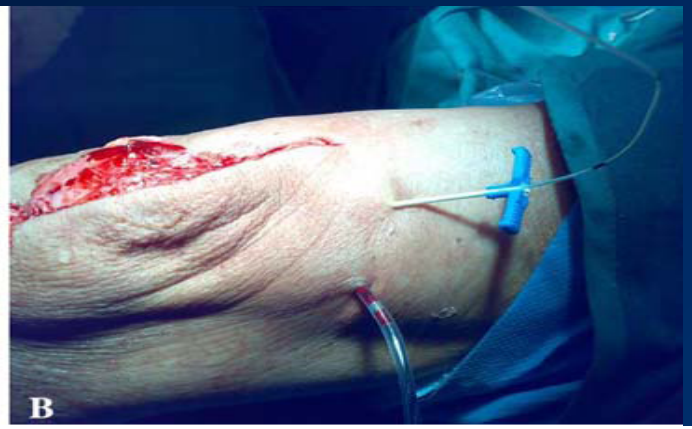


Intraarticular local anesthetics for TKA

- RCT of 160 patients, elastomeric infusion pump of 300 ml
- 0.5 % bupivacaine vs saline at 5 mls/hr
- Multimodal analgesia with spinal bupivacaine
- Results
  - ↓ in pain scores
  - ↓ narcotic consumption

Goyal N et al: Clin Orthop Rel Res 2012; September





Analgesic efficacy of local infiltration analgesia in hip & knee arthroplasty: a systematic review

- 27 RCT, n=756 patients THA and 888 TKA
- 9 RCT = 760 THA patients:
- There was strong evidence of an association between LIA and reduced pain scores at 4 hours at rest ($P < .00001$) and with motion ($P < .00001$), 6 hours with motion ($P = .02$), and 24 hours at rest ($P = .01$), and decreased analgesic consumption during 0 to 24 hours ($P = .001$)
    - Yin J J Pain 2014
    - British J Anaesthesia: 2014; 113: 360.
    - L. Ø. Andersen and H. Kehlet

Meta-Analysis of Ketamine for Perioperative Use

- 70 RCT (n=4701) and IV ketamine demonstrated ↓ opioid consumption and ↑ time to first request for analgesia

- Dose: 0.1 - 0.5 mg/ kg bolus ± 0.1- 0.5 mg/kg/hr infusion

Laskpwski K et al: *Can J Anesth* 2011; 58: 911

Intraoperative Ketamine attenuates Inflammatory response. Meta-Analysis

- 6 RCT studies examined.
- Results: Ketamine has an anti-inflammatory effect based IL-6 plasma/serum as an outcome

Dale O et al: Anesth Analg 2012;115: 934-43

CME Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial

Asokumar Buvanendran, MD*
Jeffrey S. Kroin, PhD*
Craig J. Della Valle, MD†
Maruti Kari, MD*
Mario Moric, MS*
Kenneth J. Tuman, MD*

BACKGROUND: Despite the enormous success of total knee arthroplasty (TKA), chronic neuropathic pain can develop postoperatively and is both distressing and difficult to treat once established. We hypothesized that perioperative treatment with pregabalin, a chronic pain medication, would reduce the incidence of postsurgical neuropathic pain.

METHODS: We performed a randomized, placebo-controlled, double-blind trial of pregabalin (300 mg) administered before TKA and for 14 days after TKA (150–50 mg twice daily). Patients were screened for the presence of neuropathic pain at 3 and 6 mo postoperatively using the Leeds Assessment of Neuropathic Symptoms and Signs scale. Secondary outcomes included postsurgical recovery and rehabilitation measures, including knee range of motion, opioid consumption, postoperative pain scores, sleep disturbance, and time to discharge as well as the occurrence of postoperative systemic complications.

RESULTS: Of the 240 patients randomly assigned to the 2 treatment groups (120 in each), data for the primary outcome were obtained from 113 pregabalin patients and 115 placebo patients. At both 3 and 6 mo postoperatively, the incidence of neuropathic pain was less frequent in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 mo, respectively; $P = 0.001$ and $P = 0.014$). Patients receiving pregabalin also consumed less epidural opioids ($P = 0.003$), required less oral opioid pain medication while hospitalized ($P = 0.005$), and had greater active flexion over the first 30 postoperative days ($P = 0.013$). There were no differences in the actual recorded duration of hospitalization between the 2 groups, although time to achieve hospital discharge criteria was longer for placebo patients, 69.0 ± 16.0 h (mean ± SD), than that of pregabalin patients, 60.2 ± 15.8 h ($P = 0.001$). Sedation ($P = 0.005$) and confusion ($P = 0.013$) were more frequent on the day of surgery and postoperative day 1 in patients receiving pregabalin.

CONCLUSION: Perioperative pregabalin administration reduces the incidence of chronic neuropathic pain after TKA, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. However, in the doses tested, it is associated with a higher risk of early postoperative sedation and confusion.

(Anesth Analg 2010;110:199–207)

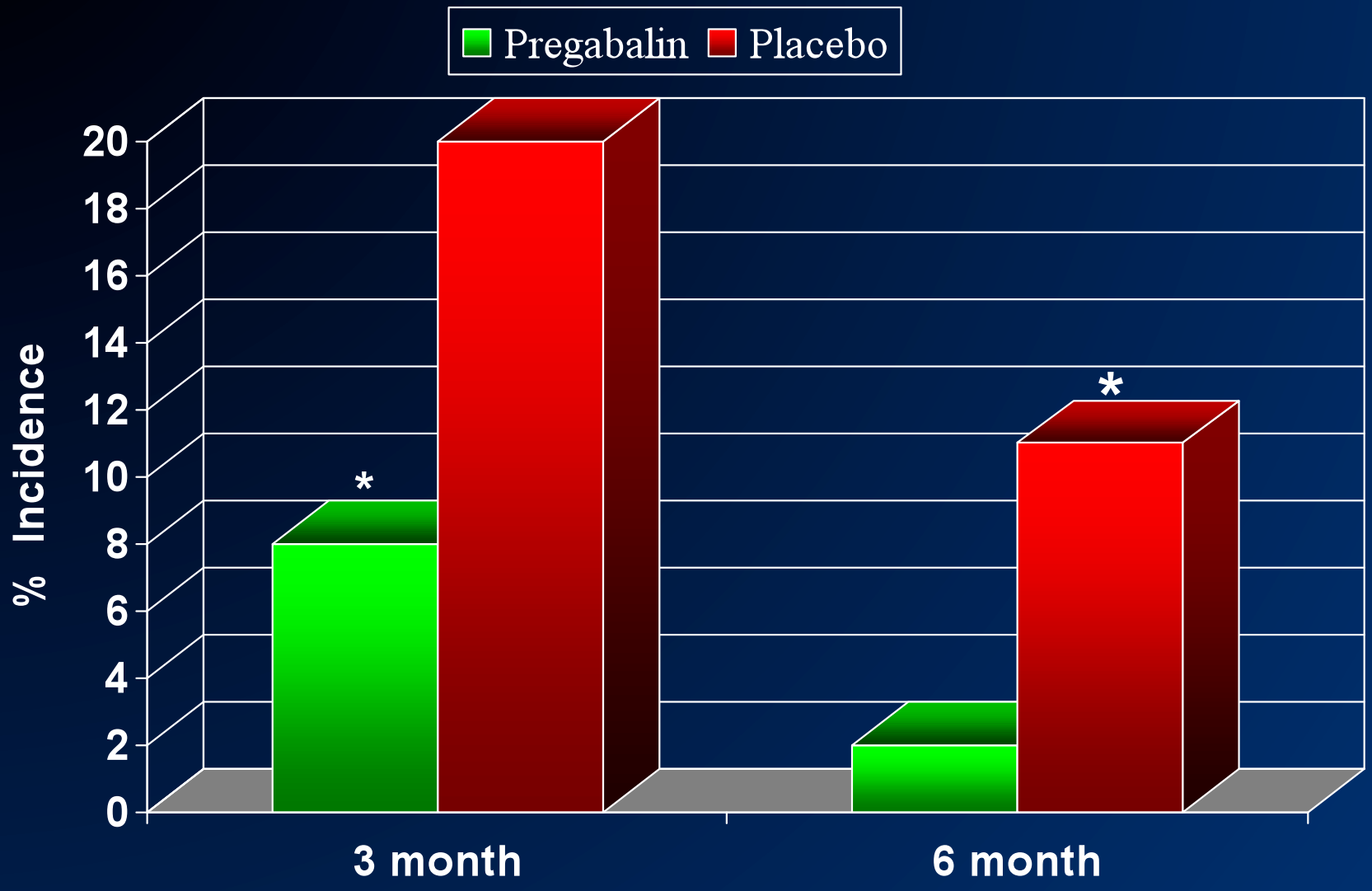
Oral Pregabalin Preop + Postoperative for TKA

Buvanendran A et al: *Anesth Analg* 2010

- RCT, 240 into 2 groups:
  - Preop pregabalin 300 mg + Postop 150 mg BID for 10 days and then 75 mg BID and titrated to 50 mg and stopped on day #14
  - Preop Placebo + Postop Placebo
- Standard surgery and anesthesia
- All patients received COX-2 inhibitor +acetaminophen

- Primary Outcomes:
  - Neuropathic pain at 3 and 6 months postop using the S-LANSS
- Follow-up data:
  - N= 113 patients for pregabalin; N=115 patients for Placebo

Allodynia or Hyperalgesia of Knee

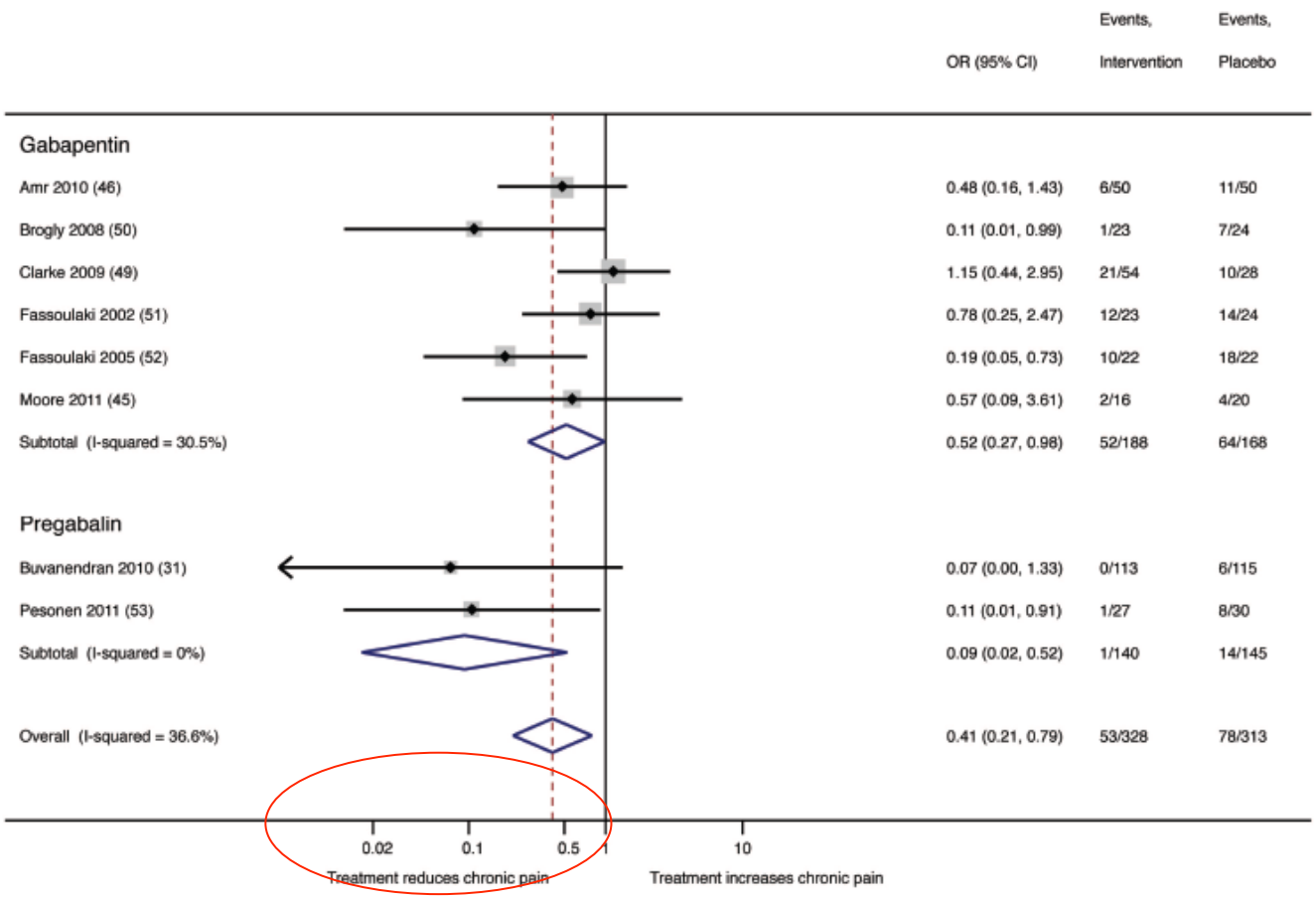


Buvanendran et al: *Anesth Analg 2010*

The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis

Hance Clarke, MSc, MD, FRCPC,*†‡ Robert P. Bonin, PhD,§ Beverley A. Orser, MD, PhD, FRCPC,†‡ Marina Englesakis, BA MLIS,‖ Duminda N. Wijeysundera, MD, PhD, FRCPC,*‡¶# and Joel Katz, PhD**

567 clinical trials screened & 11 RCT study met criteria



Anesth Analg 2012;

Perioperative Gabapentinoids

Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain

Peter C. Schmidt, M.D.,* Gabriela Ruchelli, B.A.,† Sean C. Mackey, M.D., Ph.D.,‡
Ian R. Carroll, M.D., M.S. Epi.§

November 2013

Authors	N	Surgery	Gabapentinoid Dose	Findings
Fassoulaki *et al.*[35]	60	Abdominal hysterectomy	Gabapentin 400 mg every 6 h beginning preoperatively and continuing for 5 days	Decreased incidence and intensity of pain at 1 month
Sen *et al.*[43]	60	Herniorrhaphy	Gabapentin 1,200 mg 1 h before surgery	Decreased pain scores at 1, 3, and 6 months
Sen *et al.*[42]	60	Abdominal hysterectomy	Gabapentin 1,200 mg 1 h before surgery	Decreased incidence of incisional pain at 1, 3, and 6 months
Brogly *et al.*[31]	50	Thyroidectomy	Gabapentin 1,200 mg 2 h before surgery	Decreased incidence of neuropathic pain at 6 months
Amr and Yousef[30]	150	Mastectomy	Gabapentin 300 mg/day starting the night before surgery and continuing for 10 days	Decreased incidence of burning pain at 6 months
Fassoulaki *et al.*[36]	75	Breast surgery for cancer	Gabapentin 1,200 mg/day for 10 days after surgery	Decreased incidence of burning pain at 3 months
Buvanendran *et al.*[26]	240	Total knee arthroplasty	Pregabalin 300 mg 1–2 h before surgery and a 14-day taper after surgery	Decreased incidence of neuropathic pain at 3 and 6 months
Pesonen *et al.*[41]	70	Cardiac surgery	Pregabalin 150 mg 1 h before surgery and 150 mg daily for 5 days	Decreased incidence of pain with movement at 3 months
Burke and Shorten[32]	40	Lumbar discectomy	Pregabalin 300 mg 90 min before surgery and 150 mg at 12 and 24 h after surgery	Decreased pain scores and improved function at 3 months

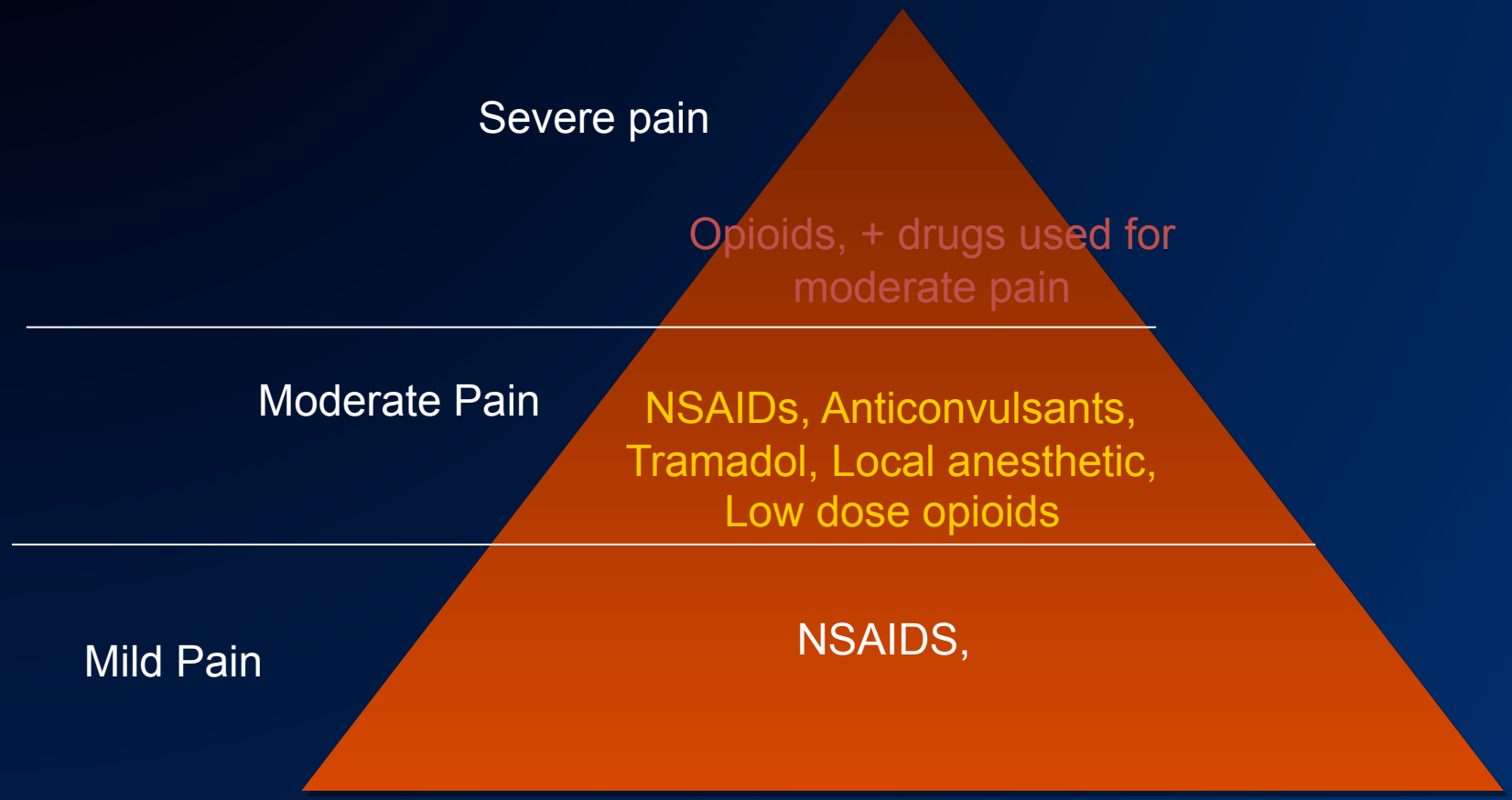
Table 4. Studies Finding No Effect on Prolonged Postoperative Pain

Authors	N	Surgery	Gabapentinoid Dose	Findings
Ucak *et al.*[44]	40	Coronary artery bypass graft	Gabapentin 1,200 mg before and for 2 days after surgery	No difference in pain scores at 1 and 3 months (all scores ≤1)
Clarke *et al.*[33]	126	Total hip arthroplasty	Gabapentin 600 mg 1–2 h before surgery or 600 mg immediately postoperatively	No difference in presence or severity of pain at 6 months
Moore *et al.*[39]	44	Cesarean section	Gabapentin 600 mg 1 h before surgery	No difference in persistent pain or abnormal wound sensation at 3 months
Nikolajsen *et al.*[40]	41	Lower limb amputation	Gabapentin titrated to 2,400 mg/day beginning on the first postoperative day and continuing for 30 days	No difference in phantom or stump pain at 3 and 6 months
Gianesello *et al.*[37]	60	Lumbar laminectomy and fusion	Pregabalin 300 mg 1 h before surgery for 2 days after surgery	No difference in pain scores at 3 months and 1 yr (quality of life measures improved at 3 months)
Kim *et al.*[38]	94	Endoscopic thyroidectomy	Pregabalin 150 mg 1 h before surgery and at 12 h after surgery	No difference in pain or hypoesthesia at 3 months
Fassoulaki *et al.*[35]	80	Abdominal hysterectomy or myomectomy	Pregabalin 150 mg every 8 h starting the afternoon before surgery and continuing 5 days	No difference in presence of pain, analgesic intake, or wound sensation at 1 and 3 months

Conclusion: 16 trials. 9 + ve. 3 of the 7 –ve trials did not have adequate sample size

- **Gabapentinoids are more likely to have a preventive effect on chronic pain after surgery**

Multimodal Approach to treatment of Acute Pain



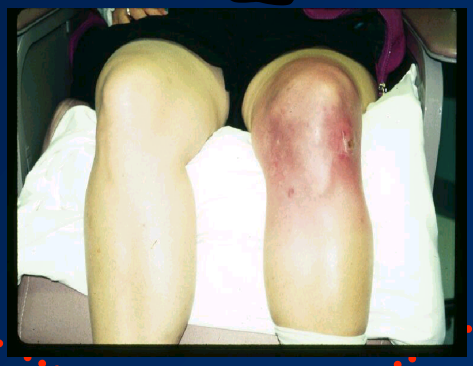
When Acute PAIN Becomes a DISEASE

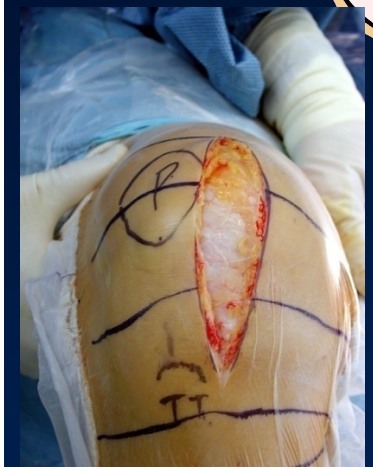
Acute Pain

Hours-to-days
Tissue Healing

Good Outcome

Weeks-to-months-years
Tissue Healing

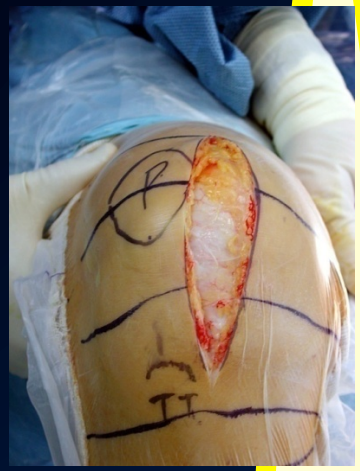




Surgery

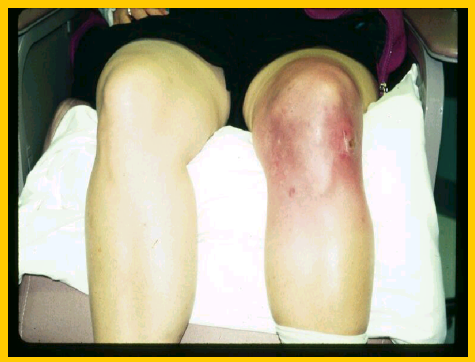
Disease: Chronic Pain
Symptom: Pain

Acute to Chronic Pain (PPP)



Pain

?

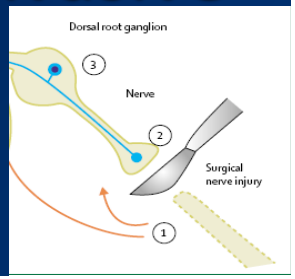


Time

Why do patients develop Chronic Pain after Surgery? And Prevention Strategy

1. On going inflammatory process from the surgery
   - Strategy to Prevent: Aggressive Multimodal Analgesia

2. Surgical injury or irritation to peripheral nerves: Leads to chronic neuropathic pain
   - Strategy to Prevent: Education of our surgical colleagues of the incidence so that less invasive or meticulous surgical techniques



Why do patients develop Chronic Pain after Surgery? And Prevention Strategy

3. Patient genetic make up or pre-operative factors such as preoperative chronic pain and opioid use:

- Prevention: With greater understanding of genetics and pain, may be in the future, we will be able to predict the patients who will develop chronic pain from gene isolation preop

Acute Postoperative Pain and PPP

- Following surgical procedures have demonstrated this relationship:
  - Craniotomy. Vijayan N: Headache 1995; 35: 98-100.
  - Total Hip replacement. Nikolajsen L, et al: Acta Anaesthesiol Scand 2006; 50: 495
  - Breast surgery. Poleshuck EL, et al: J Pain 2006; 7: 626–34
  - Cardiac surgery. Gulik L et al: Eur J Cardio thorac surg 2011; 40: 1309-131
  - Caesarean section. Nikolajsen L et al: Acta Anaesthesiol Scand 2004; 48: 111–6
  - Donor nephrectomy. Owen M et al: Eur J Pain 2010; 14: 732-34
  - Hernia surgery. Aasvang E, et al: Br J Anaesth 2005; 95: 69–76

Consequence of Patients who develop PPP

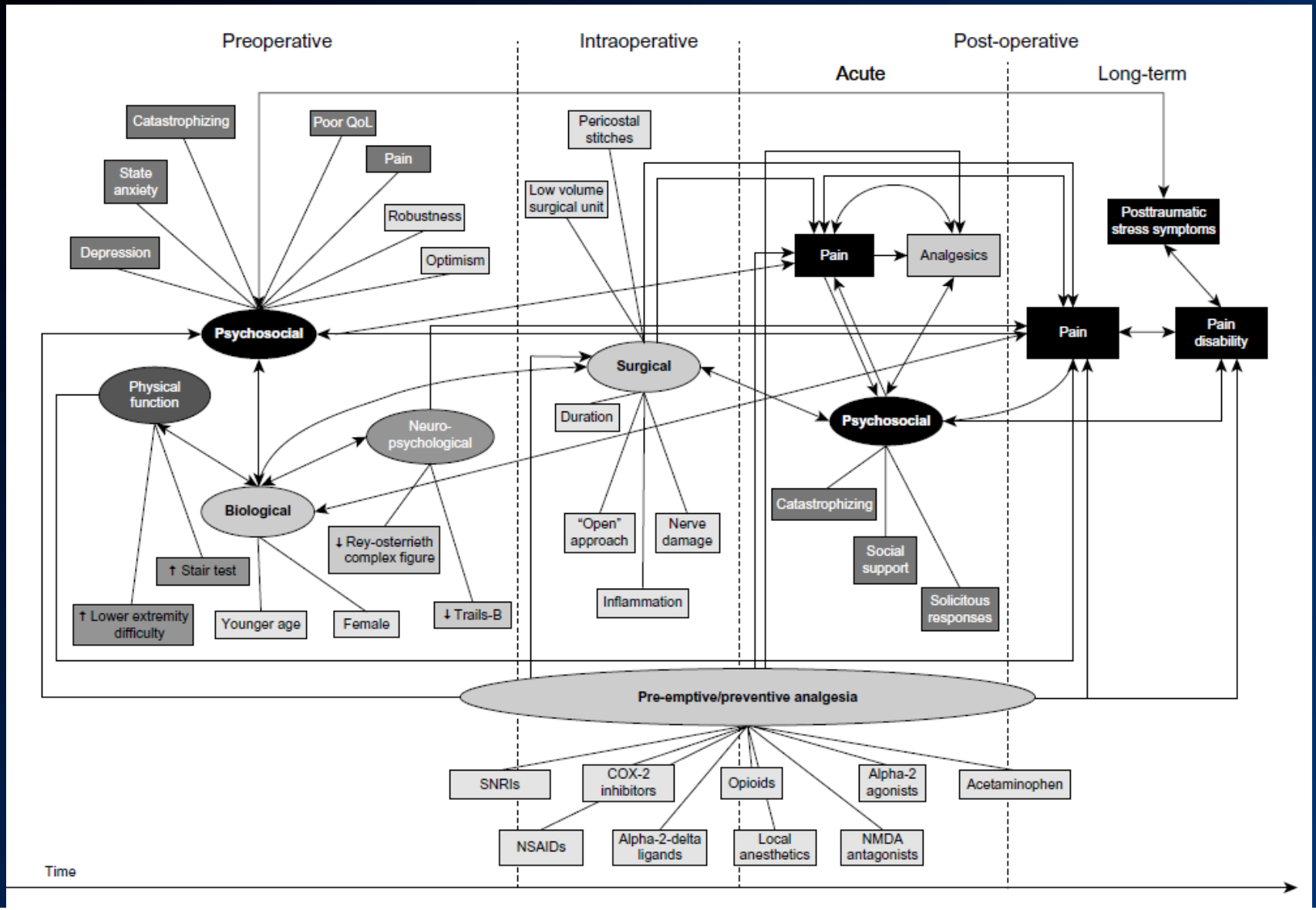
- Severity of PPP pain is related to impairment of health related quality of life, increased health care resources utilization and decreased labor force participation.

  Langley P et al: J Med Econ 2010; 13: 571-81

- ↑ health care cost as they go from physician to physician in trying to get an answer. Physicians prescribe opioids for the treatment of this Chronic pain and now the patients become tolerant to opioids.

Transition Pain Service at TGH:

Katz J et al: J of Pain Research 2015

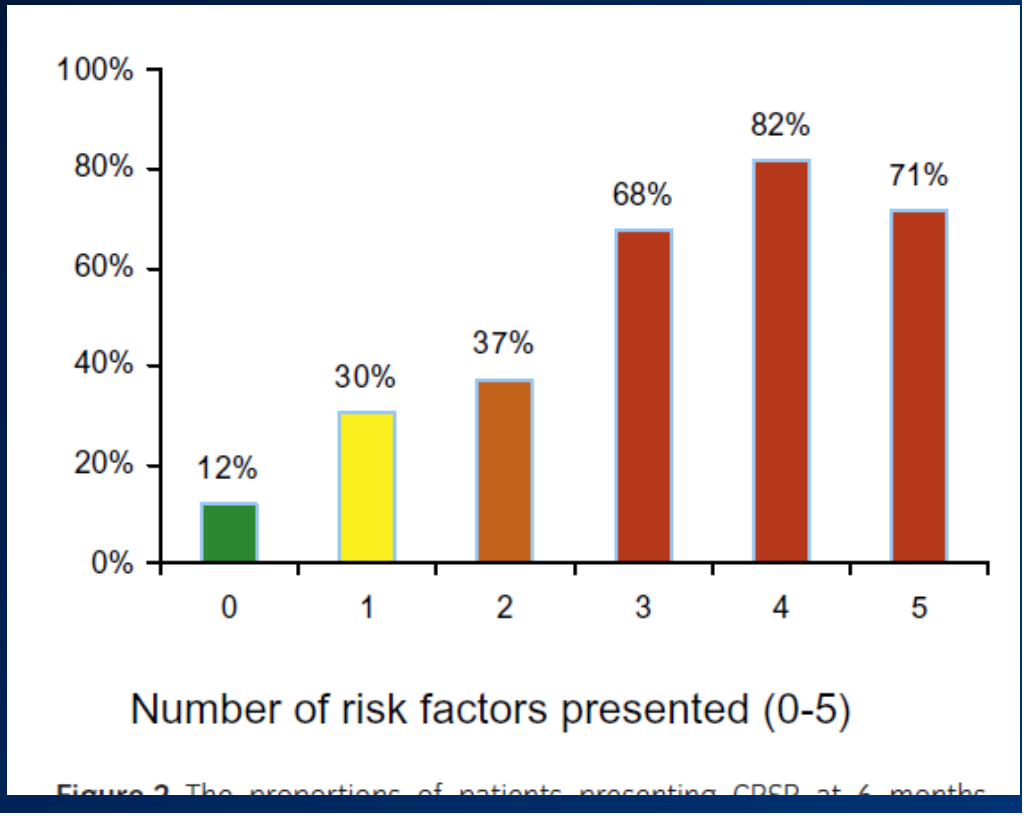


Development of a risk index for the prediction of chronic post-surgical pain

A. Althaus[1], A. Hinrichs-Rocker[1], R. Chapman[2], O. Arránz Becker[3], R. Lefering[1], C. Simanski[4], F. Weber[5], K.-H. Moser[6], R. Joppich[7], S. Trojan[7], N. Gutzeit[1], E. Neugebauer[1]

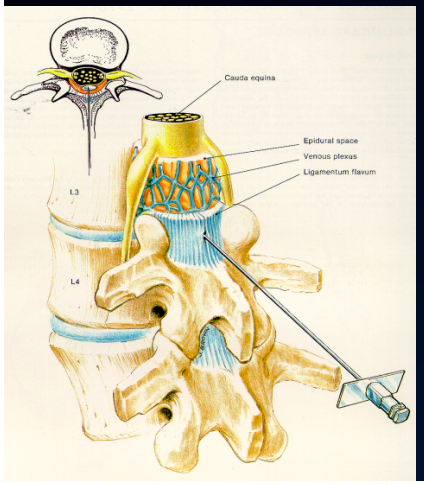
Eur J Pain 2012

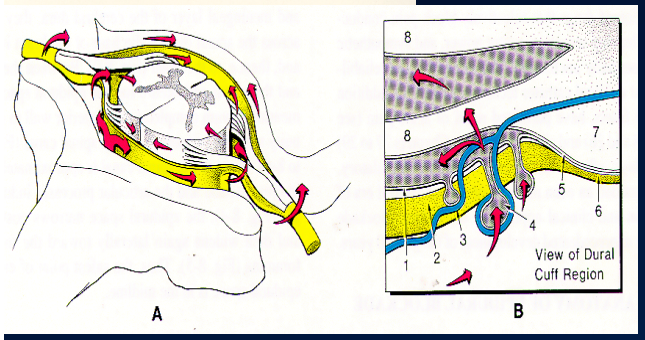
- Factors identified:
  - Preoperative Pain at site
  - Preoperative pain at other locations
  - Acute Postoperative Pain
  - Other stress factors



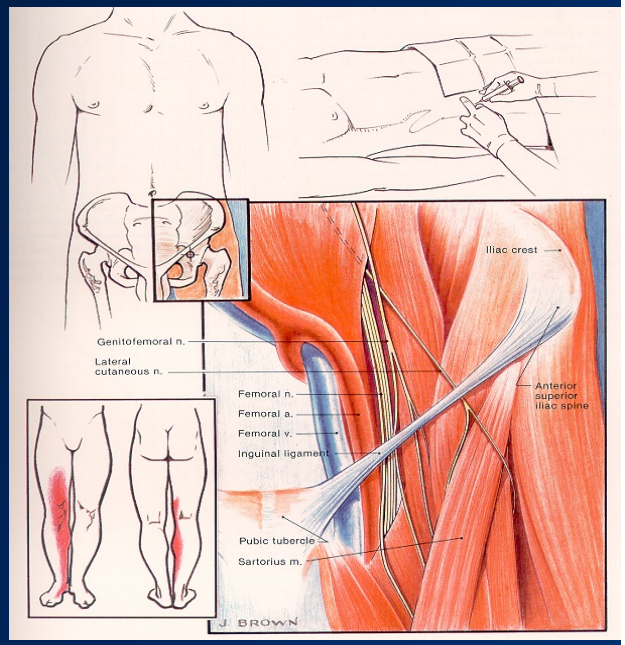
Regional Anesthesia & Analgesia for Postoperative Pain Management

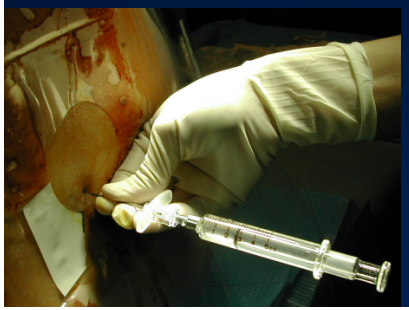
Why the change in Paradigm from Epidural to peripheral Nerve Blocks?





Ultrasound





Thrombo-embolic Recommendations by
American College of Chest Physicians and AAOS

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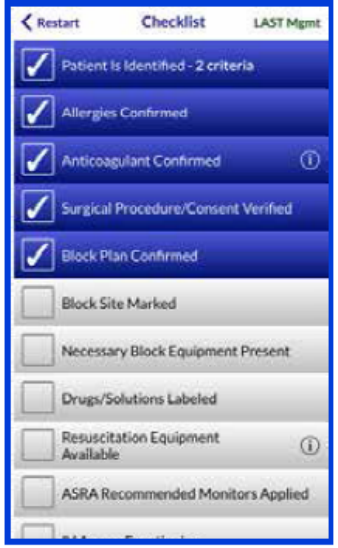

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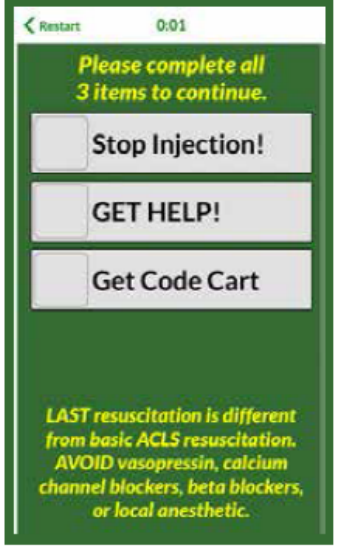
- Available for $3.99



ASRA Coags Regional, ASRA Coags Pain, and ASRA Timeout are available on iTunes for iOS and Google Play for Android.
ASRA LAST is available on iTunes for iOS.

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The information contained in the ASRA apps is based on published data and expert opinion. It is to be used as a recommendation only. Clinical judgment by a physician is required in every situation. User assumes all responsibility for decisions made in concert with the use of apps.

Code Developed By:
Mustard Seed Software

Powered by VANDERBILT

Perioperative Comparative Effectiveness of Anesthetic Technique in Orthopedic Patients

Stavros G. Memtsoudis, M.D. Anesthesiology 2013

- 400 hospitals and N=528,495 patients from 2006-2010
- Data was examined (retrospect) for 382,236
- Results:
  - 11%: Neuroaxial alone
  - 14.2%: Combined Neuroaxial + GA
  - 74.8%: GA alone

Anesthesia Type and Outcome

Incidences of Various Complications by Anesthesia Type

	Neuraxial % (N)	Neuraxial/General % (N)	General % (N)	Missing % (N)	*P* Value†
Systemic complications					
Pulmonary embolism	0.35 (129)	0.34 (172)	0.44 (1,307)	0.38 (567)	0.001
Cerebrovascular event	0.07 (28)	0.12 (58)	0.13 (374)	0.11 (146)	0.006
Pulmonary compromise	0.37 (141)	0.61 (310)	0.81 (2,234)	0.55 (816)	<0.001
Cardiac (nonmyocardial infarction)	6.20 (2,564)	6.61 (3,287)	6.42 (18,644)	6.32 (9,409)	0.07
Pneumonia	0.69 (295)	0.83 (435)	0.94 (2,669)	0.80 (1,157)	<0.001
All infections	3.11 (1,301)	3.87 (1,943)	4.50 (12,507)	4.22 (5,795)	<0.001
Acute renal failure	1.10 (456)	1.43 (731)	1.75 (4,935)	1.24 (1,821)	<0.001
Gastrointestinal complication	0.70 (285)	0.72 (366)	0.77 (2,294)	0.77 (1,122)	0.26
Acute myocardial infarction	0.24 (102)	0.26 (126)	0.28 (787)	0.26 (373)	0.47
Resource utilization					
Mechanical ventilation	0.39 (192)	0.49 (279)	0.72 (2,022)	0.94 (1,303)	<0.001
Blood product transfusion	15.15 (6,646)	15.56 (8,628)	18.53 (54,700)	22.41 (30,204)	<0.001
Mortality					
30-Day mortality	0.10 (42)	0.10 (54)	0.18 (493)	0.13 (209)	<0.001

† *P* value is to test the null hypothesis of no difference in incidence among neuraxial, general, and neuraxial/general (chi-square test).

Does the Impact of the Type of Anesthesia on Outcomes Differ by Patient Age and Comorbidity Burden?

RAMP 2014

Stavros G. Memtsoudis, MD, PhD, FCCP, Rehana Rasul, MPH, MA,† Suzuko Suzuki, MD,* Jashvant Poeran, MD, PhD,† Thomas Danninger, MD,* Christopher Wu, MD,‡ Madhu Mazumdar, PhD, MA, MS,† and Vassilios Vougioukas, MD§*

- N= 795,135 THA &TKA (2006 – 2012); 500 hospitals.
- Incidence of major complications was highest in the oldest patient group with cardiopulmonary disease (26.1%) and the lowest in the youngest group without cardiopulmonary disease (4.5%).
- Neuraxial anesthesia was associated with decreased odds for major complications, need for intensive care services, and prolonged length of stay compared with GA.
- For patients without major cardiopulmonary co-morbidities, the positive impact of neuraxial anesthesia increased with increasing age.

Differences in Short-Term Complications Between Spinal and General Anesthesia for Primary Total Knee Arthroplasty

JBJS 2013

Andrew J. Pugely, MD, Christopher T. Martin, MD, Yubo Gao, PhD, Sergio Mendoza-Lattes, MD, and John J. Callaghan, MD

- N= 14,052 TKA (2005-2010)

TABLE II Unadjusted Thirty-Day Complication Rates

	General Anesthesia (N = 8022)	Spinal Anesthesia (N = 6030)	P Value
Complications *(%)*			
Any complication	12.34	10.72	0.0032*
Blood transfusion	6.07	5.02	0.0086*
Superficial wound infection	0.92	0.68	0.0003*
Deep wound infection	0.12	0.18	0.51

Effects of Regional Versus General Anesthesia on Outcomes After Total Hip Arthroplasty

A Retrospective Propensity-Matched Cohort Study

JBJS 2015

Mohammad A. Helwani, MD, Michael S. Avidan, MBBCh, Arbi Ben Abdallah, PhD, Dagmar J. Kaiser, MD, John C. Clohisy, MD, Bruce L. Hall, MD, and Heiko A. Kaiser, MD

Investigation performed at the Washington University in St. Louis School of Medicine, St. Louis, Missouri

- N=12,929 patients with THA (2007-2011)

TABLE II Unadjusted Outcomes of Regional Versus General Anesthesia Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
Outcomes	Regional* (N = 5103)	General* (N = 7826)	OR (95% CI); P Value	Regional* (N = 5102)	General* (N = 5396)	OR (95% CI); P Value
Deep surgical site infection	11 (0.2)	61 (0.8)	0.27 (0.1-0.5); p < 0.001	11 (0.22)	30.6 (0.57)	0.38 (0.2-0.7); p < 0.01
Hospital length of stay *(days)*	3.19 ± 1.61	3.37 ± 1.62	0.95† (0.93-0.96); p < 0.001	3.19 ± 1.61	3.35 ± 1.62	0.95‡ (0.93-0.97); p < 0.001
Prolonged hospital length of stay§	256 (5.0)	556 (7.1)	0.7 (0.6-0.8); p < 0.001	256 (5)	354 (6.6)	0·75 (0.64-0.89); p < 0.01
Mortality	15 (0.3)	39 (0.5)	0.59 (0.3-1.1)	15 (0.29)	20.1 (0.37)	0.78 (0.4-1.4)
Cardiovascular complications	44 (0.9)	121 (1.5)	0.55 (0.4-0.8); p < 0.001	44 (0.86)	75.6 (1.40)	0.61 (0.4-0.9); p < 0.01
Respiratory complications	23 (0.5)	85 (1.1)	0.41 (0.3-0.7); p < 0.001	23 (0.45)	47.1 (0.87)	0.51 (0.3-0.8); p < 0.01

Neuraxial Anesthesia Decreases Post-operative Systemic Infection Risk Compared to General Anesthesia in Knee Arthroplasty

- N=16,555 examined
  - 9,167: GA
  - 7,388: Neuroaxial
- Outcomes: Infection and other morbidity
- **Results**: In favor of Neuroaxial included
  - Composite infection rate ↓↓
  - Pneumonia ↓↓
- No difference in mortality (30 day)

Liu J 2013 A&A

The Impact of Anesthetic Management on Surgical Site Infections in Patients Undergoing Total Knee or Total Hip Arthroplasty

A&A 2015

Sandra L. Kopp, MD,* Elie F. Berbari, MD,† Douglas R. Osmon, MD, MPH,† Darrell R. Schroeder, MS,‡ James R. Hebl, MD,* Terese T. Horlocker, MD,* and Arlen D. Hanssen, MD§

- Retrospective data from 1998-2008
- Primary outcome: Diagnosis of SSI occurring early (< 30 days of surgery) or late (>30 days).
- Results: 202 patients identified.
- No difference if patient had Regional or General anesthesia in terms of SSI

Inpatient Falls after Total Knee Arthroplasty

The Role of Anesthesia Type and Peripheral Nerve Blocks

Anesthesiology 2014

Stavros G. Memtsoudis, M.D., Ph.D., F.C.C.P., Thomas Danninger, M.D.,
Rehana Rasul, M.P.H., M.A., Jashvant Poeran, M.D., Ph.D., Philipp Gerner, B.S.,
Ottokar Stundner, M.D., Edward R. Mariano, M.D., M.A.S., Madhu Mazumdar, Ph.D., M.A., M.S.

- Same data base of 400 hospitals.
- Analysis of more > 190,000 patients undergoing TKA reveals an overall in-patient fall rate of 1.6%
- The incidence of falls was higher among patients undergoing their surgery under general *versus* neuraxial or neuraxial/general anesthesia. (1.6% *vs. 1.3% vs. 1.5%; P = 0.0018).*
- *The proportion of patients suffering an* IF who received a PNB or not was not significantly different (1.58 *vs. 1.62%; P = 0.6933).*
- *In addition, patients suffering a fall* had a higher co-morbidity burden (mean Deyo index, 0.77 [SD = 1.03] *vs. 0.66 [SD = 0.97]; P < 0.001), which was also evident* by the higher prevalence of individual co-morbidities

Regional Anesthesia and PPP: Meta-Analysis Data

- 23 RCT included in the analysis.
- The type of regional anesthesia & analgesia provided with surgical type was divided.

- *Thoracotomy:* Data of 250 participants in 3 studies strongly favored epidural anesthesia for with an OR of 0.34 (95% CI 0.19–0.60) P<0.0002
- *Breast Surgery*: Favored paravertebral blocks for breast cancer surgery with an OR of 0.37 (95% CI 0.14–0.94) (P<0.04)

Andrea MH et al: BJA 2013

Thoracotomy and Breast Surgery and Regional Anesthesia

Andrea MH et al: BJA 2013

Study or subgroup	Favours regional Events	Total	Conventional pain control Events	Total	Weight	OR IV, Random, 95% CI
1.1.1 Thoracotomy (epidural analgesia)						
Ju 2008	26	48	31	43	43.4%	0.46 [0.19, 1.10]
Lu 2008	9	62	12	28	31.4%	0.23 [0.08, 0.63]
Senturk 2002	25	46	18	23	25.2%	0.33 [0.10, 1.04]
Subtotal (95% CI)		156		94	100.0%	0.34 [0.19, 0.60]
Total events	60		61			
Heterogeneity: τ^2=0.00; χ^2=1.04, df=2 (P=0.59); I^2=0%						
Test for overall effect: Z=3.69 (P=0.0002)						
1.1.2 Breast cancer surgery (paravertebral block)						
Ibarra 2011	5	15	7	14	39.3%	0.50 [0.11, 2.24]
Kairaluoma 2006	5	30	12	30	60.7%	0.30 [0.09, 1.00]
Subtotal (95% CI)		45		44	100.0%	0.37 [0.14, 0.94]
Total events	10		19			
Heterogeneity: τ^2=0.00; χ^2=0.27, df=1 (P=0.60); I^2=0%						
Test for overall effect: Z=2.09 (P=0.04)						

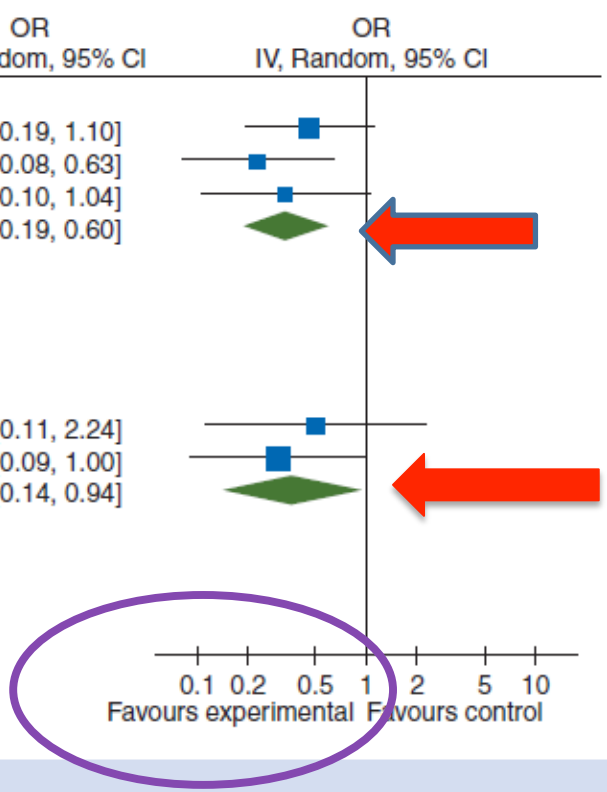


Fig 3 Forest plot: outcomes at 6 months favoured epidural anaesthesia for the prevention of PPP after thoracotomy with an OR of 0.33 (95% CI 0.20–0.56) and paravertebral block for breast cancer surgery with an OR of 0.37 (95% CI 0.14–0.94), respectively. More forest plots are published elsewhere.[18]

Approach to patients already on high dose of opiates preoperatively ?

Preoperative Consultation to determine…

- Should the patient stop taking his sustained release oxycodone before surgery?
- If the patient stops the opioids will he have excruciating pain before surgery ? If so does it matter? Withdrawal symptoms??
- Should we do a preop urine test to confirm?

Do a Preop urine test?

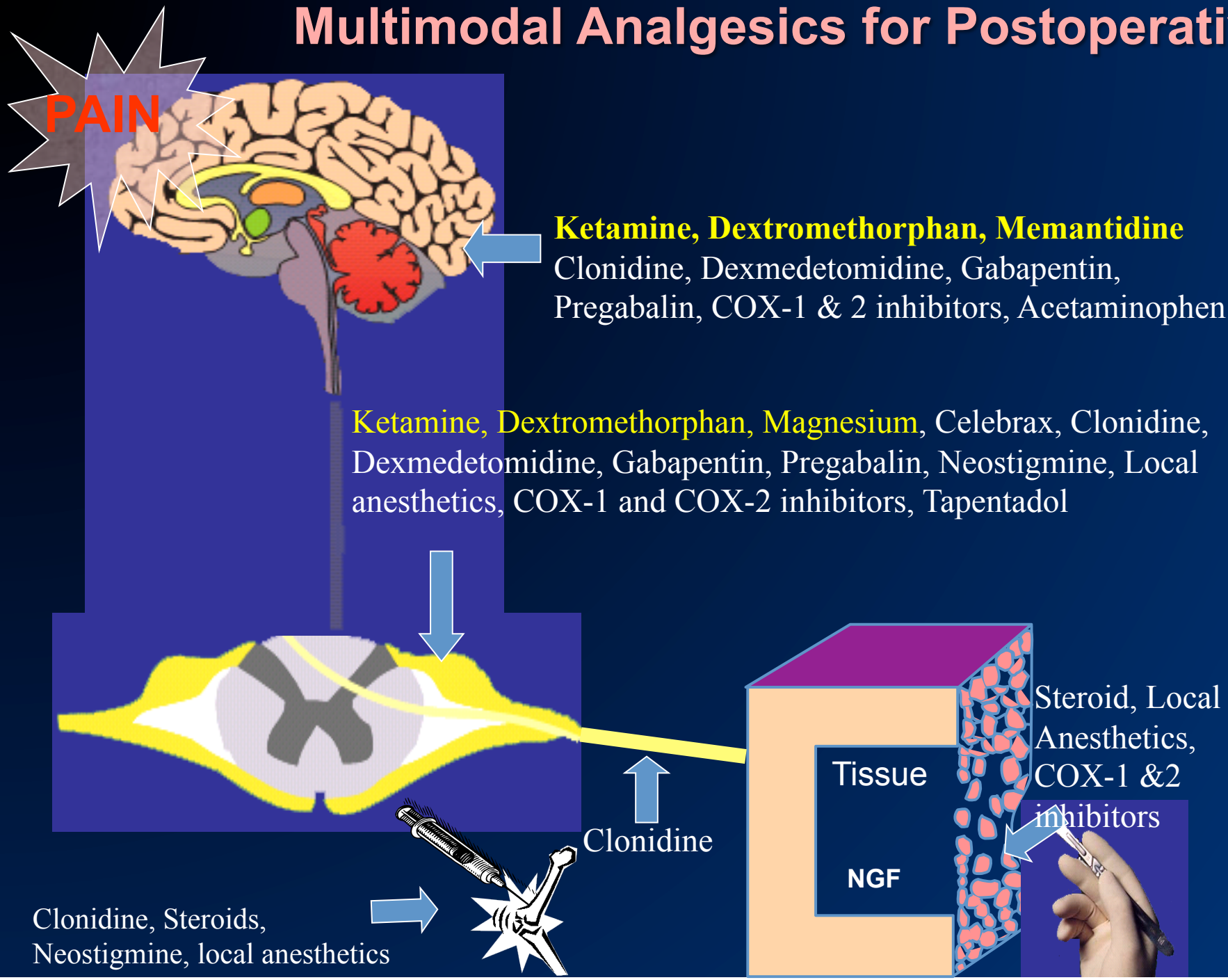
- Is this patient actually taking this large dose of opioids?
  - Qualitative and quantitative measurement of the opioid will be ideal.
  - If the qualitative testing is negative, this patient in NOT opioid tolerant.
- Evidence:
  - Study demonstrate that in chronic opioid users⇒ about 5% of patients had urine toxicology negative for the prescribed drug

    Barth KS et al: *J Addict med* 2010; 4: 167

- Is there a possibility of illicit drugs in this patient?
  - 20% of chronic pain patients on opioids will be +ve for illicit drugs:

    Compton P: *Pain management* 2007

Multimodal Analgesics for Postoperative Pai



Intraoperative Goals

- Maintain baseline opioids
- IV ketamine infusion
- Local anesthetic infiltration by surgeon.

- Convert from oral to intravenous morphine/day
  - Divide to give 50% of daily morphine intake
  - Divide by 24 to give hourly dose
  - Appropriate background infusion needs to be formulated

Opioid Tolerance: Management

- If opioid tolerance occurred due to activity at the opioid receptor, the management of these patients must include opioid-independent analgesics.

- The 2 drugs that fit this category are:
  - Ketamine (NMDA)
  - Dexmedetomidine (alpha 2)

NMDA Antagonists for Pain Management Administered during Perioperative Period

- Ketamine
- Dextromethorphan: Not sufficient evidence
- Magnesium
- Amantadine / Memantine
- Methadone

Intraoperative Ketamine reduces Perioperative Opioid Consumption in Opioid-Dependent Patients

- All patients were Opioid Dependent: Opioid use for at least 6 weeks before spine surgery (patients just on ultram were excluded)

- RCT of n=101 into two groups
  - Ketamine group: 0.5 mg/kg bolus at induction + 0.1 mg/kg/hr infusion till skin closure
  - Placebo: Bolus + infusion of saline

Loftus R et al: Anesthesiology 2010; Sept; 639

Ketamine in Opioid Dependent Patients: Results

	Ketamine	Placebo	P Value	%
PACU Morphine (mg)	18 ± 14	22 ± 20	0.21	↓ 18.0
PACU VAS	4.1 ± 3.1	5.6 ± 3.0	0.03	↓ 26.7
24 h Morphine (mg)	142 ± 82	202 ± 176	0.03	↓ 30
48 h Morphine (mg)	203 ± 109	323 ± 347	0.04	↓ 37
48 VAS	5.4 ± 2.1	5.3 ± 2.2	0.83	↑ 1.0
6 week Morphine (mg/hr) equivalents IV/hr	0.8 ± 1.1	2.8 ± 6.9	0.04	↓ 71
6 week VAS	**3.1 ± 2.4**	**4.2 ± 2.4**	**0.02**	**↓ 26.2**
Hospital Discharge (min)	4,364	4571	0.73	↓ 3.45 hour

Ketamine in Opioid Dependent Patients Undergoing Spine Surgery

- Ketamine ↓ 52% 48 hour morphine consumption in patients taking > 0.5 mg/hr IV dose preop
- However NO effect was observed when the Preop morphine was < 0.5 mg/hr IV dosing
- Conclusion: Intraoperative ketamine, particularly for patients taking > 40 mg oral morphine preop will lead reduced postop Acute and Chronic postoperative opioid consumption

Loftus R et al: Anesthesiology 2010; Sept: 639

Opioid tolerance & Postoperative requirements for TKA

- 40 patients with single surgeon, non-RCT
- Mean dose of opioid tolerant patient 1 week before surgery was 330 mg/day of morphine

Morphine use (mg)	Opioid Navie (n=20	Opioid Tolerant (n=9)
Intraop	30	56.0 *
PACU	8.2	56.0 *
24 hours	20.5	108 *
48 hours	25.0	152.3 *

- Opioid requirement was 180-200% higher than the baseline used for the opioid tolerant patients

Patanwala AE et al: *Pharmacotherapy* 2008; 28: 1453

Postoperative Pain Management in patients with prior opioid use

- Of 3058 patients, 202 patients were on opioids prior to surgery (6.6%)
- Mean preoperative morphine equivalents was IV 12.7 mg/day (40 mg PO)
- Postoperative morphine consumption in case control patients
  - Opioid naïve: 47 mg
  - Preop Opioid users: 136 mg
- 2.89 ≈ **3 times more**

Rapp SE et al: *Pain* 1995;61:195-201

Obama State of the Union-2013

- We'll bring down costs by changing the way our government pays for Medicare, because our medical bills shouldn't be based on the number of tests ordered or days spent in the hospital.

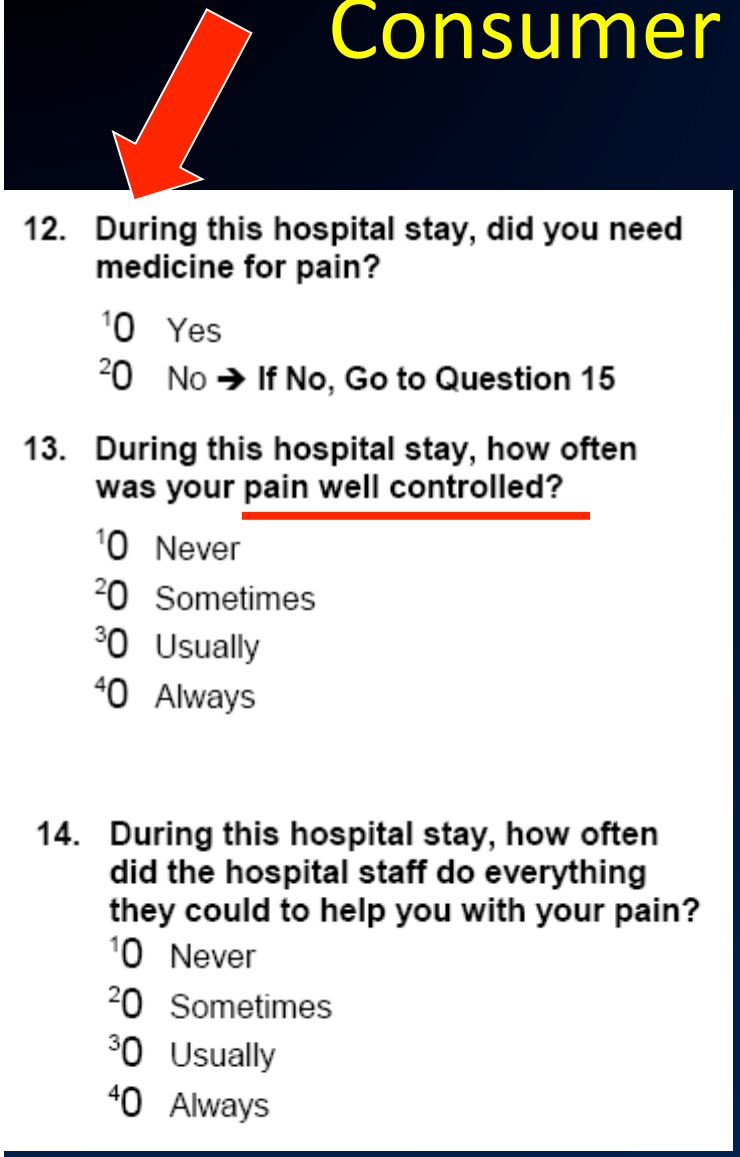
- **They should be based on the quality of care that our seniors receive.**

H-CAHPS Domains

Questions are grouped under 8 “domains” of care

- Communication with Nurses
- Communications with Doctors
- Staff Responsiveness
- **Pain Management**
- Communications about Medicines
- Discharge Information
- Hospital Environment
- Care Transitions

Hospital Care Quality Information from the Consumer Perspective (HCAHPS)



12. **During this hospital stay, did you need medicine for pain?**

    [1] 0 Yes
    [2] 0 No ➔ **If No, Go to Question 15**

13. **During this hospital stay, how often was your pain well controlled?**

    [1] 0 Never
    [2] 0 Sometimes
    [3] 0 Usually
    [4] 0 Always

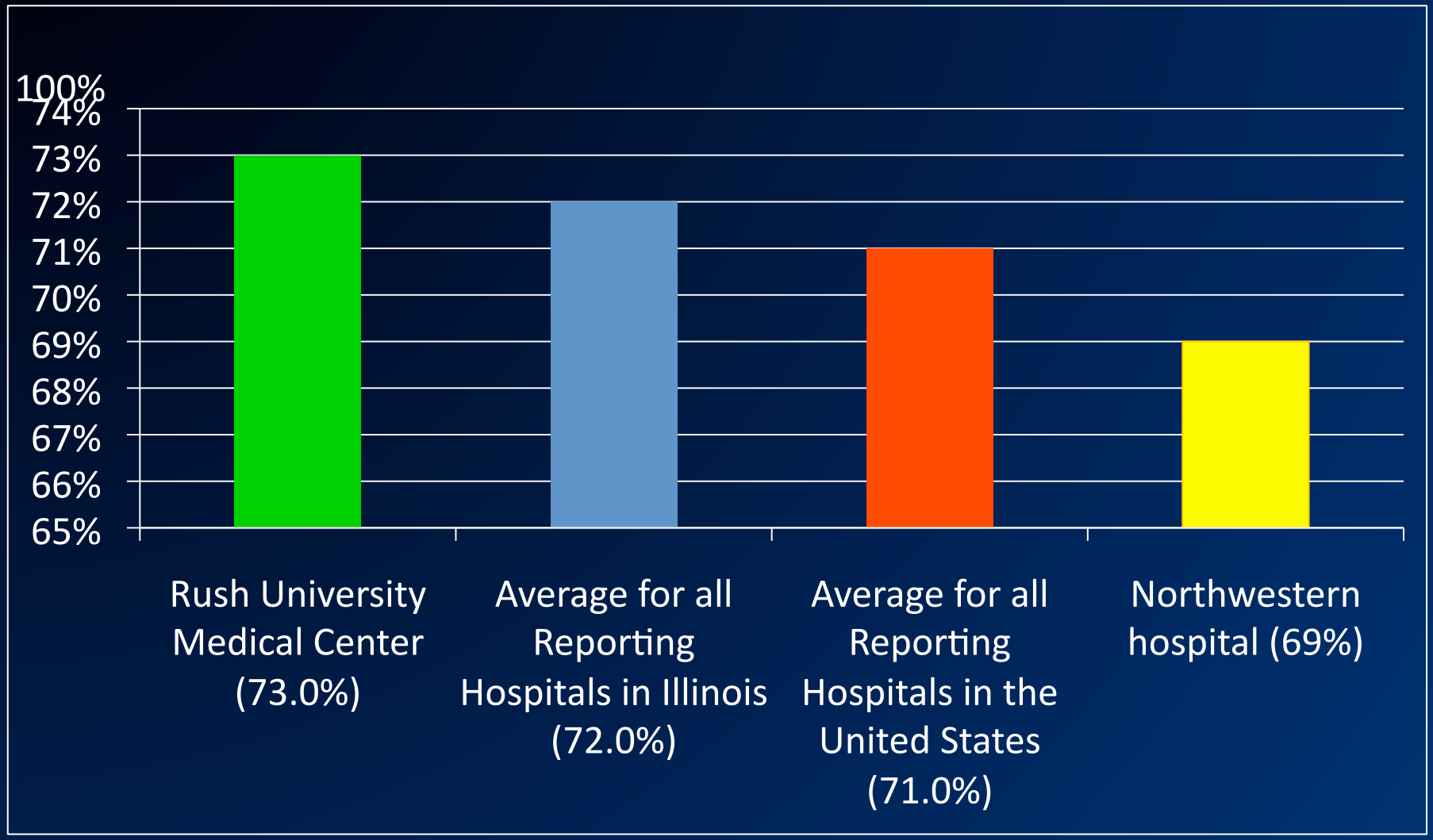
14. **During this hospital stay, how often did the hospital staff do everything they could to help you with your pain?**

    [1] 0 Never
    [2] 0 Sometimes
    [3] 0 Usually
    [4] 0 Always

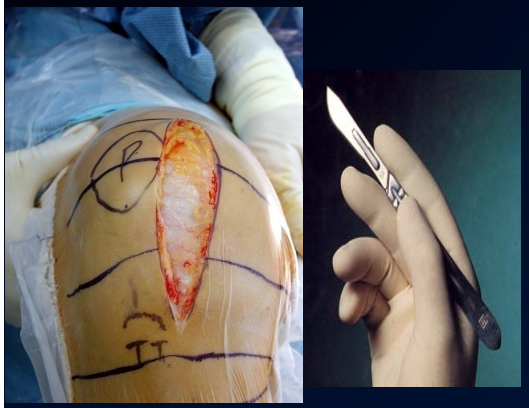
- The intent of the HCAHPS is to provide a standard survey for measuring patient's perspective on hospital care
- CMS payment to hospital is going to be based on the percentile of the summed score
- Pain Management for 2015:
  - Rush University: 73%
  - Average for the state: 72%
  - National average: 71%

http://www.hospitalcompare.hhs.gov/

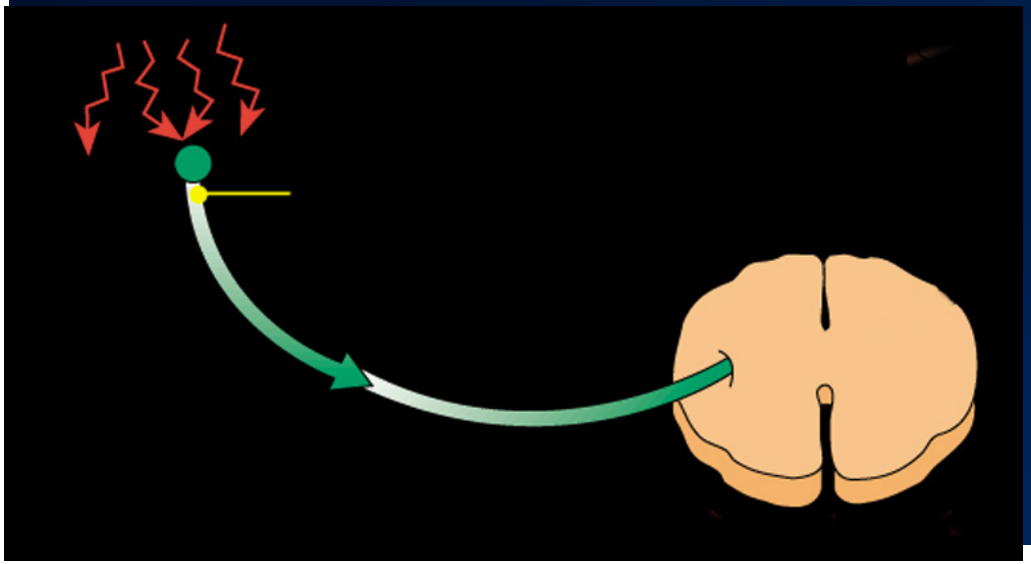
Patients who reported that their pain was “Always” well controlled



Where will Acute Pain Management be in 3-5 years ?



Greater Understanding



- Precision Medicine with greater understanding of genetics

Genetics and Pain Management

- To optimize postoperative pain control, improvement in knowledge about the large inter-individual variability in the pain response to similar noxious surgical stimuli from both a neurophysiological and a genetic viewpoint, without excluding the inter-individual neuropsychological differences would be benefit.

- Genetic test may become useful as bedside screening in order to predict the development of chronic pain and in order to individualize postoperative pain therapy.

Opioids and Genetics

- The human μ-opioid receptor (MOR), coded by the *OPRM1 gene*, is a primary candidate for the pharmacogenetic variability of the clinical effects of opioid analgesics because it is the major site of action for the most common opioids currently used.

- *OPRM1* is the primary site of action for the most commonly used opioids, including morphine, heroin, fentanyl, and methadone.

MOR Gene (OPRM1)

- OPRM1 is also the primary receptor for endogenous opioid peptides, beta-endorphins and enkephalins act to produce analgesia.

- Over 700 SNPs have been identified in the OPRM1 gene.

- *OPRM1* is highly polymorphic; one of the most frequent polymorphisms, the SNP A118G in exon 1, causes a change in the corresponding protein, which seems to be associated with reduced potency of one of its morphine metabolites, morphine-6-glucuronide (M6G).

A Genetic Association Study of the Functional A118G Polymorphism of the Human -Opioid Receptor Gene in Patients with Acute Pain

- The A118G polymorphism at OPRM1 affects an individual's response to analgesics. Individuals who are carriers of an A118G polymorphism (either GG or GA) experience *half the potency or less from the active metabolite of morphine, morphine-6-glucuronide*, compared with wild type (AA) carriers.

- The *A118G* polymorphism may also be associated with *substance dependence* and susceptibility to other disorders such as schizophrenia.

Association between SNP of OPRM1 gene and Sensitivity

- The following have SNP have been associated with Pain Sensitivity:
  - IVS1-C2994T and IVS2+G31A
  - A118G

- The following SNP have been associated with Opioid sensitivity:
  - A118G
  - IVS2+C691G and IVS3+A8449G

Kasai S et al: Fut Med 2011

A118 and opioid consumption after surgery

- Studies of patients who are G118 homozygous (GG) and undergoing TKA (120 patients) or abdominal hysterectomy (80 females) reported significantly higher morphine consumption than by patients with the A118 homozygous (AA) genotype for each study:
  - 40.4 mg [GG] vs 25.3 mg [AA] consumed in the first 48 h [P <. 05]
  - 33 mg [GG] vs 27 mg [AA] in the first 24 hours [P ¼ .02])
- **Conclusion:** Patients with homozygous A118G OPRM1 genotype may experience less pain and have a decreased analgesic and side effect response to morphine

Methods

- With IRB approval, 14 patients with a history of osteoarthritis scheduled for primary TKA had whole blood samples obtained presurgery and at 48 hours postsurgery.

- RNA expression (*approximately 47,000 transcripts*) was assayed using the Affymetrix HG-U133 plus 2.0 microarray, with RNA normalization.

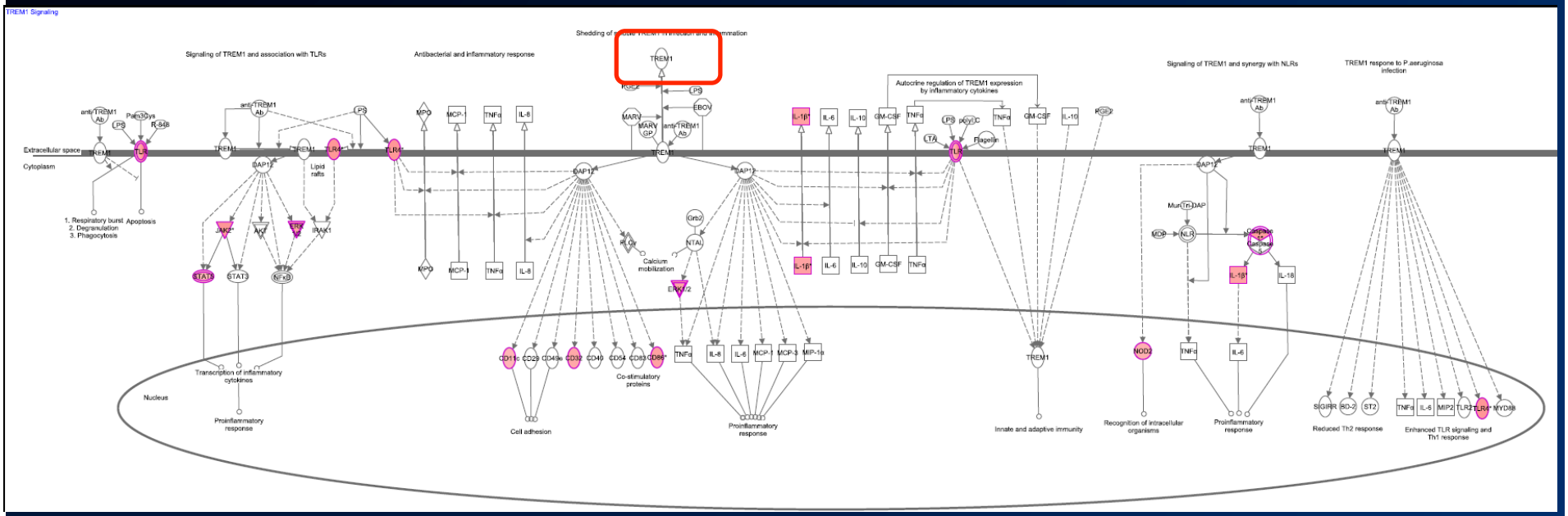
- The primary source of the RNA will be from leukocytes.

Biochemical Pathways

- The most significant (P=0.00002) biochemical pathway was TREM1 (triggering receptor expressed on myeloid cells 1).

- TREM1, involves a cell surface receptor exclusive to neutrophils that when activated upregulates expression of genes that contribute to the inflammatory response (e.g. chemokines, cytokines).

TREM1 signaling



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Available online at www.jpain.org and www.sciencedirect.com

Guidelines on the Management of Postoperative Pain

Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council

- 32 recommendations.

Conclusion

- Clinical studies for multimodal analgesia should have at least more than two groups in the study group
- Outcomes assessed should include reduction in opioid related side effects
- Improved outcomes of functionality need to be assessed in the early and late time periods
- With the changing health care paradigm, taking part in the improvement of quality of care provided will be goal standard

Please Complete your Evaluations

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