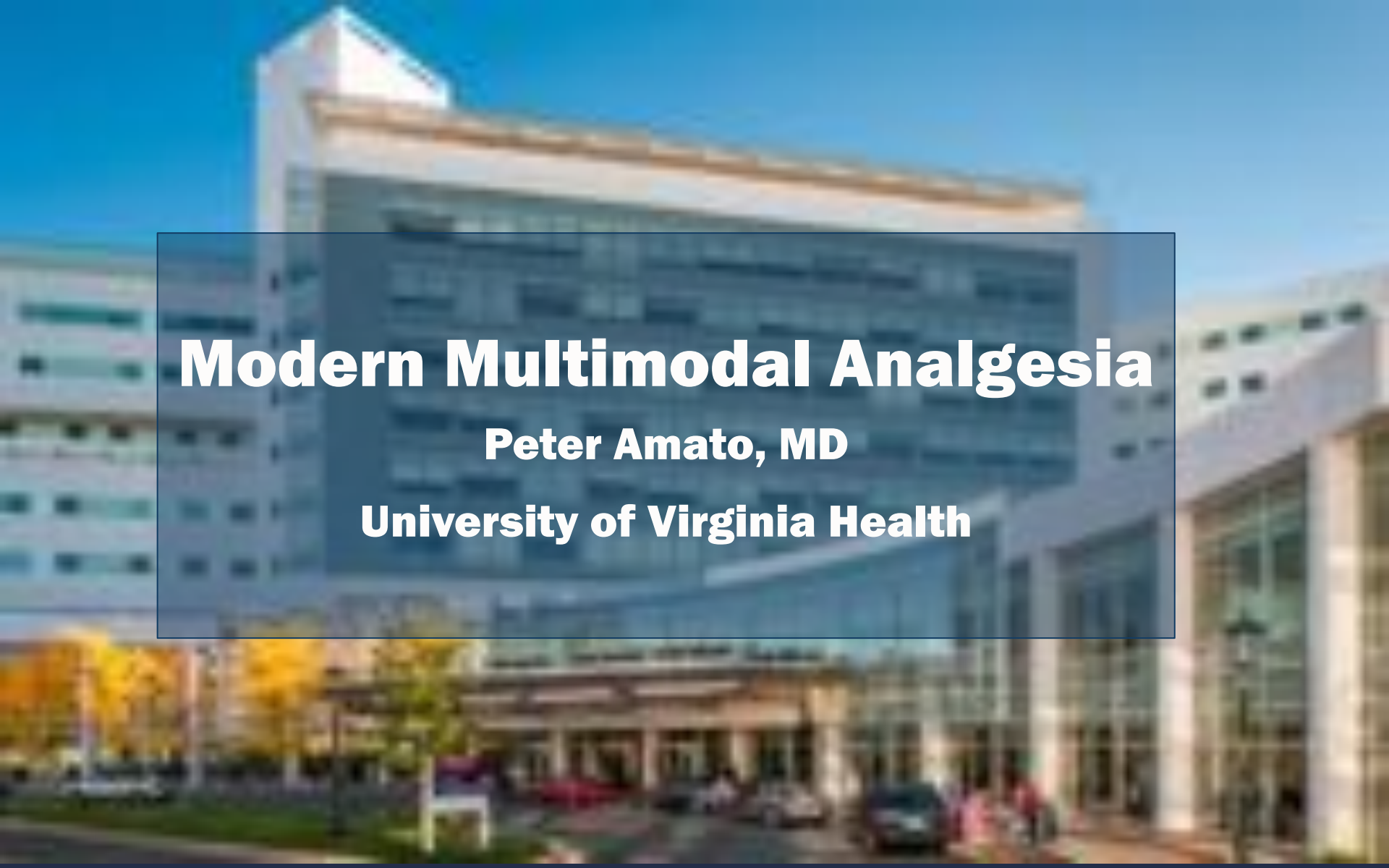


Modern Multimodal Analgesia

Peter Amato, MD

University of Virginia Health

University of Virginia Health System

Outline

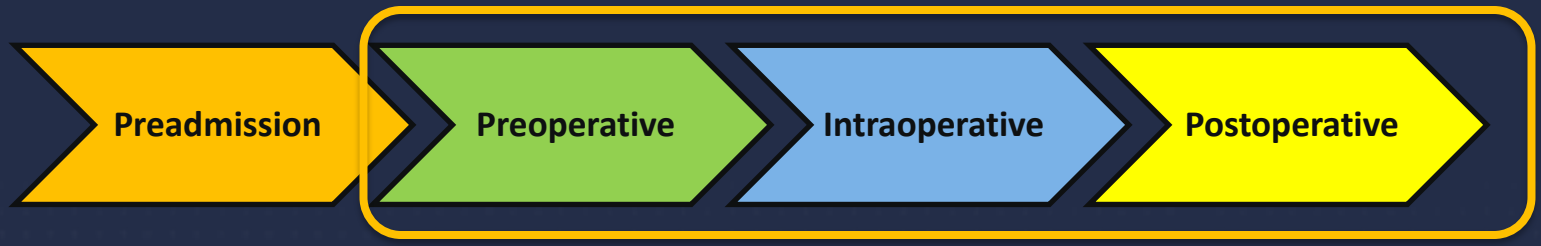
- Why Multimodal Analgesia (MMA)?
- The Age of ERAS
- Pain Pathways and MMA
- Major Classes of Analgesics
    - Mechanisms of action
    - Evidence for use
    - Dosing
    - Side Effects
    - Costs

Why Multimodal Analgesia?

- **Multimodal = many mechanisms together to treat pain**
- **Synergism – improved pain control**
- **ASA recommended practice**
- **Reduction in opioid use**
    - Respiratory depression, Nausea, Ileus, Dependence
    - Availability
- **Major component of modern ERAS protocols**

Enhanced Recovery After Surgery (ERAS)

- Better outcomes with protocolized multidisciplinary approach
- Shorter hospital stays
- Fewer complications
- Better patient satisfaction



Nutritional support
Lifestyle mod
Medical optimization
Patient Education

Oral Hydration
Carb loading
Selective bowel preps
PONV prophylaxis
MMA

Minimize drains and lines
Regional anesthesia
Opioid-sparing
MMA
Fluid balance
Temperature cntrl

Stop IVF
Remove tubes
MMA
Early mobilization and oral intake

Potential for major impact with MMA!

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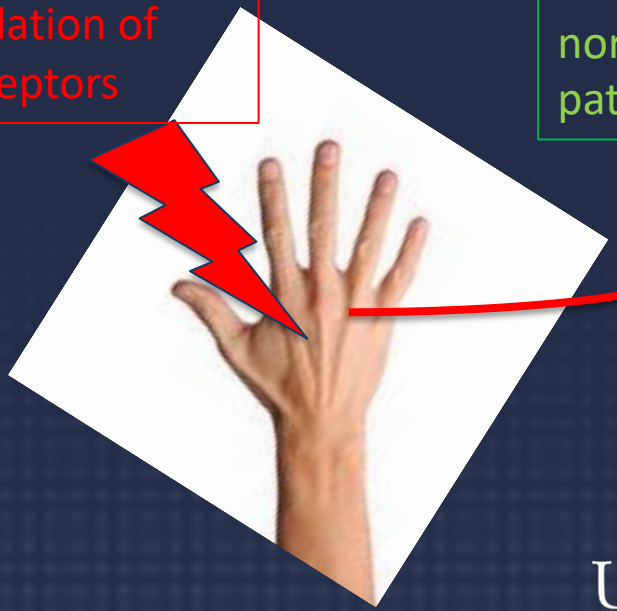
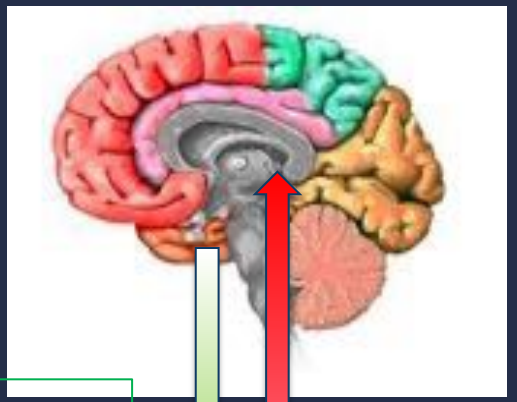
Pain Pathways

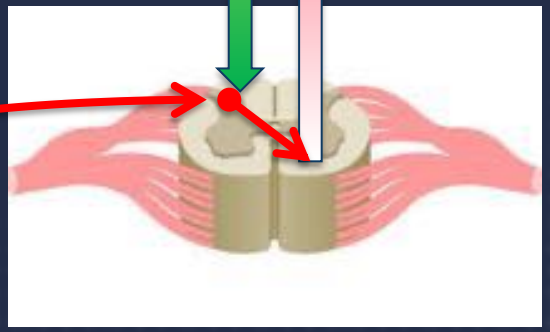
INJURY: Prostaglandins, H+, bradykinins, histamine, stimulation of Nociceptors



Descending modulation via serotonergic and noradrenergic pathways

Ascending input via spinothalamic tract to thalamus





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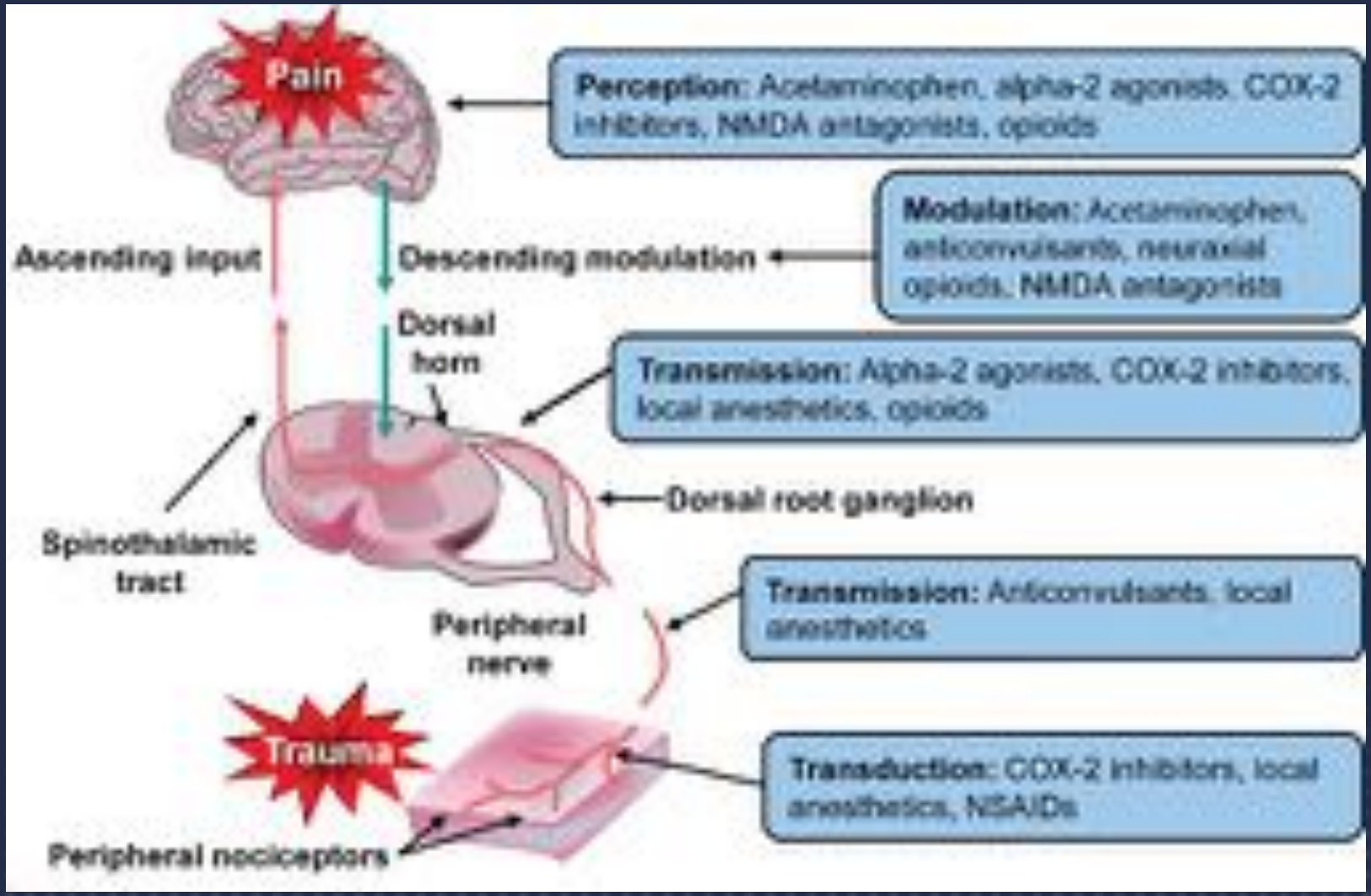


Sullivan D et al. 2016.

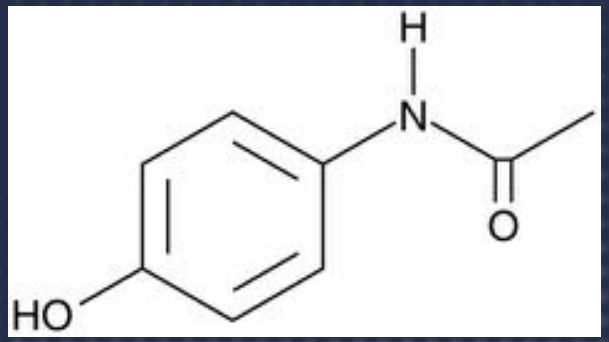
Classes of Analgesics

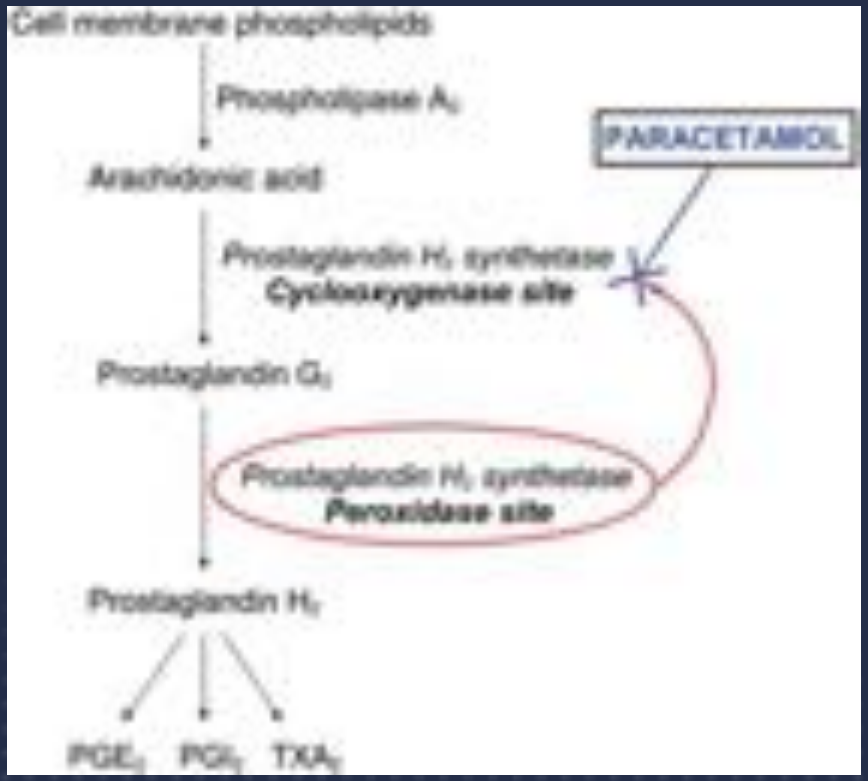
- Acetaminophen
- NSAIDS
- Anticonvulsants
- Local anesthetics
- NMDA antagonists
- Alpha-2 agonists
- Opioids

Acetaminophen

Potential mechanisms of action:

- **Inhibition of prostaglandin synthesis by COX2 and/or COX3**
- **Central activation of descending serotonergic pathways**
- **Endocannabinoid reuptake inhibition**
- **Does not possess the anti-inflammatory effects of NSAIDS**





Sharma CV 2013

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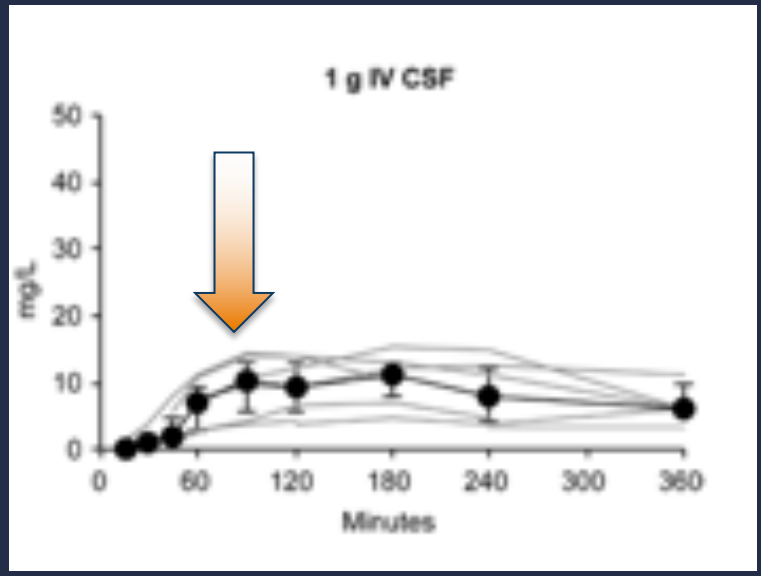
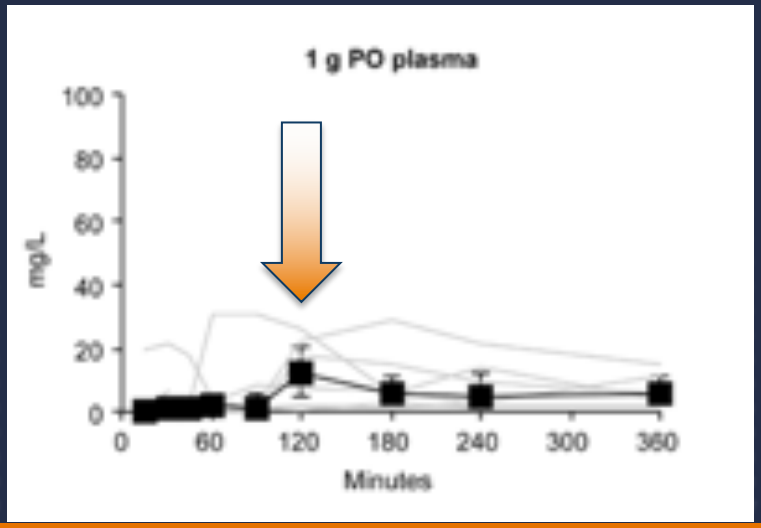
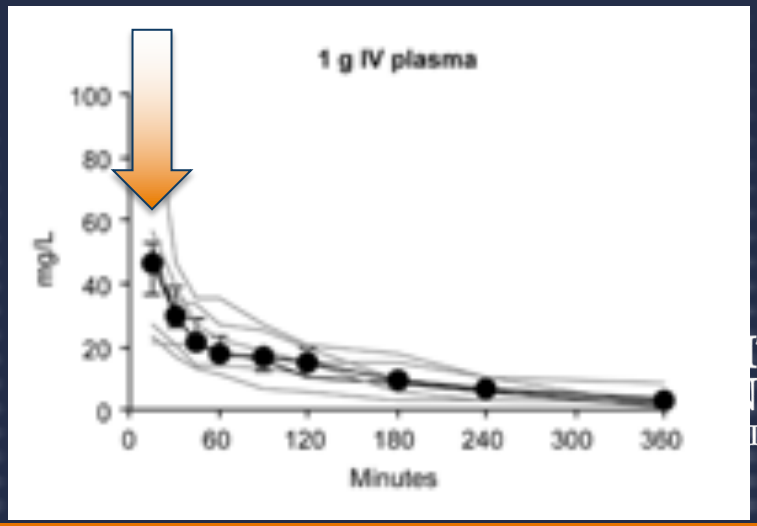
Acetaminophen - Pharmacokinetics

- Langford et al 2016
- Intravenous vs Oral
- Plasma concentrations







Acetaminophen – IV vs Oral

- **Politi et al 2017**
  - 120 total hip and knee replacements
  - Either 1 g IV or oral beginning in preop then Q6 hours (randomized but not blinded)
  - 1 VAS point improvement at PACU tine 0 favoring IV acetaminophen (p=0.033)
  - No other time point showed a difference in VAS or opioid use
- **Westrich et al 2019**
  - 154 total hip replacements
  - Either 1g IV or oral plus the opposite placebo Q6 hours beginning in PACU
  - No difference in pain scores, opioid use, or opioid side effects on POD1

Acetaminophen – IV vs Oral

- **Patel et al 2019**
  - 100 Ambulatory lap unilateral inguinal hernia repairs
  - Either 1 g IV or 975 oral preop(randomized + triple blinded)
  - No difference in pain scores or opioid use at any time point within first 24 hours, PACU length of stay, or patient satisfaction

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Acetaminophen - Efficacy

Preventive Acetaminophen Reduces Postoperative Opioid Consumption, Vomiting, and Pain Scores After Surgery

Systematic Review and Meta-Analysis

Brett Doleman, MBBS, David Read, BMBS, Jonathan N. Lund, DM, and John P. Williams, PhD

- **2015 Meta-analysis – *Regional Anesthesia & Pain Medicine***
- **6 included studies, 544 patients**
- **Abdominal, orthopedic, ENT, obstetric**
- **Two doses used in all included studies**
- **Either 1000 mg or 15 mg/kg used preoperatively, and again at end of case**

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Acetaminophen - Efficacy

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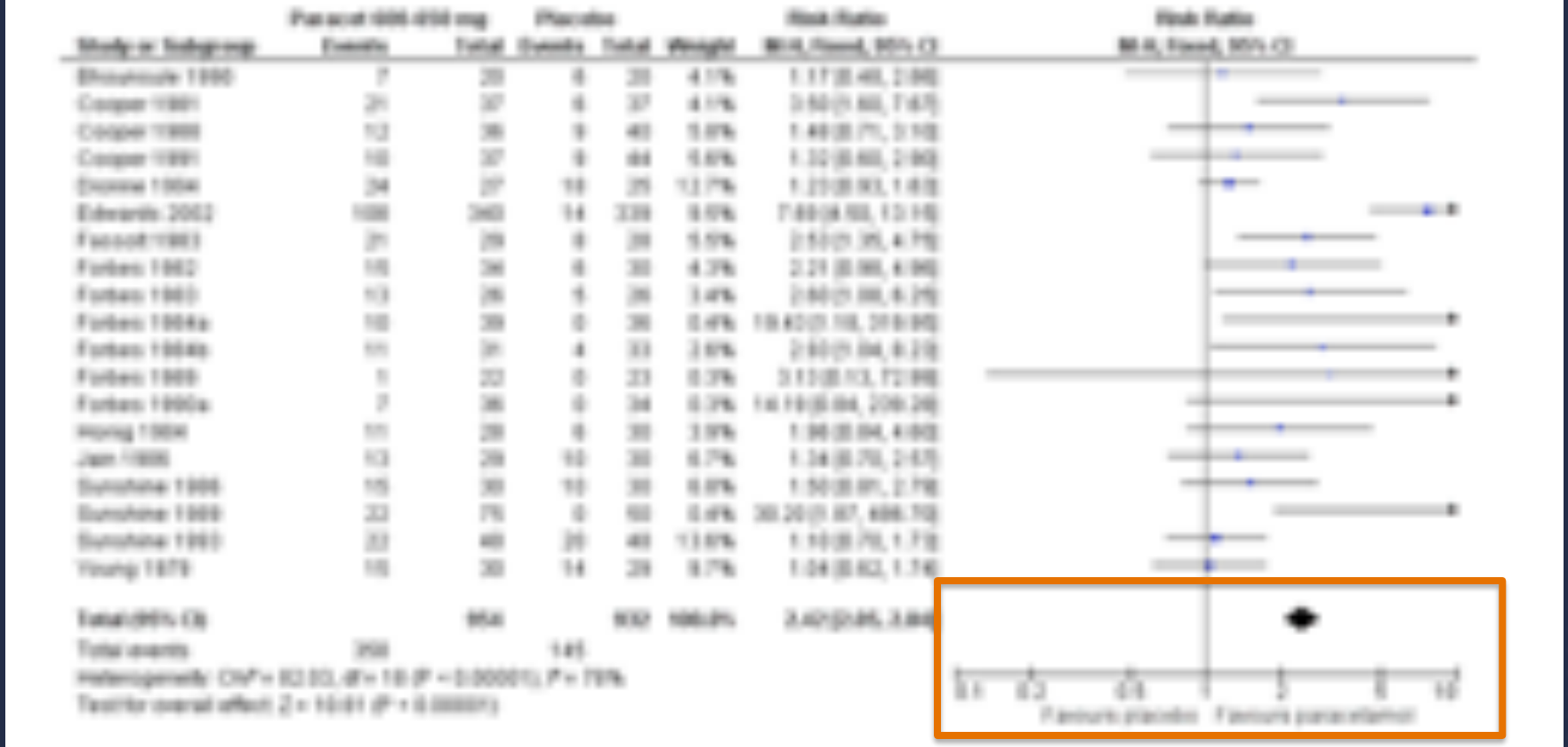
Systematic Review and Meta-Analysis

Brett Doleman, MBBS, David Read, BMBS, Jonathan N. Lund, DM, and John P. Williams, PhD

- **Small reduction in pain score (<1 VAS)**
- **Small reduction in opioid consumption and time to first analgesia**
- **Reduction in vomiting RR 0.5**

Acetaminophen - Efficacy

Figure 2. Forest plot of comparison: 4 Paracetamol 600-650 mg versus placebo, outcome: 4.1 Participants with at least 50% pain relief over 4 to 6 hours.



Cochrane review by Toms L, et al 2008

Acetaminophen - Dosing

Group	Loading Dose	Repeat Dosing
Adults	650-975 PO, 1000 mg IV Some use 2000 mg load	Up to 1000 mg Q4-6 hours (max 3g/24h)
Kids, or <50 kg	• 15 mg/kg PO/IV • 40 mg/kg PR	• 15 mg/kg PO/IV Q6 hours • 20 mg/kg PR Q6 hours
Special groups	Reduce dose for infants (by half), elderly, cirrhosis, malabsorption	Q6-8 hours for GFR <= 30 mL/min

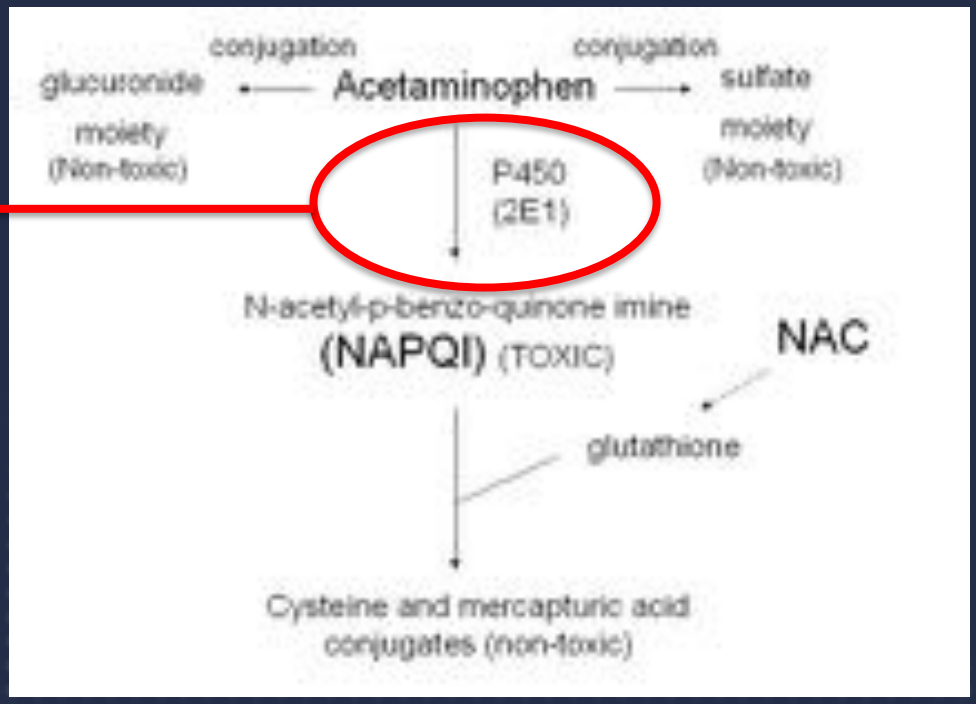
Acetaminophen - Side Effects

- GI – nausea, diarrhea – possibly related to formulations
- Rash, Allergic reactions, Stevens Johnson - rare
- Vein irritation from rapid IV infusion
- Hepatic and Renal Toxicity with large doses (low therapeutic index)

Toxic Dose Ranges

- Adults: 7.5-10 g
- Children: 150 mg/kg; 200 mg/kg in healthy children aged 1-6 years

CYP2E1 inducers
ETOH
Nicotine
Isoniazid
Colchicine
Dexamethasone?

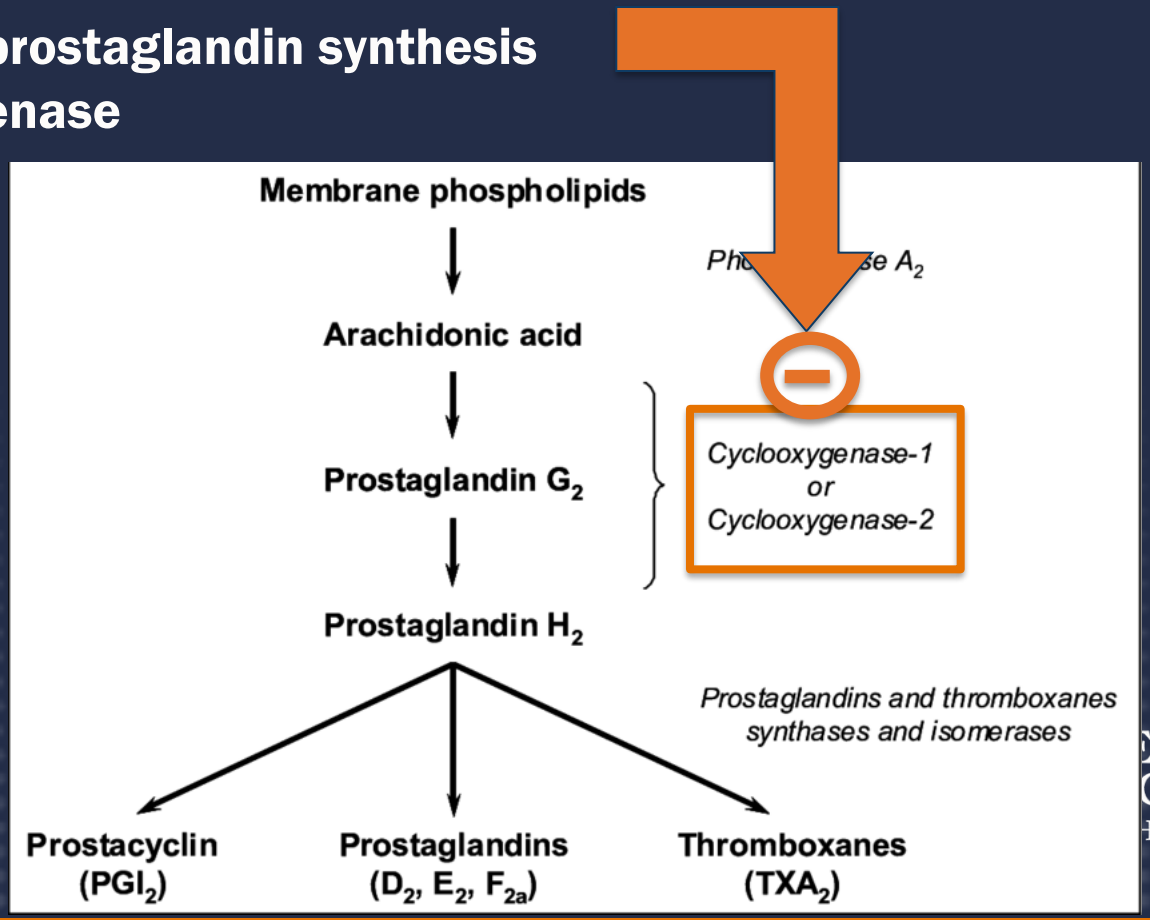


NSAIDS

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Mechanism of action:

- Inhibition of prostaglandin synthesis by cyclooxygenase



Novella S, 2011

NSAIDS and Cyclooxygenase

COX1	COX2
Constitutively active Housekeeping role TXA2 – Platelet aggregation PGI2 – Prevents aggregation Vasodilation PGI2/E2 – gastric mucosal protection Renal Blood Flow Regulation of GFR Renin secretion	Inducible enzyme? Inflammation Some PGI2 in vessels

NSAIDS and Cyclooxygenase

Non-selective NSAIDS
Aspirin
Ibuprofen
Diclofenac
Ketorolac
Indomethacin
Naproxen

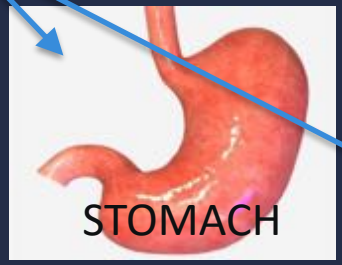
COX2 Preferential
Meloxicam
Nimesulide
Etodolac

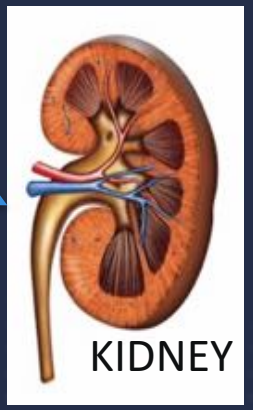
COX2 Specific
Celecoxib
Rofecoxib
Etoricoxib
Valdecoxib

COX1

COX2


PLATELETS


STOMACH


KIDNEY

Varga 2017

NSAIDS – Thrombotic Risks

Aspirin
Naproxen

Coxibs
Ibuprofen
Diclofenac
Ketorolac

ANTITHROMBOSIS
PGI2

THROMBOSIS
TXA2

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Varga 2017, Trelle 2011, Gerstein 2014

NSAIDS – Bleeding Risks

Ketorolac Does Not Increase Perioperative Bleeding: A Meta-Analysis of Randomized Controlled Trials

Ryan M. Gobble, M.D.
Han L. T. Hoang, M.D.
Bart Kachniarz, B.A.
Dennis P. Orgill, M.D., Ph.D.
Boston, Mass.; and New York, N.Y.

- **2104 Meta-analysis – *Journal of Plastic and Reconstructive Surgery***
  27 Double blind RCT studies, 2314 patients
- **Surgery types – upper abdominal, cholecystectomy, hysterectomy and myomectomy, total joint replacements, tonsillectomy, ACL, spinal fusion, C section, D&C, major urologic, dental, plastics, hand**
- **Total Odds ratio of bleeding 1.12 (0.61-2.06), Z = 0.59 (P=0.55)**
- **Pain control superior to placebo, narcotic sparing, reduced sedation and respiratory events**

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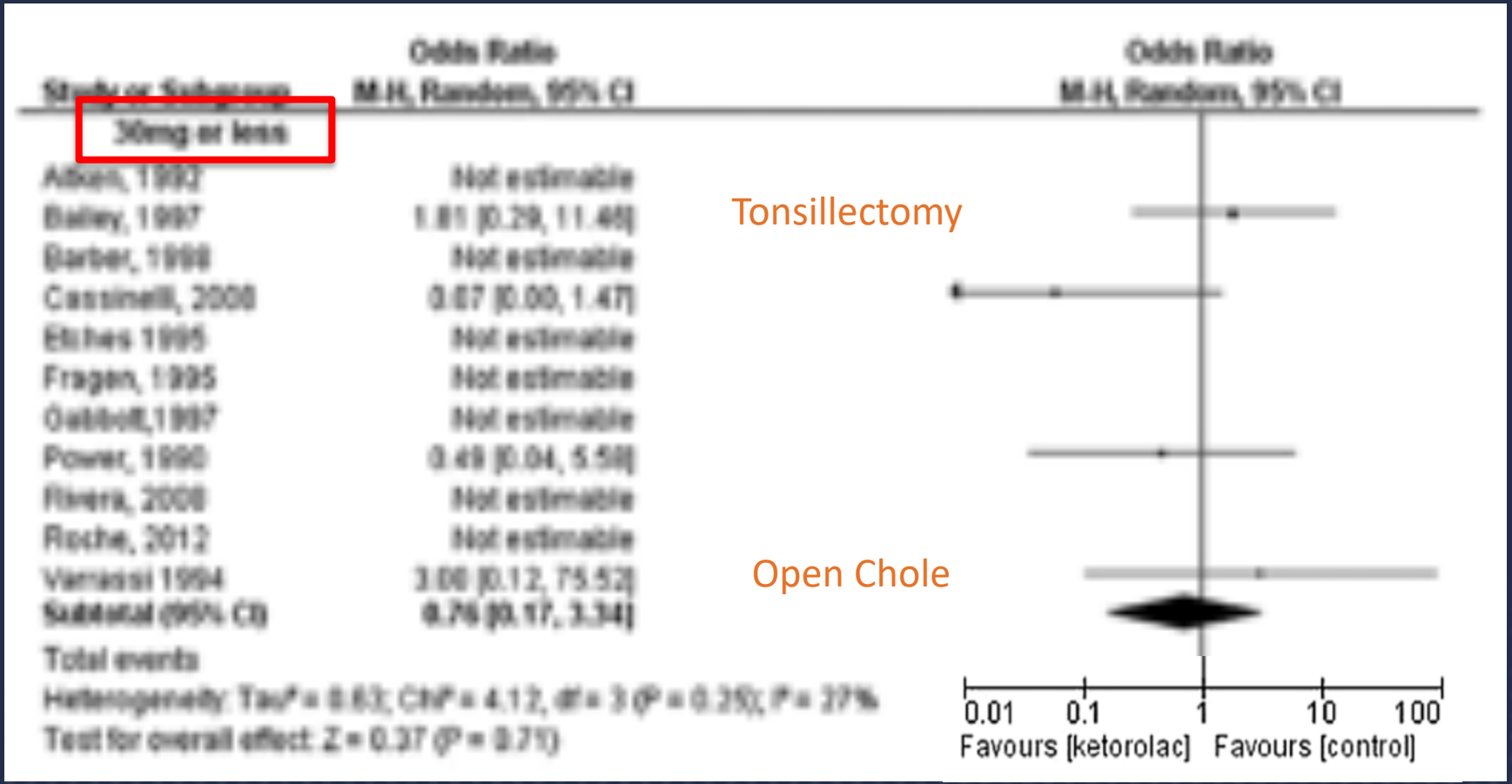
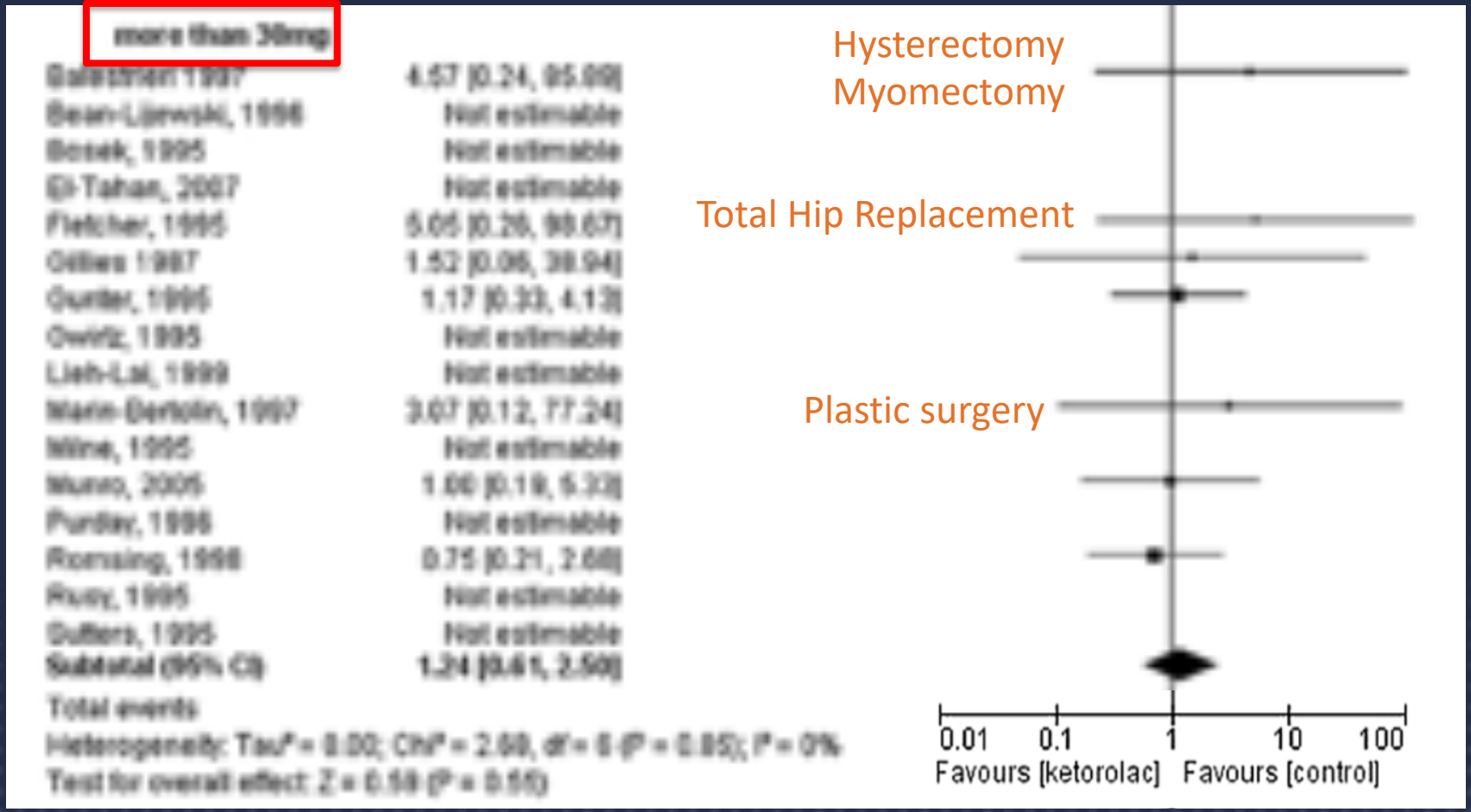
NSAIDS – Bleeding Risks



NSAIDS – Bleeding Risks



NSAIDS – COX2 Bleeding Risks

Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: A systematic review and meta-analysis

Choochai Teerawattananon, MD[a], Pongchirat Tantayakom, MD[b], Bundarika Suwanawiboon, MD[c], Wanruchada Katchamart, MD, MSc (Clin Epi)[d,*]

- **2017 Meta-analysis – *Seminars in Arthritis and Rheumatism***
- **35 Studies reviewed, 16 used in meta-analysis (1704 patients)**
- **Cases included – tonsillectomy, major abdominal surgery, thyroid/parathyroid, lap cholecystectomy, total abdominal hysterectomy**

NSAIDS – COX2 Bleeding Risks

Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: A systematic review and meta-analysis

Choochai Teerawattananon, MD[a], Pongchirat Tantayakom, MD[b], Bundarika Suwanawiboon, MD[c], Wanruchada Katchamart, MD, MSc (Clin Epi)[d,*]

Comparison	Odds ratio (95% CI)	Z-score (p-value)	Heterogeneity I^2	Interpretation
COX2 vs Nonselective NSAIDs	0.89 (0.58-1.37)	0.53 (0.60)	0%	BLEEDING OUTCOMES SAME
COX2 vs APAP	1.1 (0.07-16.8)	0.07 (0.95)	NA	BLEEDING OUTCOMES SAME
COX2 vs Placebo	0.96 (0.48-1.9)	0.13 (0.90)	0%	BLEEDING OUTCOMES SAME
ALL Comparisons	**0.92 (0.63-1.33)**	**0.45 (0.65)**	**0%**	**NO EFFECT ON BLEEDING OUTCOMES**

NSAIDS – COX2 Bleeding Risks

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Platelet function analyzer closure time

- **Decreased with use of COX2 inhibitors (WMD = -22.22; 95% CI: -44.03 to -0.41; p < 0.00001)**

Platelet aggregation tests

- **Measured using triggers such as arachidonic acid, ADP, epinephrine**
- **COX2 inhibitors did not inhibit platelet aggregation compared to NSAIDs or placebo**

Grove EL 2012 with permission from Siemens

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NSAIDS – Renal Function

- 2007 Review - 23 RCTs with 1459 patients all with normal preop function.

- <u>Creatinine Clearance Reduction</u>
  Across all studies -16 ml/min (-5 to -28) on Day 1 (18% of preop)
  No significant reduction on Day 2
  Multiple dose NSAIDs -25 mL/min, (-7 to -42) on Day 1
  Single dose NSAID -10 mL/min (-26 to +5) on Day 1

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NSAIDS – Renal Function

- 2007 Review - 23 RCTs with 1459 patients all with normal preop function.

- Urinary K Reduction
  -38 mmol/L (-56 to -19) on Day 1

- No significant change in serum creatinine, UOP, FeNa, FeK, or urinary sodium levels.

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NSAIDS and bone healing

?

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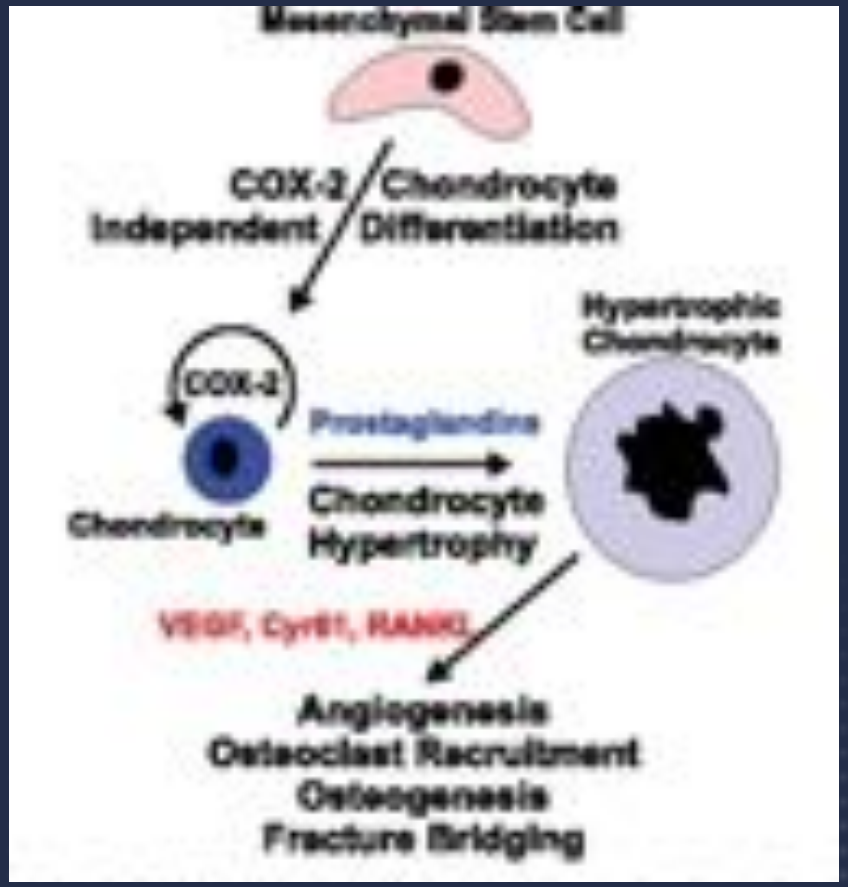
NSAIDS and bone healing

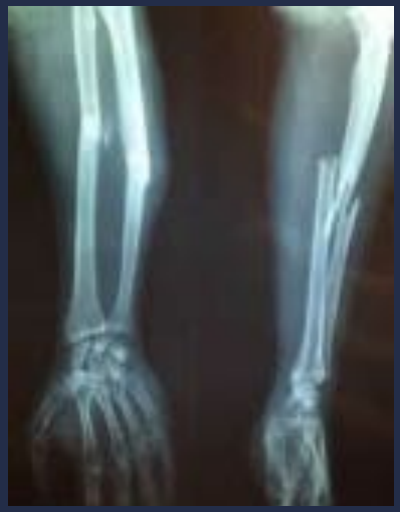
Physiology

- Prostaglandins have both osteoclastic and osteoblastic effects on bone



Bailey et al 2013

NSAIDS and bone healing



Literature is fractured!

Animal Studies

- Prolonged exposure (6 weeks) may inhibit or delay bone healing

Human studies

- Literature extremely heterogeneous
- Different NSAIDs, different types of fractures and procedures
- Many pro and con studies of varying quality

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NSAIDS and bone healing

- Search found 263 records, 36 met the criteria for review
- Huge variability
- Those trials, reviews, and meta-analyses that deemed NSAIDs safe tended to be of higher quality
- No clear consensus reached by authors
- "NSAIDs may affect bone-healing, but the effect depends on dose, timing, and length of exposure"

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Marquez-Lara, J Bone and Joint Surg 2016

NSAIDS and bone healing

My Two Cents

- Risk benefit analysis
- Opioid sparing benefits vs nonunion risk factors★
  - Age
  - Smoking
  - Diabetes
  - Fracture location
- Avoid in surgical repairs of actual nonunion or prior failed surgical fracture repair
- Short courses are probably safe

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★Zura et al 2016

NSAIDS - Efficacy

Ketorolac

- Reduces early pain[1]
- Spares opioids[1,2]
- Reduces PONV[1,2]

Ibuprofen

- Reduces pain[3-5]
  - 400 mg – 52% of patients had > 50% pain reduction (NNT 2.5)[3]
  - NNT is < 2 when you add acetaminophen[4]
- Spares opioids[5]
  - Up to 46% reduction at 800 mg (ortho and abdominal)
- Low rate of AEs[5]

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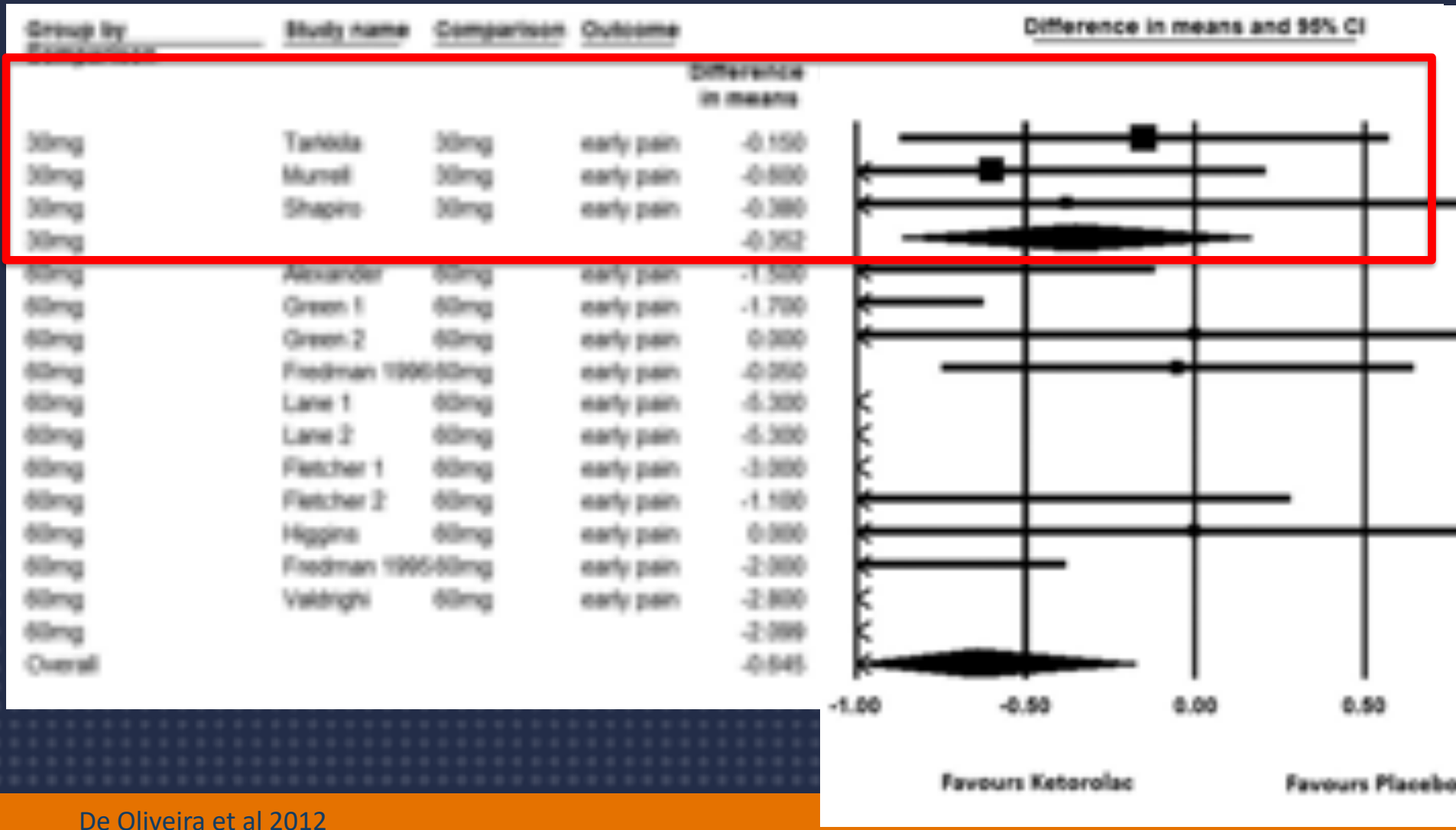
1.De Oliveira et al 2012 2.Cepeda et al 2005 3. Derry et al 2004. 4. Moore et al 2015 5. Martinez et al 2019

De. Oliveira et al 2012 Meta-analysis

Affect on Early Pain



De Oliveira et al 2012

Cepeda et al – Ketorolac and Morphine

- Over 1000 patients randomized to 30 mg ketorolac vs 0.1 mg/kg morphine in PACU.
- Abdominal and orthopedic surgery were over 70% of the population
- Measured pain and subsequent morphine consumption.

Table 3. Morphine Requirements in the Two Experimental Groups

	Ketorolac–Morphine	Morphine	*P* Value
Mean ± SD, mg	4.5 ± 5.3	11.1 ± 6.2	0.00001
Median, mg	2.5	8.9	
Range, mg	0–27.5	0–42	

NSAIDS - Efficacy

Celecoxib - fewer studies

- Reduced pain in dental and orthopedic surgery[1,2]
  - 400 mg better than 200 mg[1,3]
  - Probably as good as ibuprofen at 400 mg[3]
  - As good as ketorolac[4]
- Spares opioids[5]

- Remember that Celebrex contains a sulfa moiety and is considered contraindicated in those with sulfonamide allergy.

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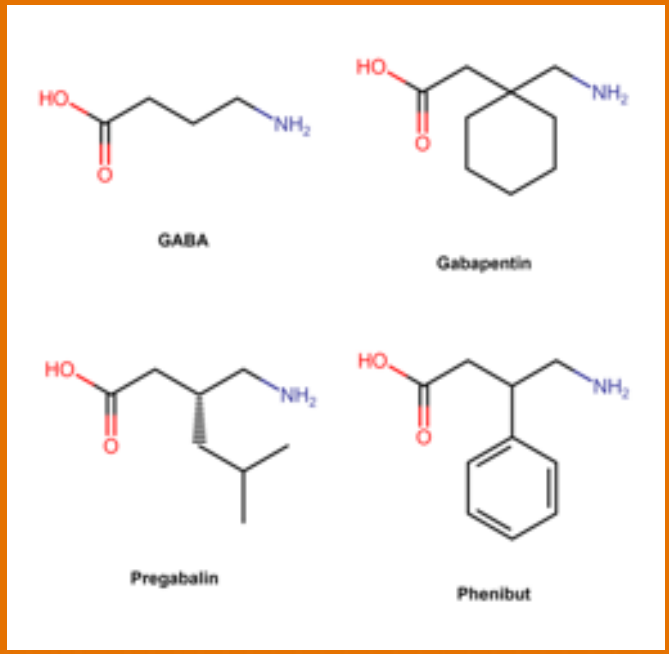
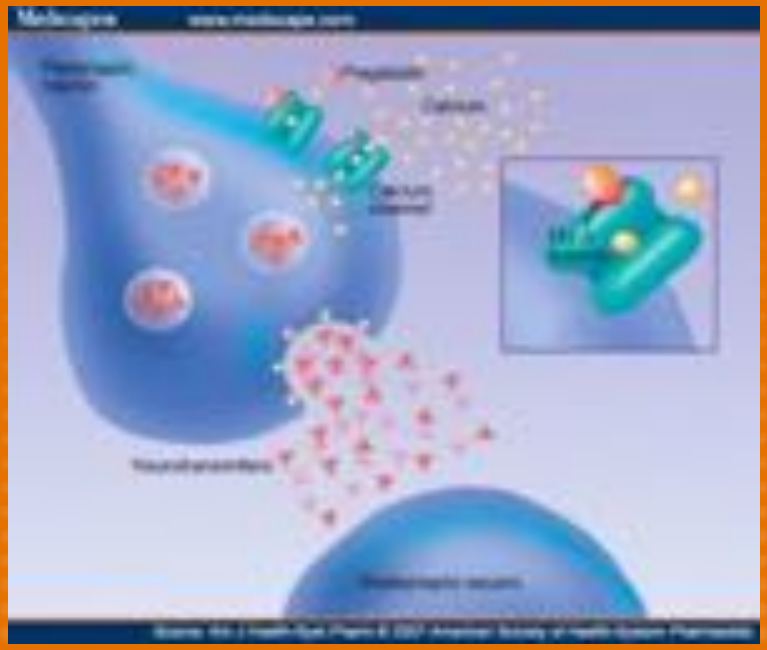
1.Derry et al 2013 2.Kahlenberg et al 2017 3.Rømsing et al 2004 4.Ulm et al 2018 5.Rømsing et al 2005

GABAPENTINOIDS

- Derivatives of GABA
- Do not have direct activity at GABA receptors
- They bind the $\alpha 2\delta$ subunit of voltage-gated calcium channels causing inhibition



Wikipedia open source



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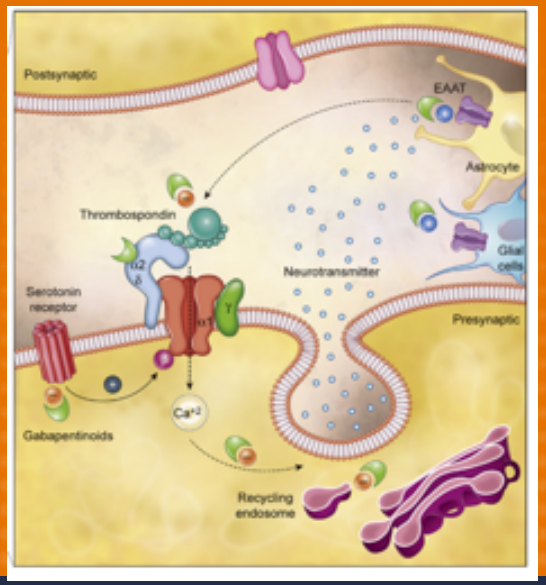
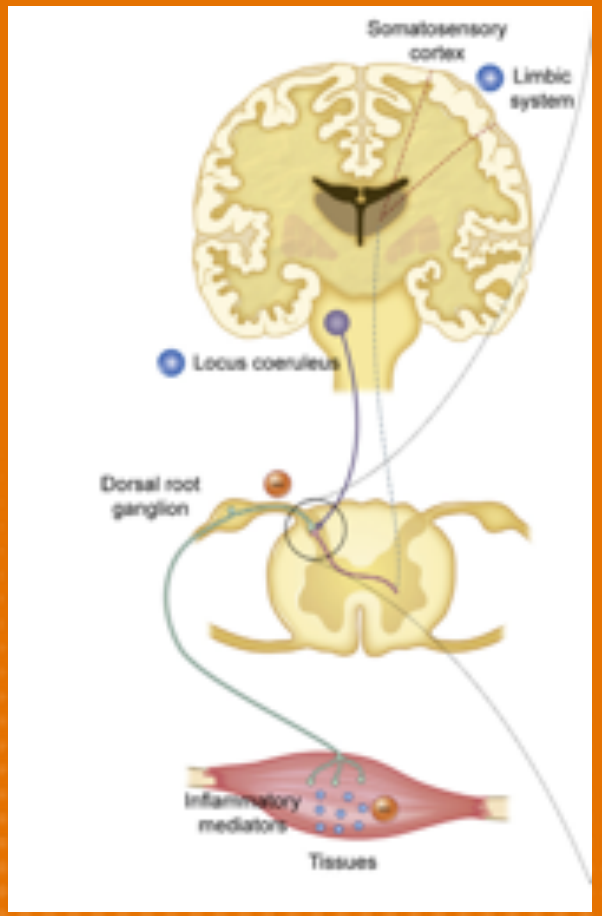
GABAPENTINOIDS

Potential Mechanisms of Action for Analgesia

- Increase in synaptic GABA
- Reduction in release of excitatory neurotransmitters
- Depression of dorsal horn sensitivity
- Stimulation of descending inhibition
- Inhibition of descending serotonergic facilitation
- Antiinflammatory effects?

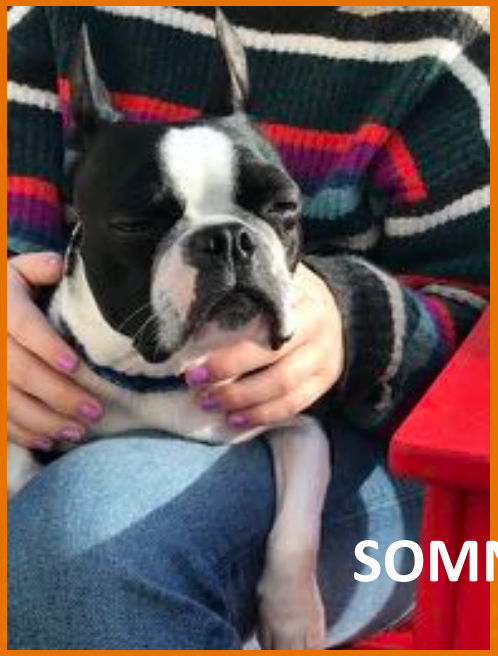




GABAPENTINOIDS

Side Effects

- Sedation
- Dizziness
- Ataxia
- Nystagmus
- Tremor



SOMNOLENCE

GABAPENTINOIDS

Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression

Alexandre N. Cavalcante, MD,* Juraj Sprung, MD, PhD,* Darrell R. Schroeder, MS,† and Toby N. Weingarten, MD*

- Multivariate analysis of over 8500 patients having laparoscopic surgery
- Gabapentin was associated with respiratory depression
- OR 1.47 (1.22–1.76); P < .001
- Patients at risk were older, received midazolam, and had slightly more intraoperative opioids

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Cavalcante et al A&A 2017

GABAPENTINOIDS

Gabapentin Efficacy

- Small Reduction in pain scores[1-4]
- Modest Reduction in 24 hour opioid use[1-7]
- Reduction in nausea and vomiting[1-6]
- Cholecystectomy, hysterectomy, mastectomy, orthopedic surgery, thoracic, breast, spine

Reference	Surgery	Mean Difference 24h Morphine use	Nausea RR
Jiang 2018	Breast	-4.59 (-7.07, -2.11)	0.54 (0.37, 0.78)
Han 2017	Spine	-9.3 (-12.22, -6.37)	0.77 (0.55-1.07) NS
Fabritius 2017	Mixed	-5.00 (-11.15, -1.15)	Not evlauated

1.Jiang et al 2018
2.Han et al 2017
3.Wang et al 2017
4.Li et al 2017
5.Mao et al 2016
6.Hamiton et al 2016
7.Fabritius et al 2017

GABAPENTINOIDS

Pregabalin Efficacy

- Compared to gabapentin similar opioid sparing properties[1]
- Pain reduction potential may be better when used for chronic neuropathic pain[2]
- May have a greater incidence of adverse events[1,3]

Reference	Surgery	Mean Difference 24h morphine consumption	Serious Adverse Events OR
Fabritius 2017-2	Mixed	-10.83 (-13.19, -8.46)	2.39 (1.37, 4.16)

SAEs = readmission, prolonged hospital stay, postponed operation 2/2 sedation, allergic reaction, stroke, PE, MI, AKI, pneumonia, wound infection, bleeding, hematoma, and death.

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1.Fabritius 2017-2 2. Bockbrader et al 2010 3.Robertson 2019

GABAPENTINOIDS

Pharmacokinetics

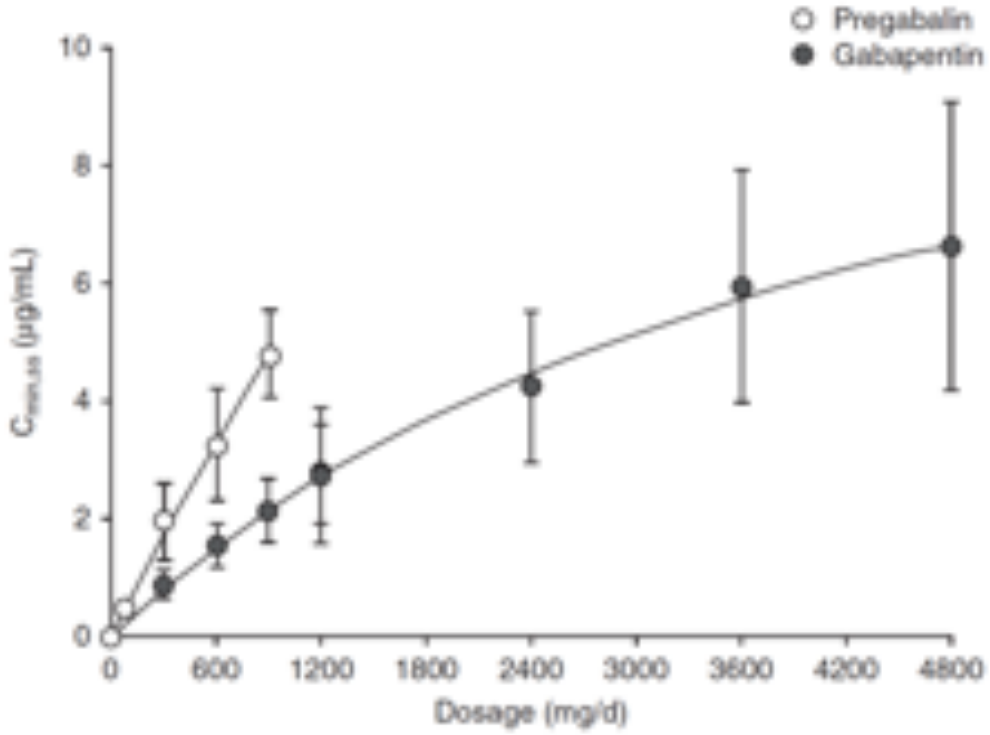

Fig. 2. Mean (± SD) steady-state minimum plasma drug concentration ($C_{min,ss}$) values in healthy subjects given pregabalin or gabapentin every 8 h.[14,20]

Metabolism/Excretion

Liver: Both drugs have minimal conversion to an N-methyl metabolite (<1%).

Renal: Both drugs undergo similar, primarily renal elimination. Gabapentin clearance is slightly faster than Pregabalin.

Dosing should be adjusted in renal disease.

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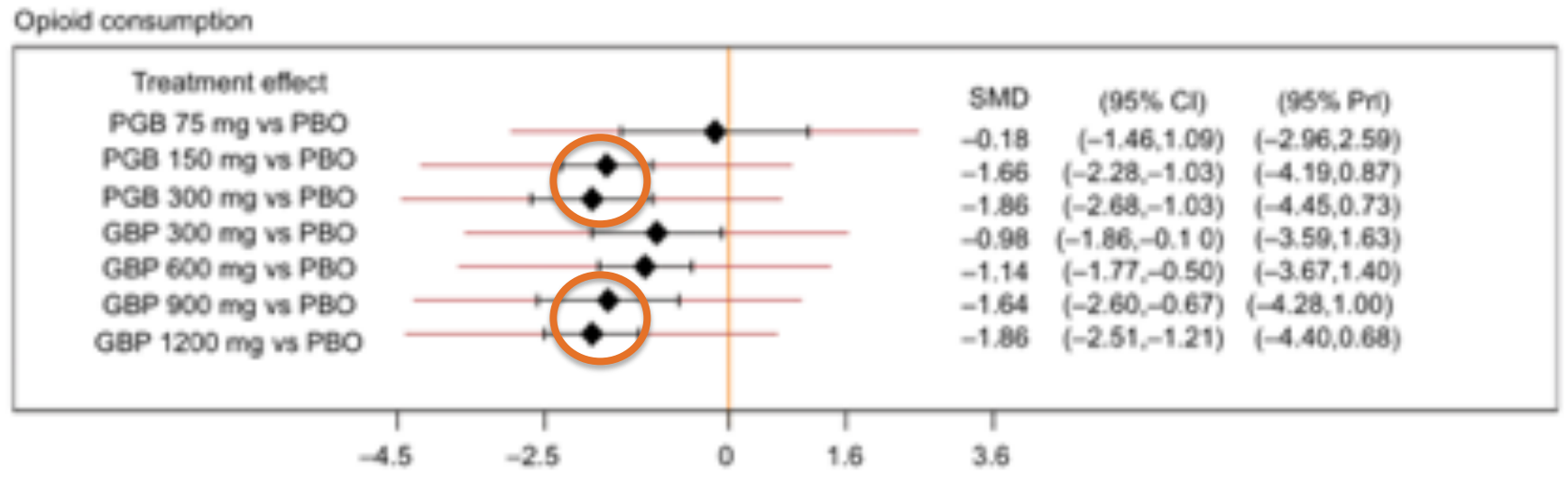
Bockbrader et al 2010

GABAPENTINOIDS

How to Dose?



Maximal opioid sparing doses

Gabapentin: 900 -1200 mg

Pregabalin: 150 – 300 mg

Side Effects, sedation, dizziness higher with increasing dose

Recommend using Gabapentin in the 600-900 mg range

Recommend avoiding Pregabalin

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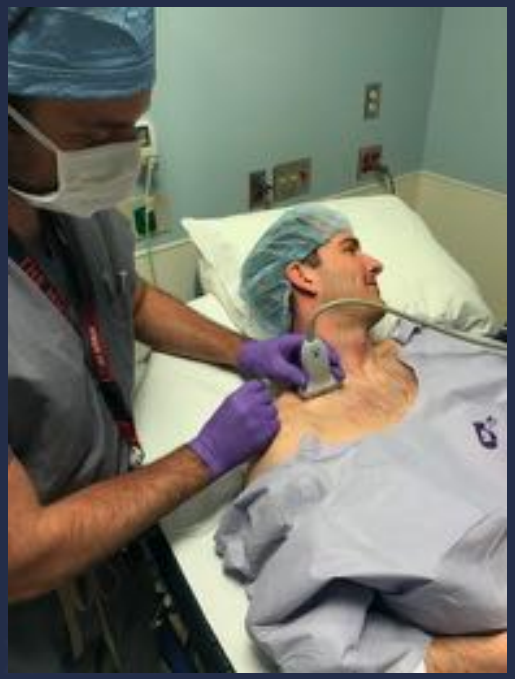
Hu et al 2018

Local Anesthetics

- **Nerve blocks**
  - Exparel®
- **Intravenous**
  - Lidocaine
- **Local Infiltration**



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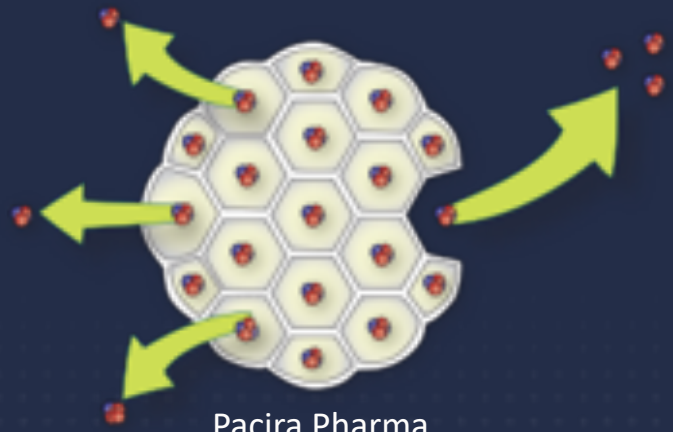
Local Anesthetics

Exparel® - Liposomal Bupivacaine

- Lipid microspheres release bupivacaine slowly
- Will prolong nerve blocks
- Longer times to opioids
- Safe
- Expensive ($315 cost)



Pacira Pharma

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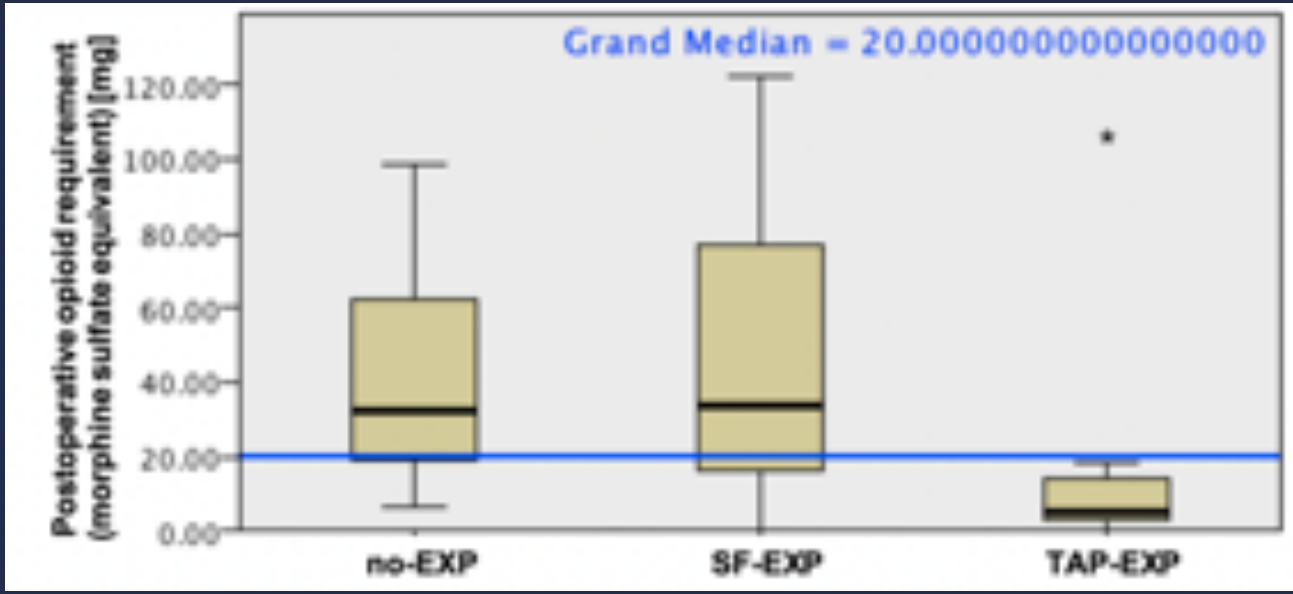
Local Anesthetics - Exparel®

TAP Blocks with Exparel Reduce Opioids



- Living donor nephrectomy patients received no Exparel (no-EXP), surgeon injected Exparel(SF-EXP), or Exparel TAP blocks (TAP-EXP).
- Data presented at American Transplant Congress 2018
- Nickkholgh, Amato et al

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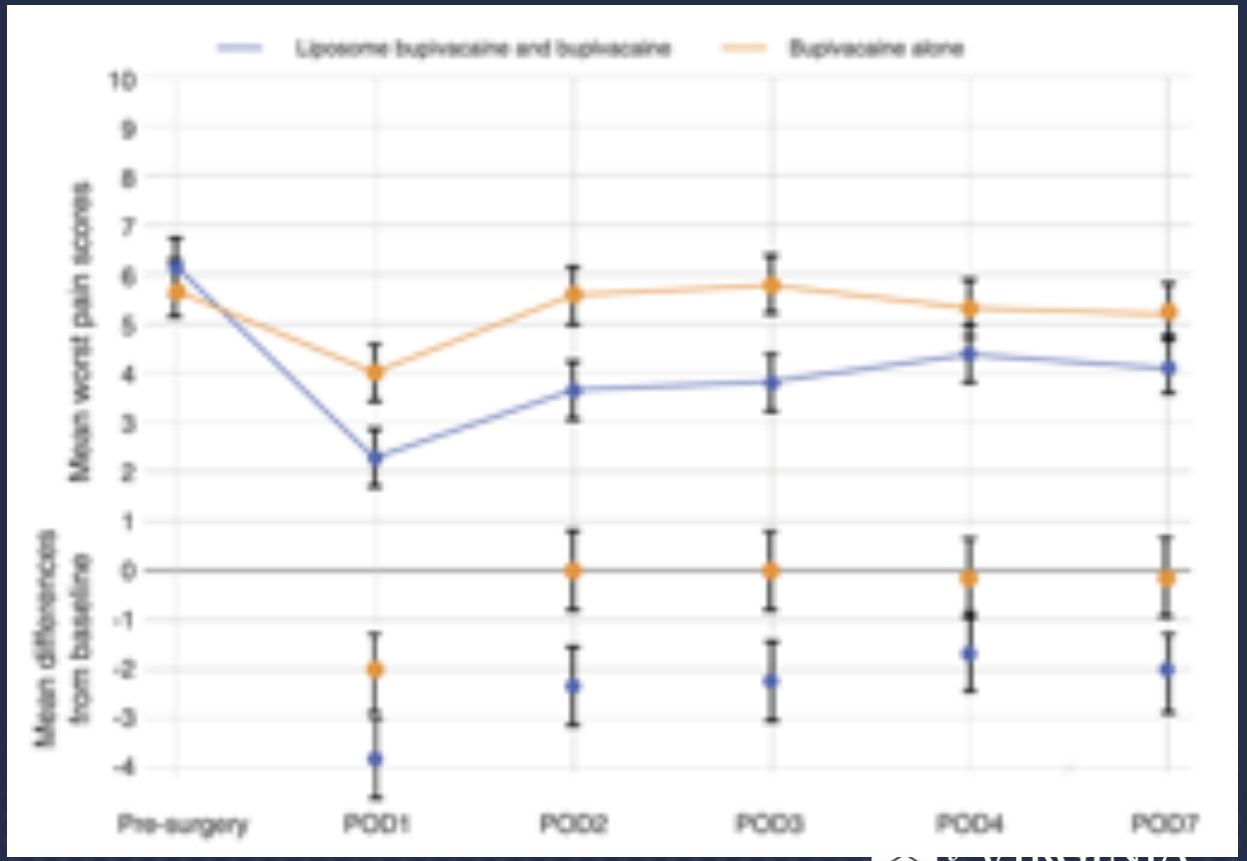
Local Anesthetics - Exparel®

Interscalene Blocks with Exparel® Reduce Pain

- 55 patients randomized to 2 different interscalene blocks: **Blue line** - ISB with 10 mL Exparel + 5 mL 0.25% Bupiv **Orange Line** - 15 mL 0.25% plain Bupiv
- Exparel provided lower worst pain scores for 7 days



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Vandepitte et al RAPM 2017

Local Anesthetics - Exparel®

Tips for Success

- Max approved dose for infiltration and TAP Block is 20 mL (266 mg)
- Max approved dose for interscalene block is 10 mL (133 mg)
- Mix in free bupivacaine for immediate onset (Exparel can take has a lag in onset)
- Use saline first to confirm needle placement (Exparel tends to make bubbles)

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Local Anesthetics - Exparel®

Tips for Success

My Recipes

- TAP Blocks (posterior) – Mix 20 mL Exparel and 20 mL 0.25% bupivacaine (Inject 20 mL per side).

- Interscalene block – Mix 10 mL Exparel and 10 mL 0.5% bupivacaine (Total 20 mL injected)

- Can increase the volume further with a max of 60 mL 0.25% bupivacaine. Useful for PECS where 30 mL per side is needed.

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Local Anesthetics – IV lidocaine

Benefits of IV Lidocaine

IMPROVED:

- Pain
- PONV
- Ileus rate
- Opioid use
- Length of stay

- MAC Reduction (20-30%)

Effects outlast infusion duration and half life of lidocaine by many hours

Kranke et al 2015, Dunn and Durieux 2017

Local Anesthetics – IV lidocaine

Mechanism of Action?

- Systemic levels at recommended dosages mimic those with epidural (1 μM)
- Interactions with inflammatory cells (PMN priming)
- Possible neuronal affect on wide-dynamic range neurons
- Clinical effect outlasts duration of infusion and the half-life of the drug substantially

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Local Anesthetics – IV lidocaine

Impact on Specific Surgery Types

Surgery Type(s)	Benefit
Lap abdominal	Reduced pain scores up to 24h postop Reduced opioid needs
Breast	Reduced incidence of chronic pain at 3 and 6 months
Ambulatory (general, endocrine, breast, gyn, uro, plastics, minor ortho, minor ENT)	Reduced pain scores, PACU opioid requirements, time to discharge. Better recovery scores.

Overall, evidence is greater for use in abdominal procedures

Local Anesthetics – IV lidocaine

Recommended Dosing

- Reduce dose or omit with liver or renal disease
- Can contribute to slower wakeup (anecdotal) if you continue through emergence, but will help with airway reactivity

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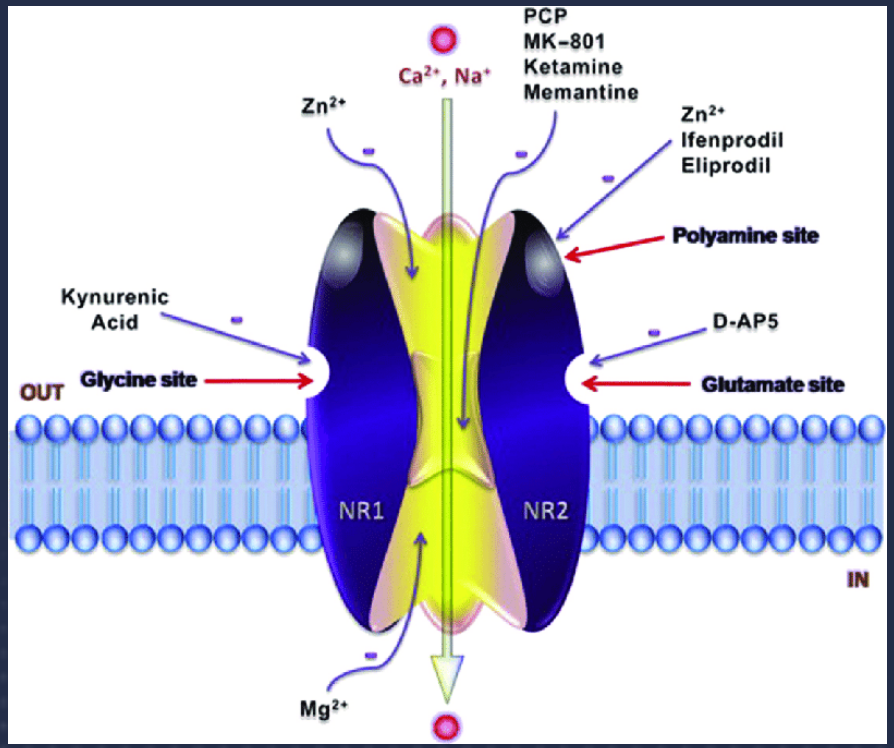
NMDA Antagonists

- Ketamine
- Magnesium
- Nitrous Oxide
- Tramadol
- Methadone
- Dextromethorphan



Ghasemi et al 2011

NMDA Antagonists - Ketamine

- Complicated physiologic effects
  - Activity at NMDA, opioid, cholinergic receptors
  - Modulation of serotonergic and noradrenergic activation and reuptake
  - Increasing dopaminergic activity
  - Reverses *μ*-opioid receptor desensitization
  - Inhibits nitric oxide synthase

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Sleigh et al 2014, Peltoniemi et al 2016

NMDA Antagonists - Ketamine

Pros

- Acute Analgesia
- Hypnosis, MAC reduction
- Reduction in opioid use
- ?modulation/prevention central sensitization and wind up
- ?attenuation of development of opioid tolerance
- Antidepressant Effects

Cons

- Sympathetic release
- Psychotomimetic side effects at higher doses
- Contribute to somnolence in PACU
- Increases in secretions

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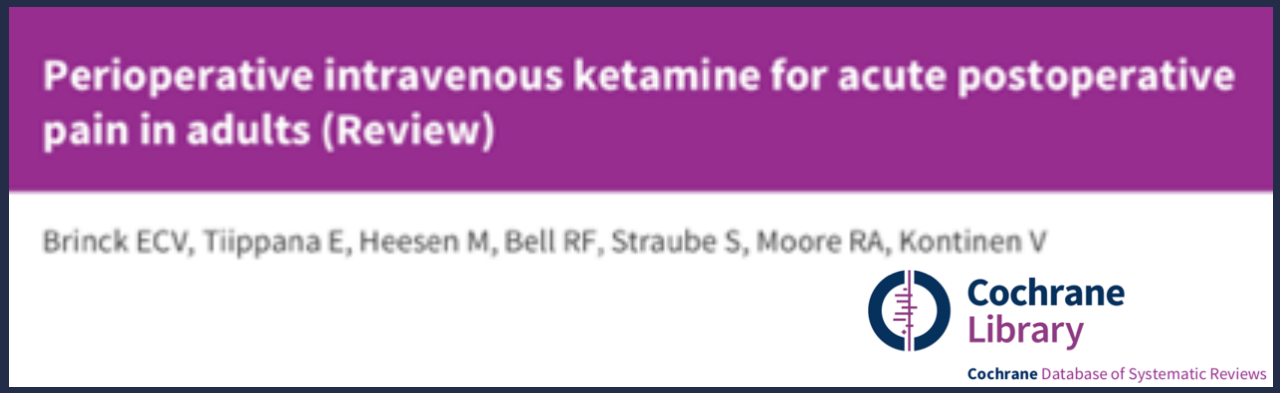
Sleigh et al 2014, Peltoniemi et al 2016

NMDA Antagonists - Ketamine



- Reduced postop opioid consumption at 24h (-8 mg) and 48 h (-13 mg)
- Reduced VAS pain score at 24h b(-5/100) and 48 h (-5/100)
- Reduced the area of postoperative hyperalgesia (-7 cm^2)
- Reduced PONV (RR 0.88)

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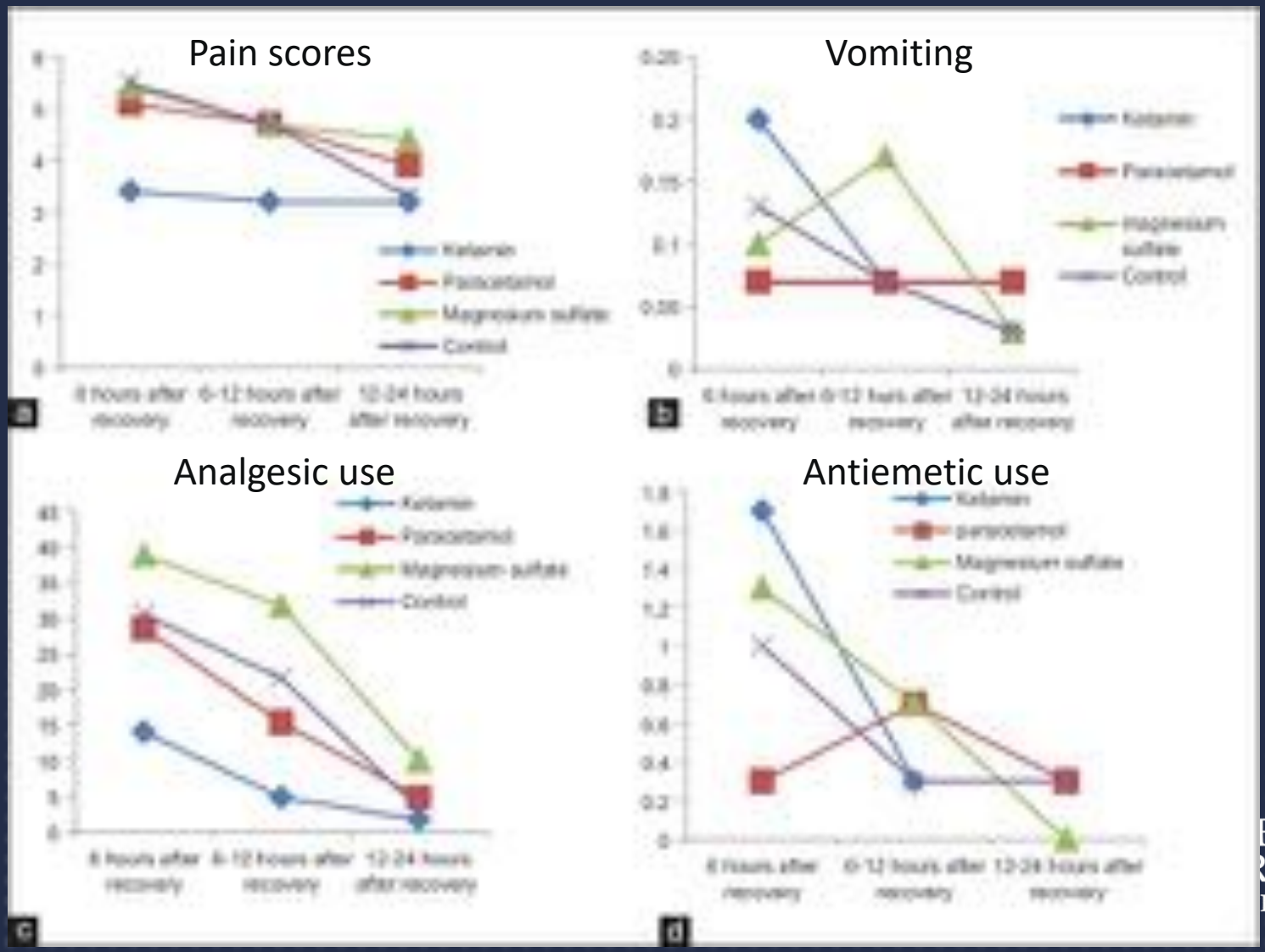
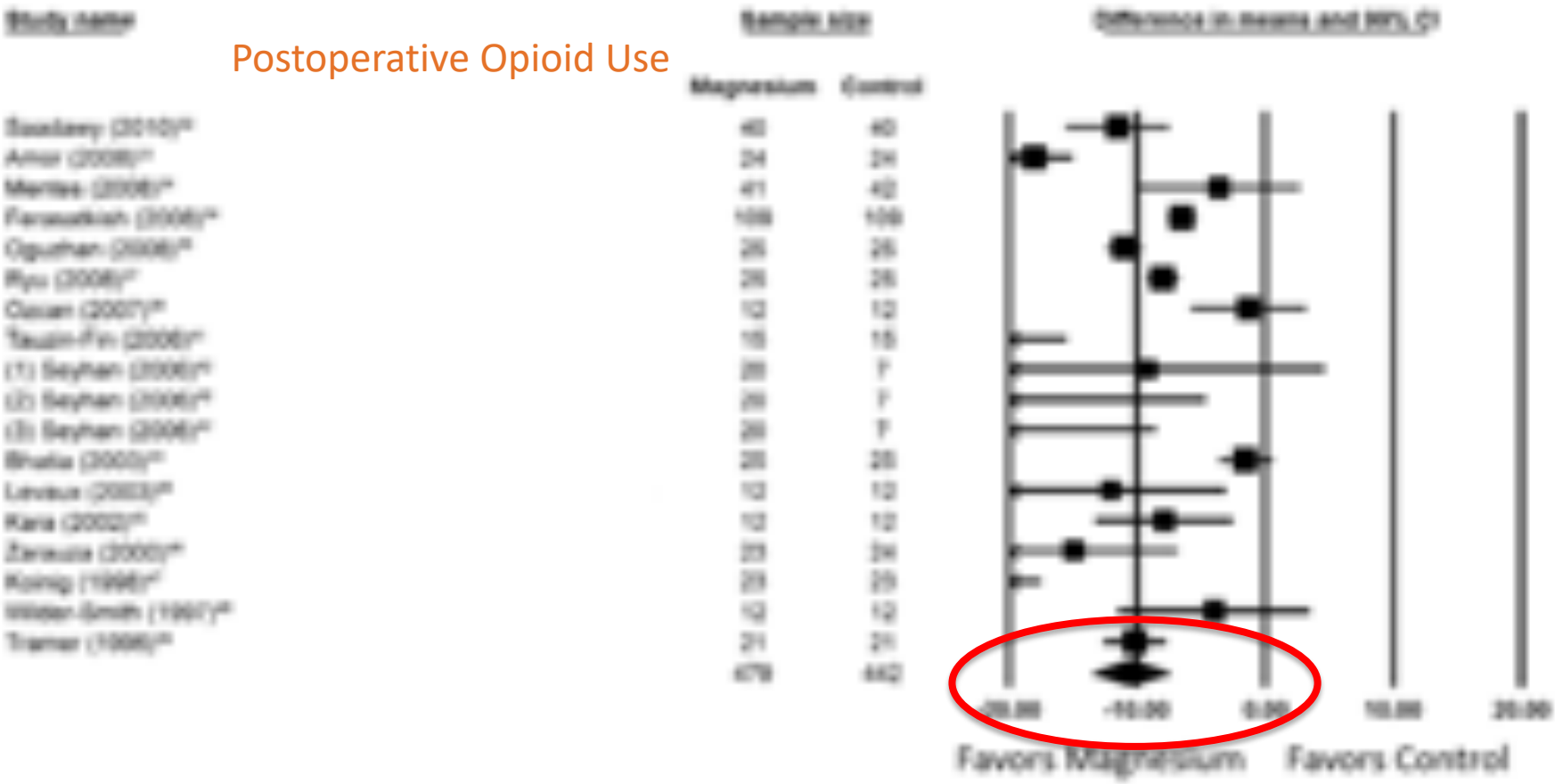
NMDA Antagonists – Ketamine, Magnesium



Heydari et al 2017

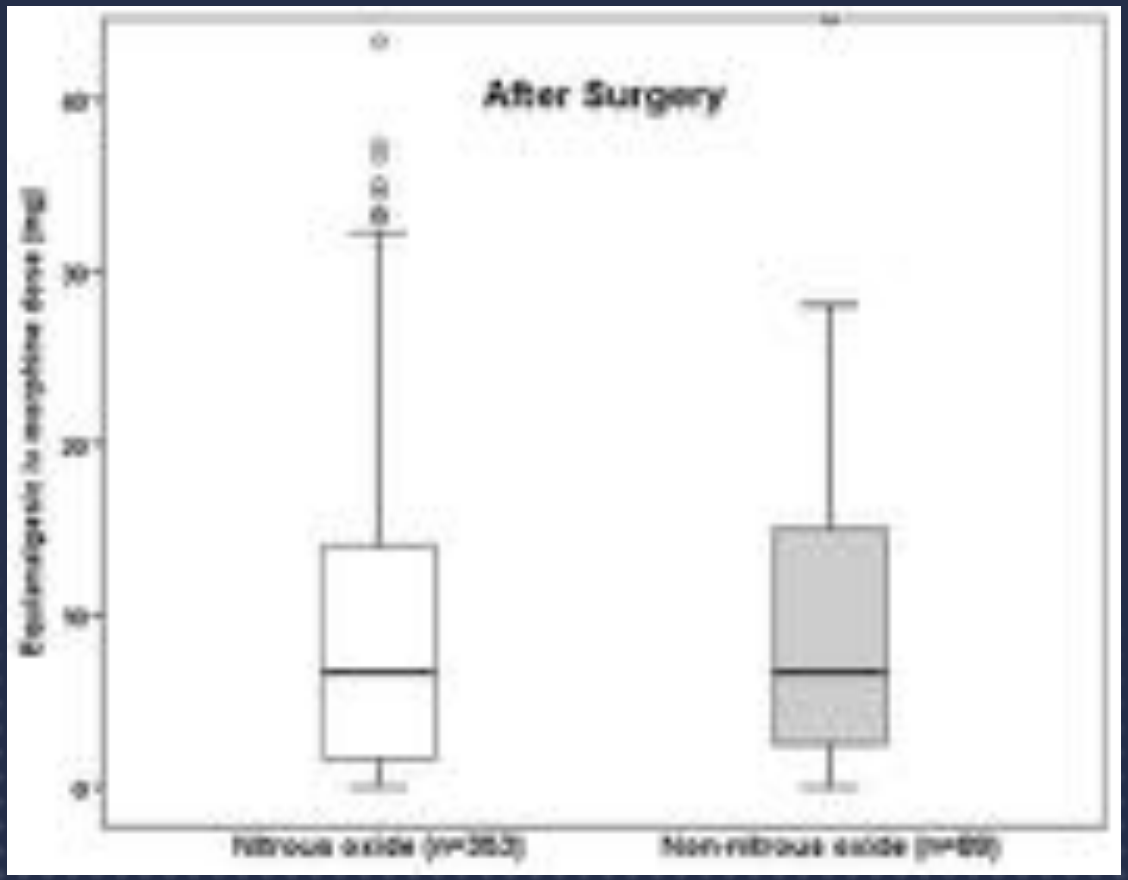
NMDA Antagonists – Magnesium

Postoperative Opioid Use



De Oliveira et al Anesthesiology 2013

NMDA Antagonists – Nitrous Oxide

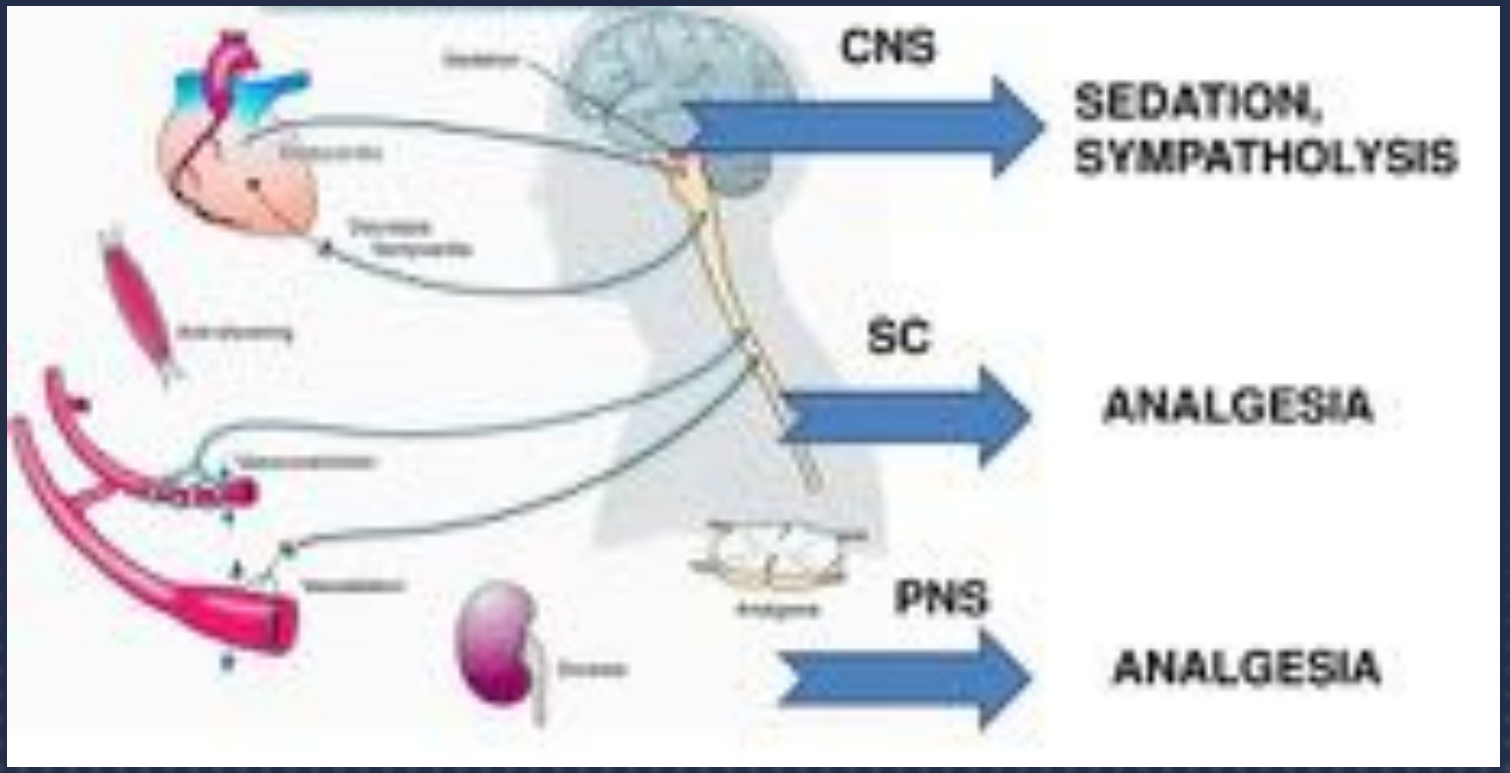


PACU Opioid Consumption

NMDA Antagonists – Dosing

Drug	Dose	Notes
Ketamine	0.25-0.5 mg/kg bolus +/- Infusion 0.25 mg/kg/hr	For longer cases stop infusions 45 min - hour before emergence
Magnesium	30-50 mg/kg	
Dextromethorphan	40 mg IM 90 mg PO	Not on most ASC formularies

α2 agonists – Dexmedetomidine



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Modified from Kumar, GK

α2 agonists – Dexmedetomidine

Pros

- Small impact on pain, opioid use
- Anxiolysis
- Can be helpful hemodynamically if HTN, etc.

Cons

- Bradycardia
- Sedation in PACU
- $$$

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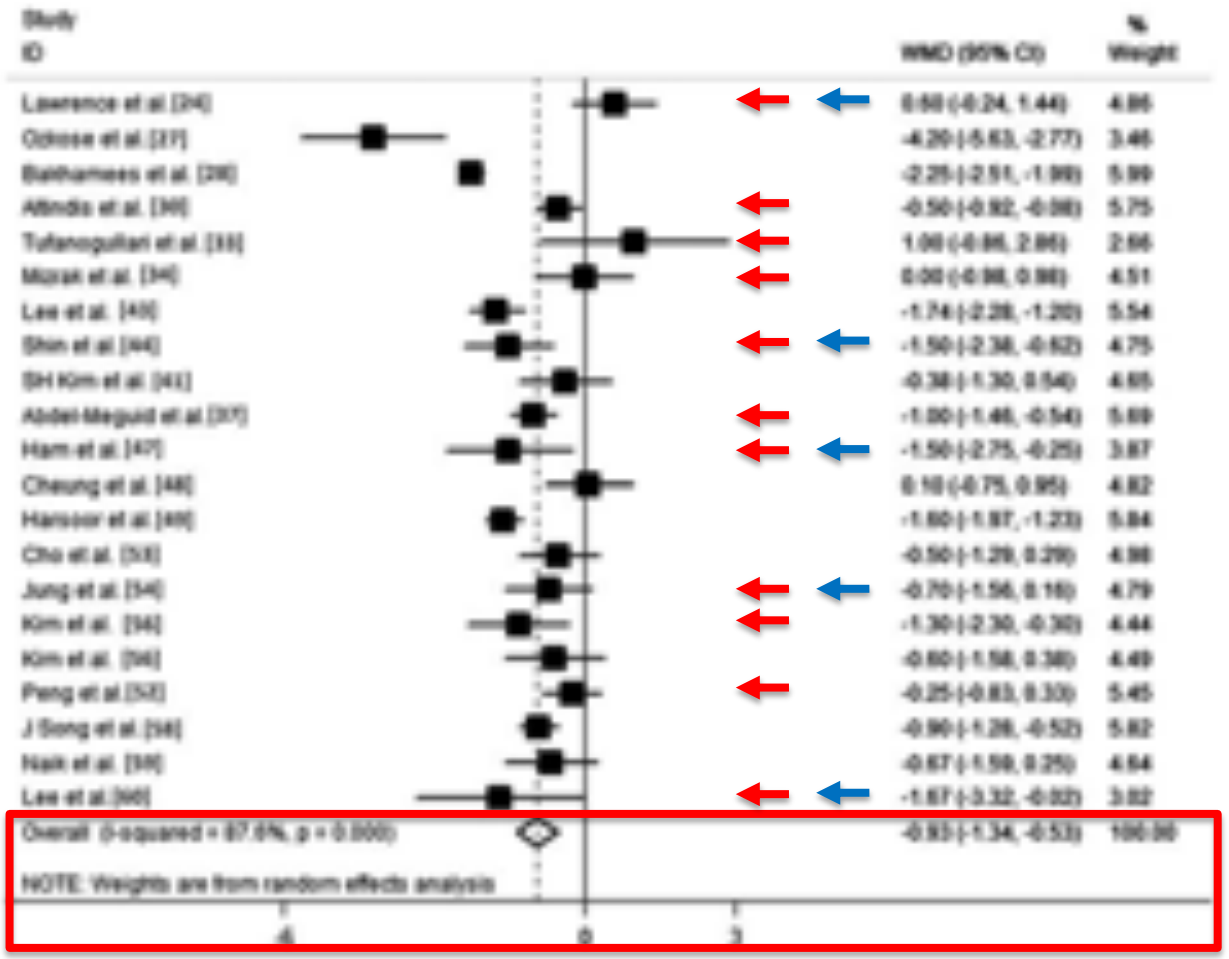
Dexmedetomidine – Pain Scores within 6 hours



- 1000 patients
- Heterogenous surgery types
- Heterogeneous dosing

Bolus 0.5-2 mcg/kg
+/- infusion

Just Bolus ←
Bolus ≥1 mcg/kg ←

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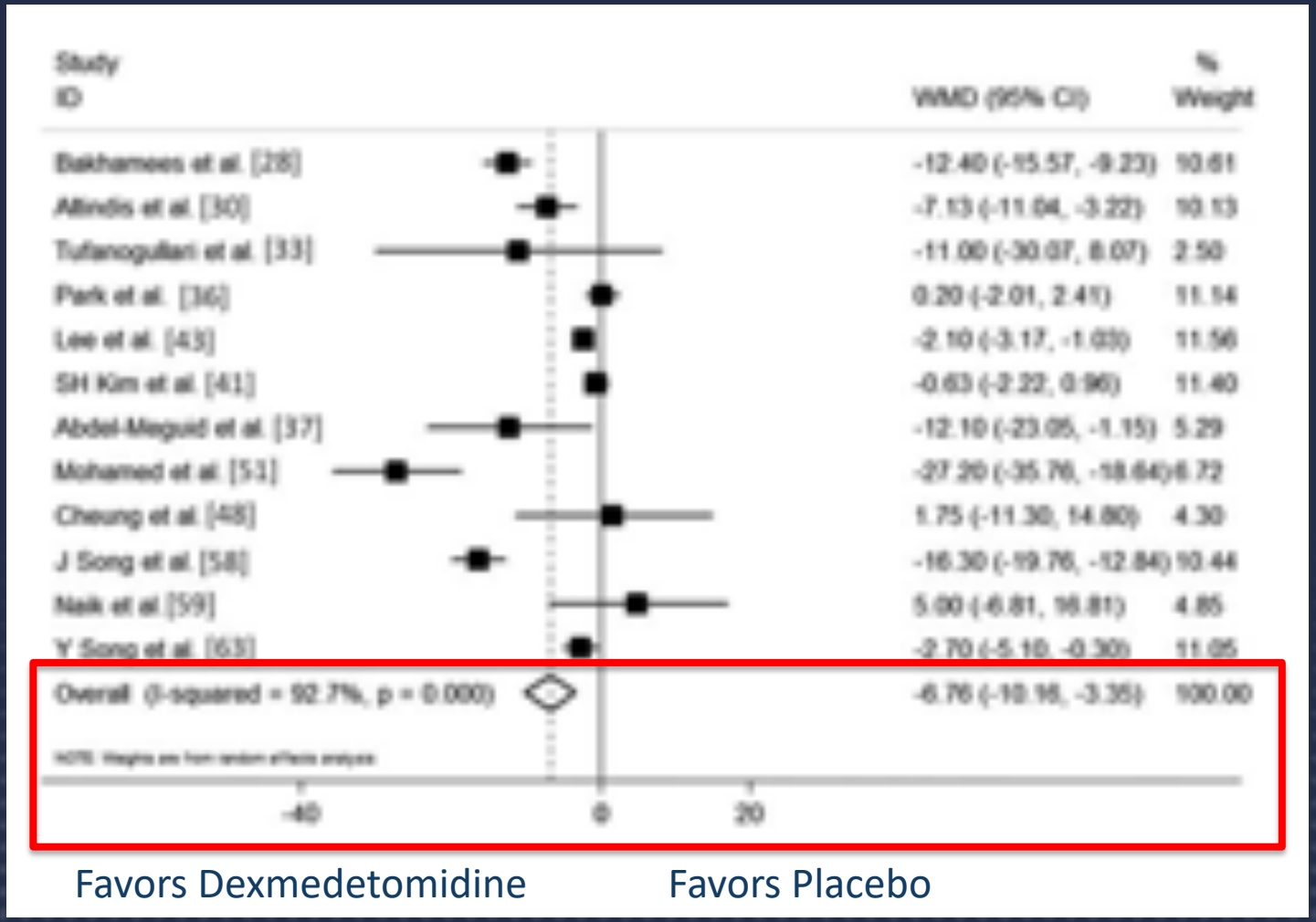
Wang et al Clin J Pain 2018

Dexmedetomidine – 24h Opioid Reduction



PACU Opioid Reduction:
-3.11 mg (-5.2, -1.03; p<0.05

Time to 1st request:
-34.93 min; (-20.27,-49.59; P< 0.05)

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Wang et al Clin J Pain 2018

Dexmedetomidine – Sedation/Delays

Colonoscopy (Propofol +/- 0.3 mcg/kg DEX)

Edokpolo et al, Anesthesiology 2019

- % Patients ready for discharge at 30 min post-procedure
  - DEX + Propofol - 26/51 (51%)
  - Propofol alone - 44/50 (88%) ($P < 0.001$)

- BP reduction greater post-procedure with DEX
- No significant difference in bradycardia

1.Edokpolo et al, Anesthesiology 2019

Dexmedetomidine

Tips for Success

- Patient and Procedure – Risk/Benefit
  - Age, Liver function[1], cardiac function/rhythm, OSA and sedative sensitivities
  - Duration of procedure and expected pain impact
- Dosing for pain effect probably at least 1 mcg/kg
- Dose early (Elimination half life is 2.1-3.1 hours in healthy adults)[1]

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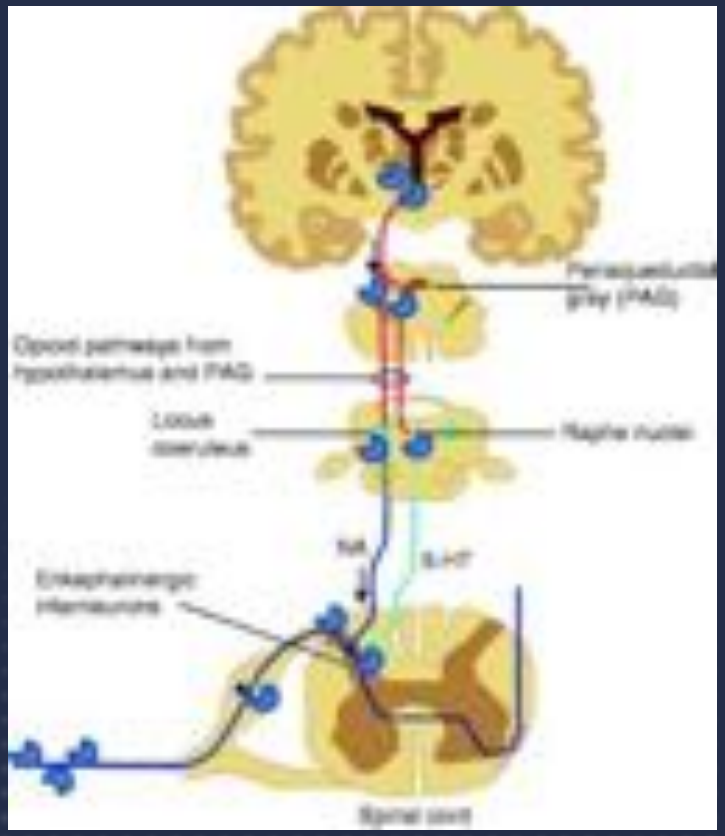
1. Weerink et al, Clin Pharmacokinetics 2017

Opioids



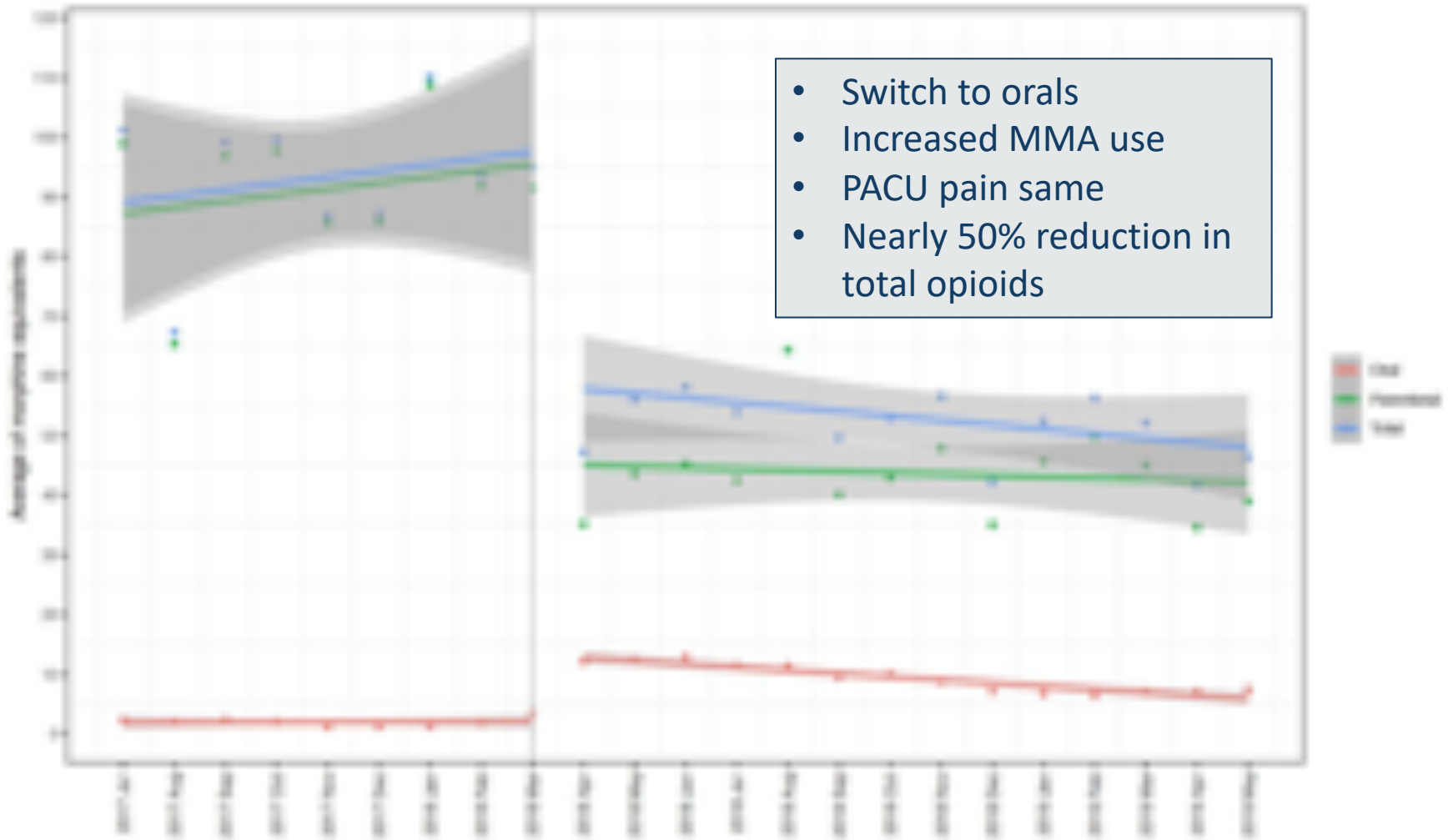
Schafer, M In: Evers, AS 2011

- Work on spinal cord, midbrain
- Highly effective for acute pain
- Side effects – nausea, sedation, respiratory depression
- Still play a major role in care!!!

Opioids

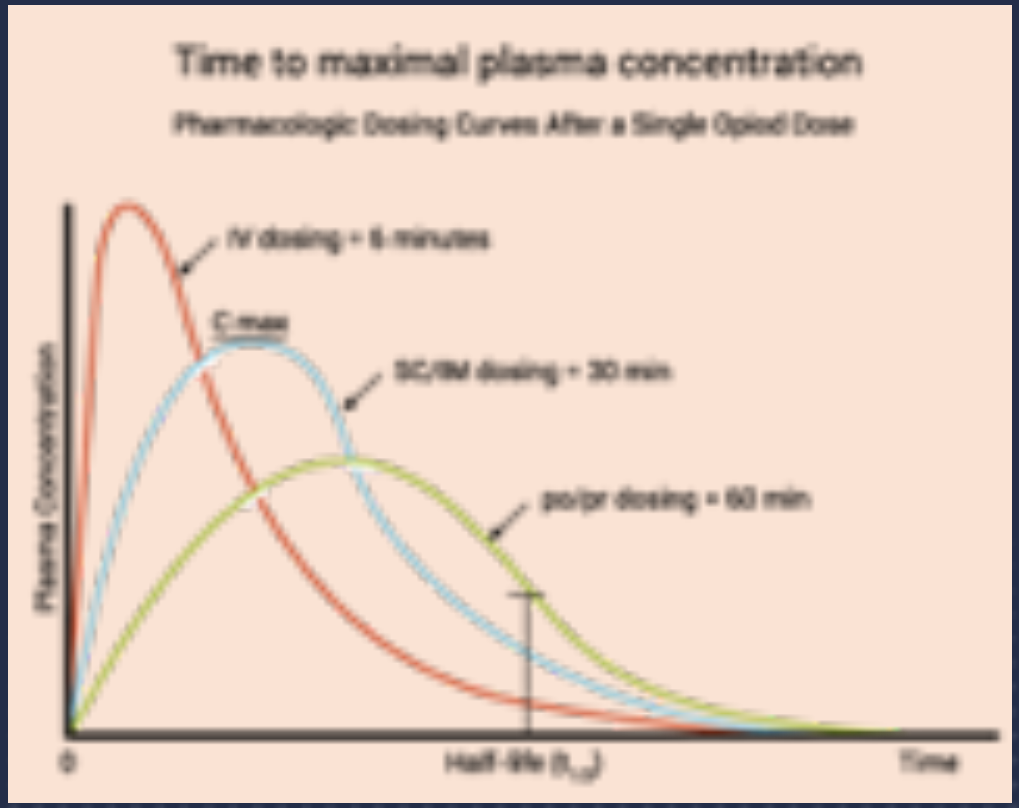
- Consider orals
- Consider duration of action
- Consider simplicity of metabolism
- Reduce doses when combining with other sedating multimodal agents

Reduction in total opioids when switching to orals and encouraging multimodal



Salajegheh R, Nemergut E, Naik B 2019 unpublished data

Opioids



https://geri-em.com/symptom-management/opioids/

PO Dosing often gives more favorable duration, at the expense of onset time.

Super short and potent IV opioids probably cause opioid-induced hyperalgesia and tolerance faster

NMDA antagonist may reverse this[2]

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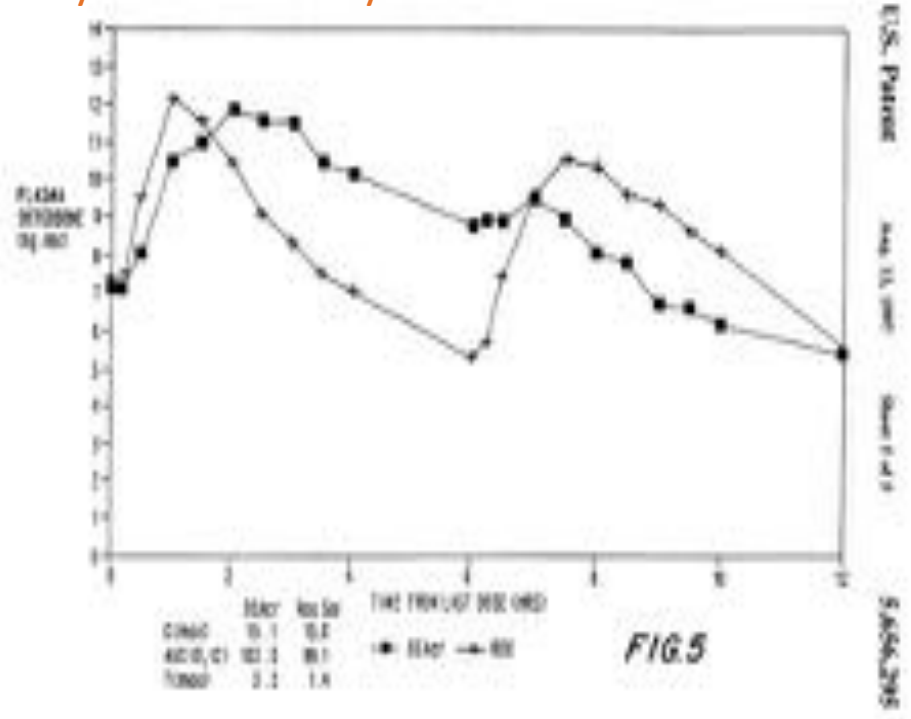
1. Fletcher et al, Anaesth 2014 2.Echevarria et al, BJA 2011

Opioids

OxyContin® vs Oxycodone Pharmacokinetics

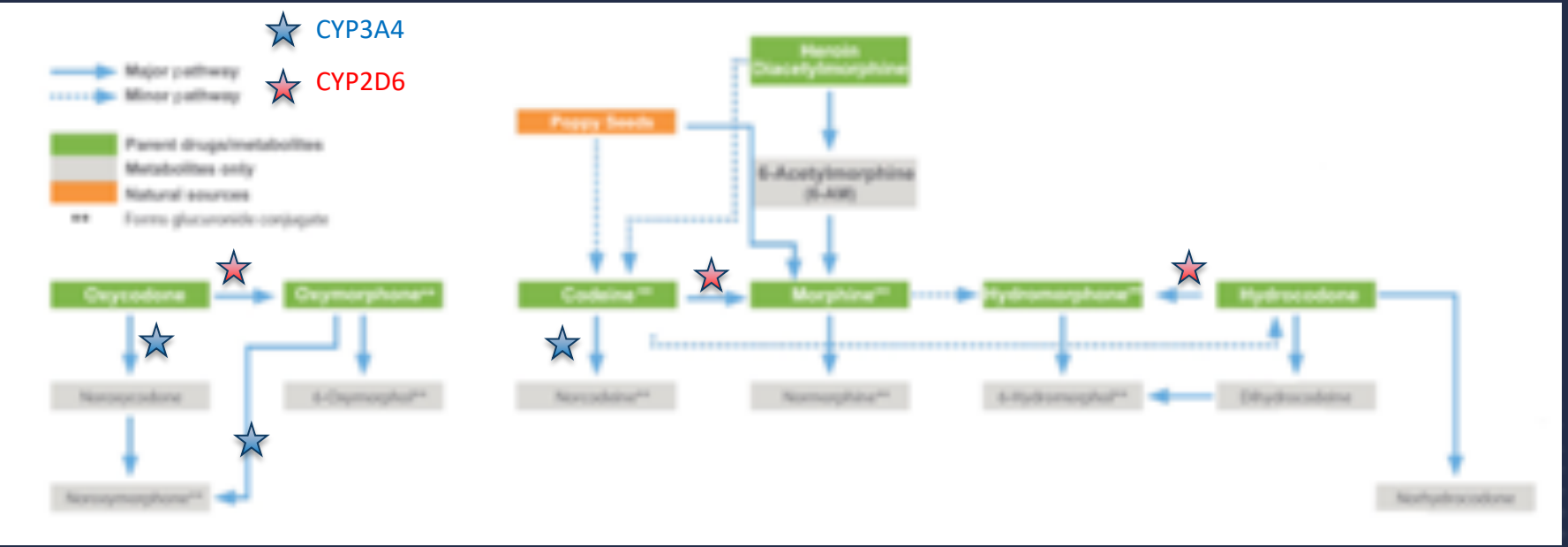


- 20 mg CR vs 20 mg IR.
- Onset similar but longer duration
- If you know the surgery will be ≥3 hours, think about CR.

Oshlack B et al, US Patent 5656295A, Purdue Pharma 1997

Opioids – Cytochrome Variability

Opioids without phase I metabolism may have more predictable response



https://cordantsolutions.com/resources/opioid-metabolism-resource/

Oshlack B et al, US Patent 5656295A, Purdue Pharma 1997

Cost – the most expensive meds

Drug	Cost
Acetaminophen 1000 mg IV	**43.68**
Acetaminophen 325 mg tab	0.02
Ketamine 30 mg syringe	3.8
Ketamine 100 mg vials (10mg/ ml 20ml vial)	**17.79**
Ketamine 500 mg vials	7.53
Dexmedetomidine 200 mcg/50 mL vial	**41.31**
Celecoxib 200 mg tab	1.49
Ketorolac 30 mg vial for IV	0.9
Gabapentin 300 mg tab	0.11

Summary Examples
Develop what works for you

Case Type	Pain Level	Regimen
Breast Biopsy/small lumpectomy Inguinal Hernia Repair	Low	Acetaminophen NSAID Local/Ilioinguinal Block
Lap Chole	Low-Med	Acetaminophen NSAID Gabapentin 600 Lidocaine infusion Ketamine +/- Opioid
Rotator cuff repair	High	Exparel interscalene Acetaminophen NSAID ketamine
ACL Repair Hip Scope	High	Acetaminophen NSAID Gabapentin 600mg Nerve Blocks Opioid Ketamine +/-Dexmedetomidine

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SUMMARY

- **Attack pain from multiple angles and classes of drugs**
  - Acetaminophen
  - NSAIDs
  - Local anesthetics/Regional when possible
  - Gabapentinoids
  - NMDA Antagonists
  - Dexmedetomidine
  - Opioids when needed

- **MMA must start before surgery!**
  - Interrupt the pain pathways
  - Get comfortable with oral medications

- **Be careful of causing sedation/PACU delays**
  - Gabapentin, Ketamine, Dexmedetomidine, Opioids

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