MULTIMODAL ANALGESIA (MMA)

SEIHA KIM, DO, MPH, PHARMD

MAY 22, 2021

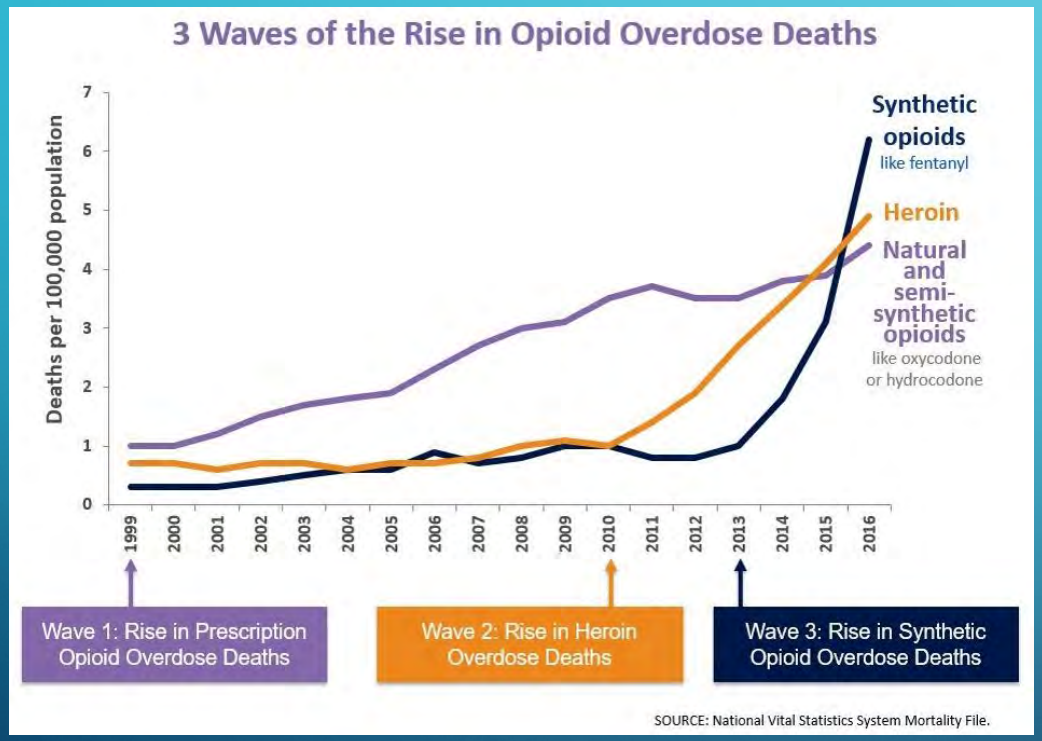
DISCLOSURES

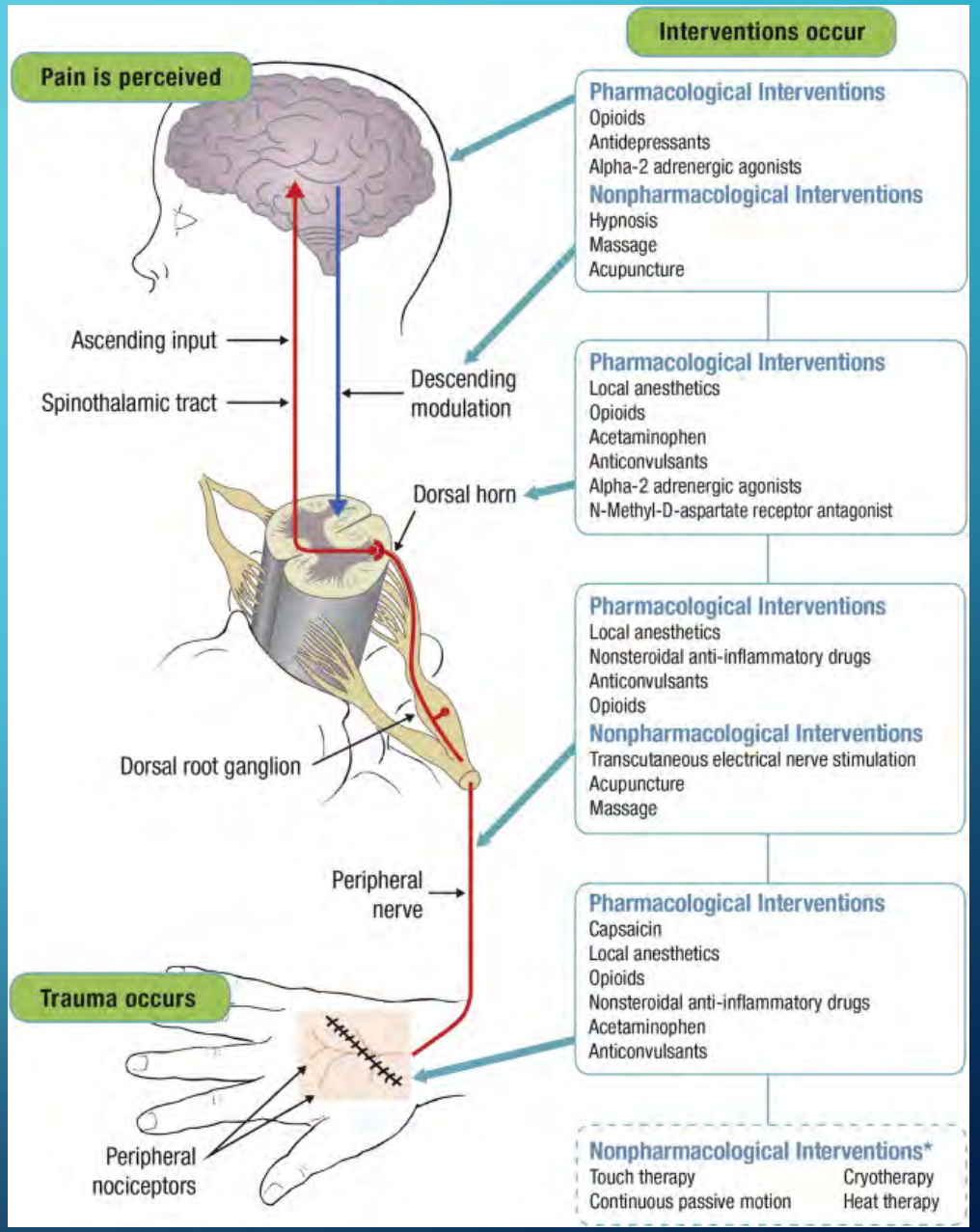
- None ☹

OBJECTIVES

- Review physiology of pain transmission
- Review pharmacology of multimodal analgesics
- Discuss literature about multimodal analgesics

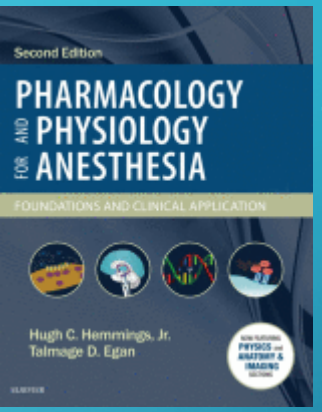
WHY MULTIMODAL?



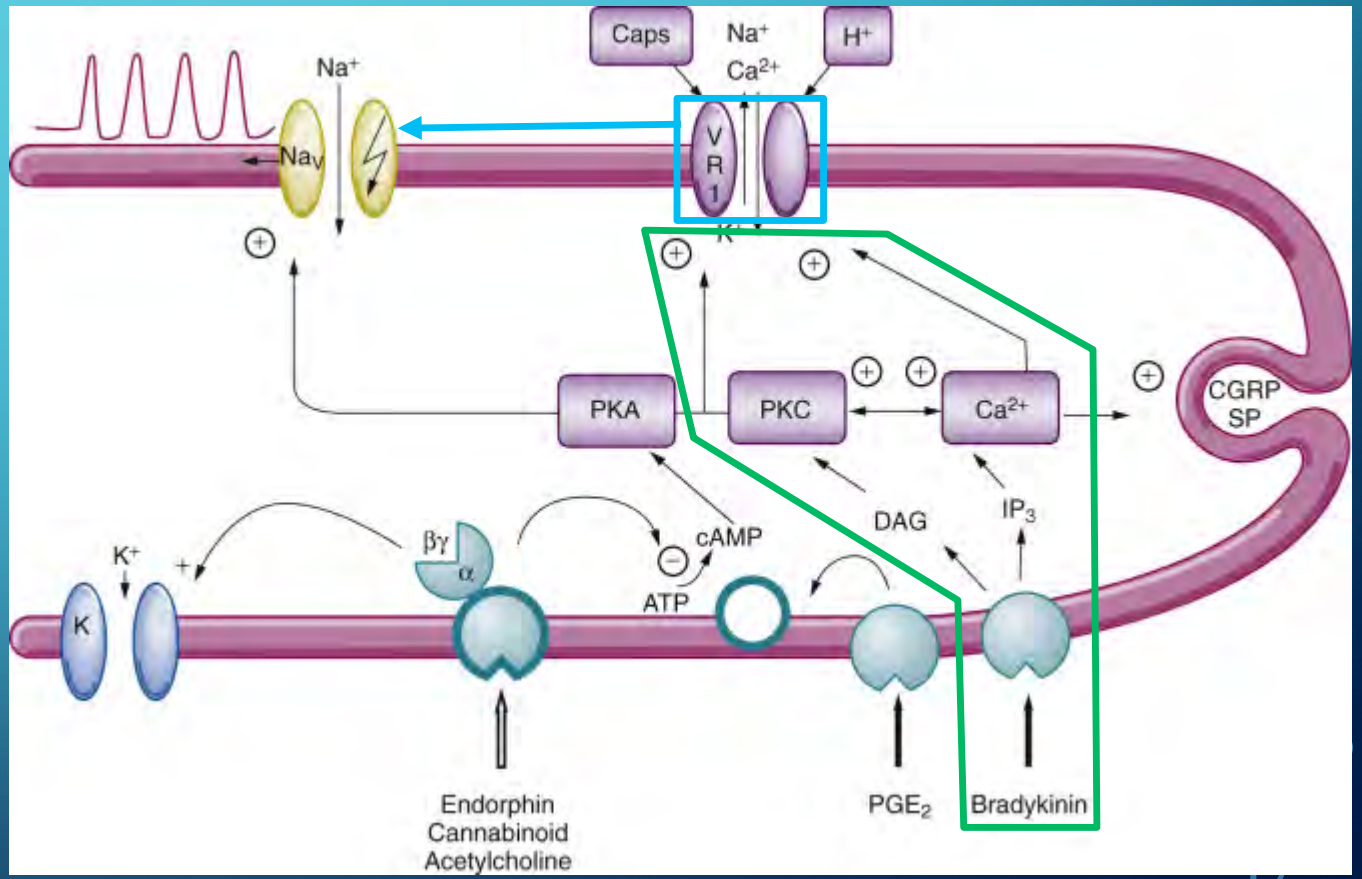


Manworren RC. Multimodal pain management and the future of a personalized medicine approach to pain. *AORN J*. 2015 Mar;101(3):308-14.

PAIN TRANSMISSION



- Vanilloid 1 receptor (VR1)
  - Noxious heat, capsaicin, H^+ ions
- (+) by bradykinin, PGE2, etc.
  - Phosphorylation of VR1 leads to increased permeability of Na/Ca



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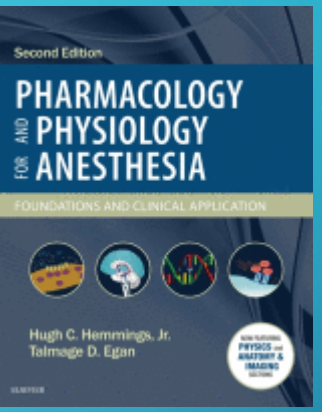

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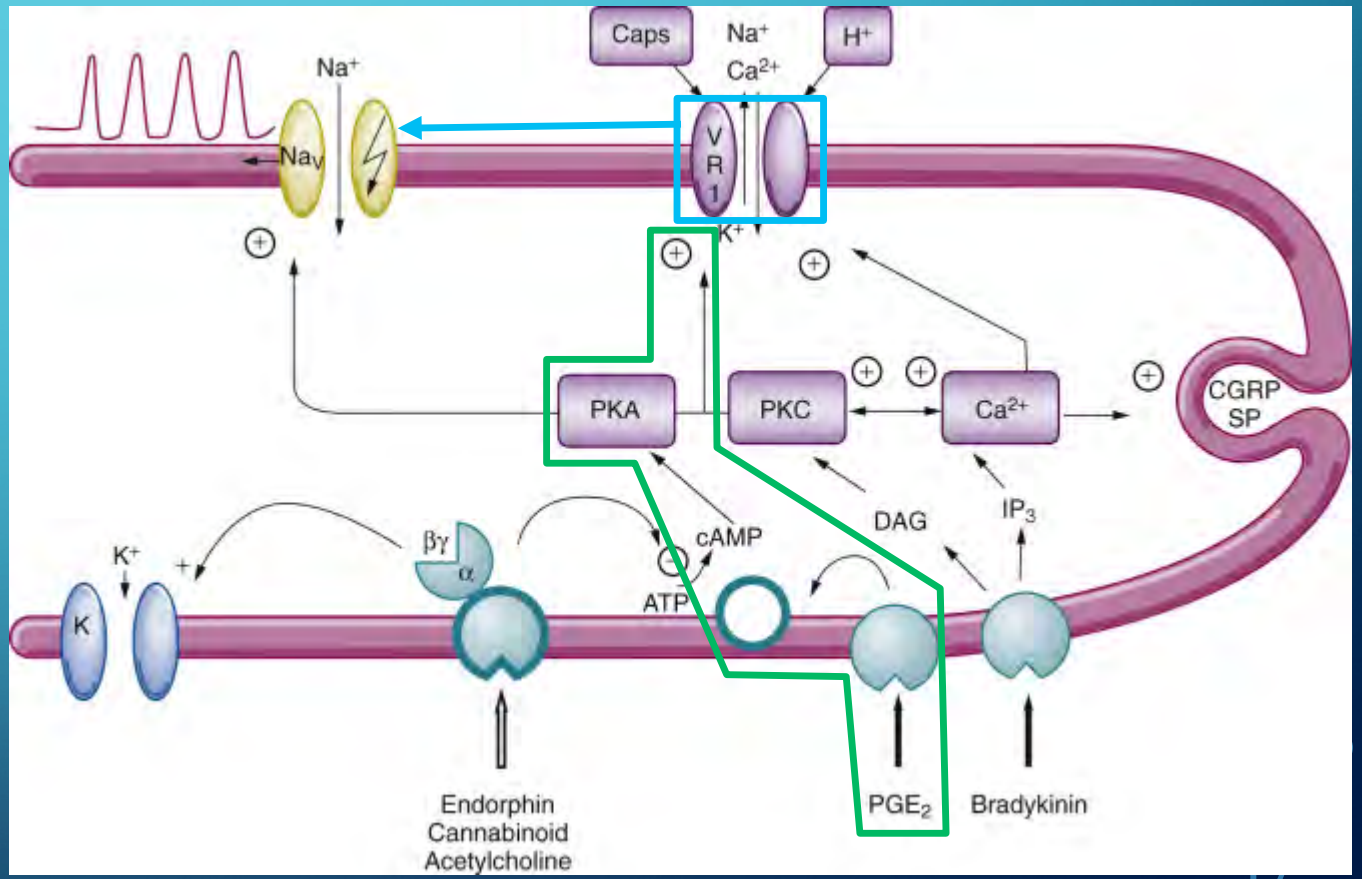

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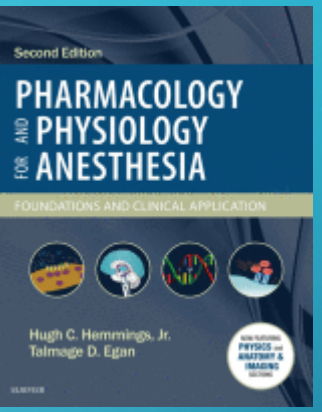
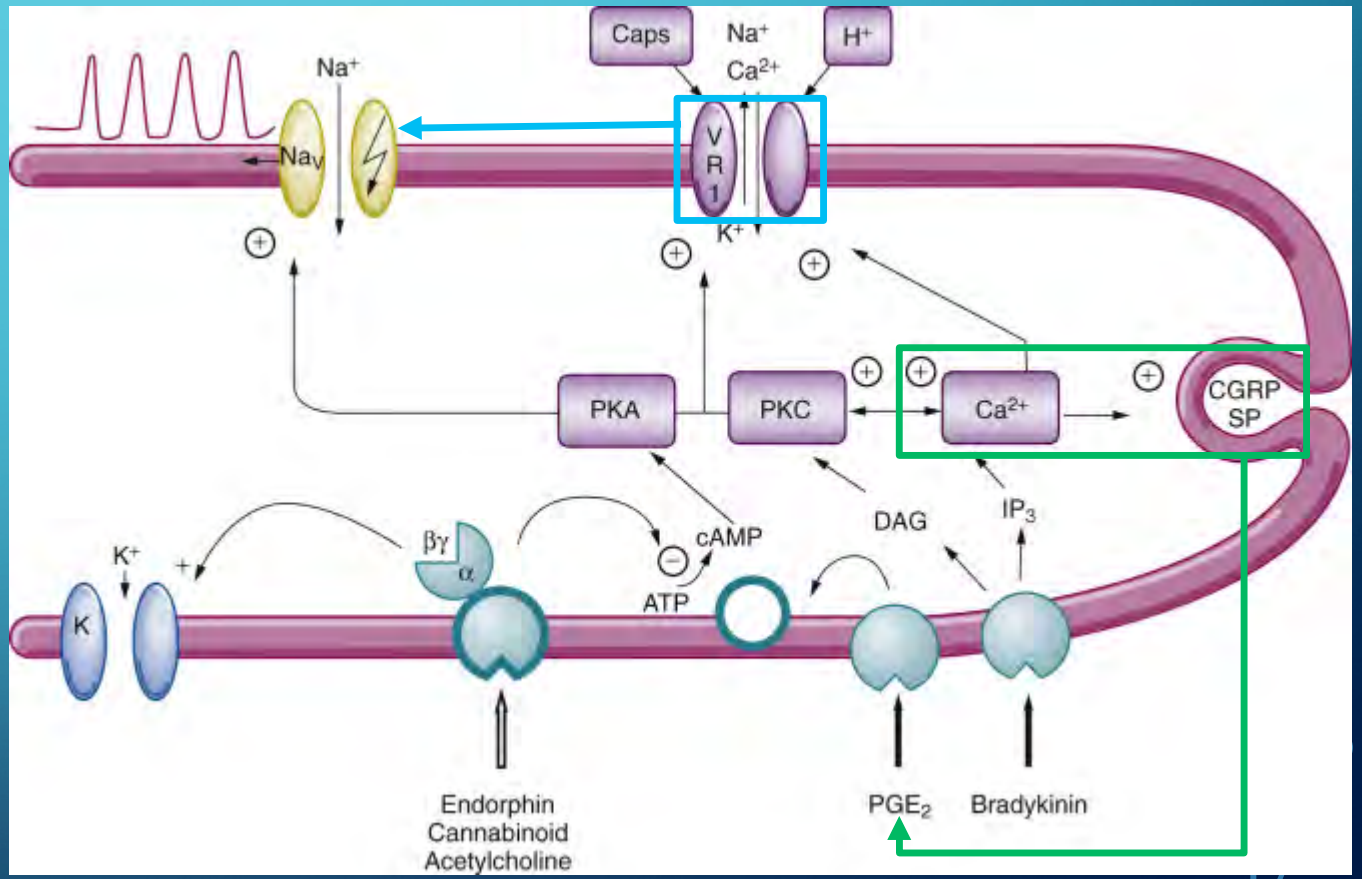


- Vanilloid 1 receptor (VR1)
  - Noxious heat, capsaicin, H^+ ions
- (+) by bradykinin, PGE2, etc.
  - Phosphorylation of VR1 leads to increased permeability of Na/Ca
- Calcitonin gene-related protein, substance P, and calcium trigger further peripheral inflammation



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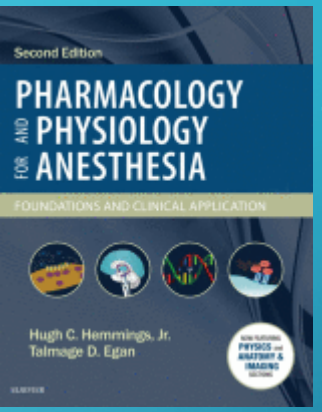
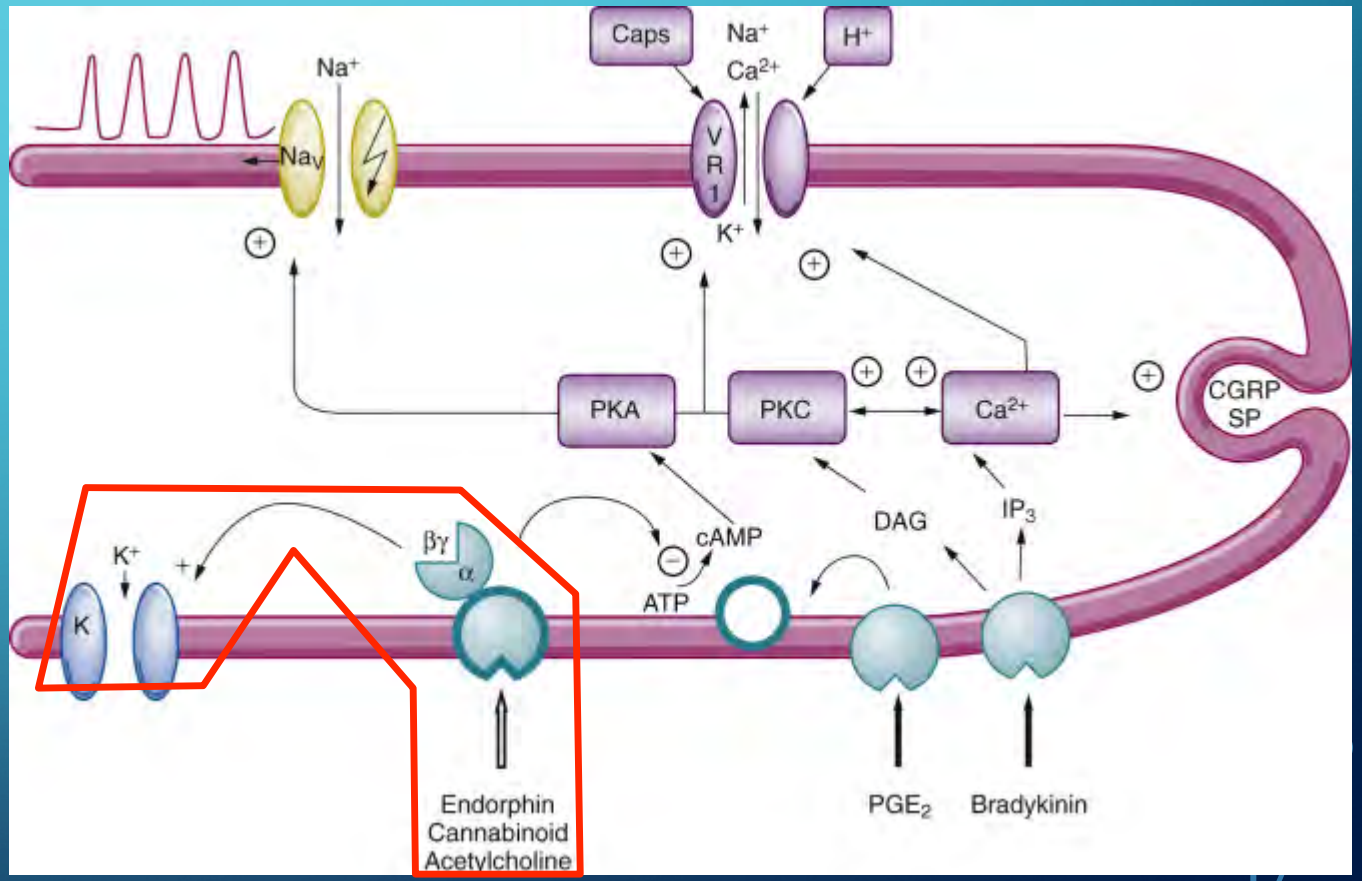


- Vanilloid 1 receptor (VR1)
  - Noxious heat, capsaicin, H^+ ions
- (–) by endorphins, ACh, and endocannabinoids
  - K^+ outflow opposes depolarization



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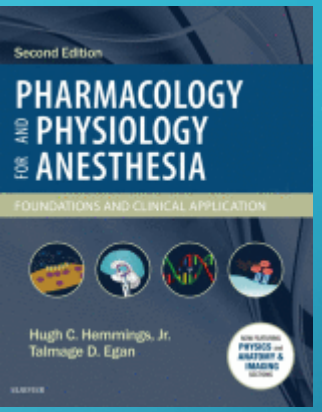
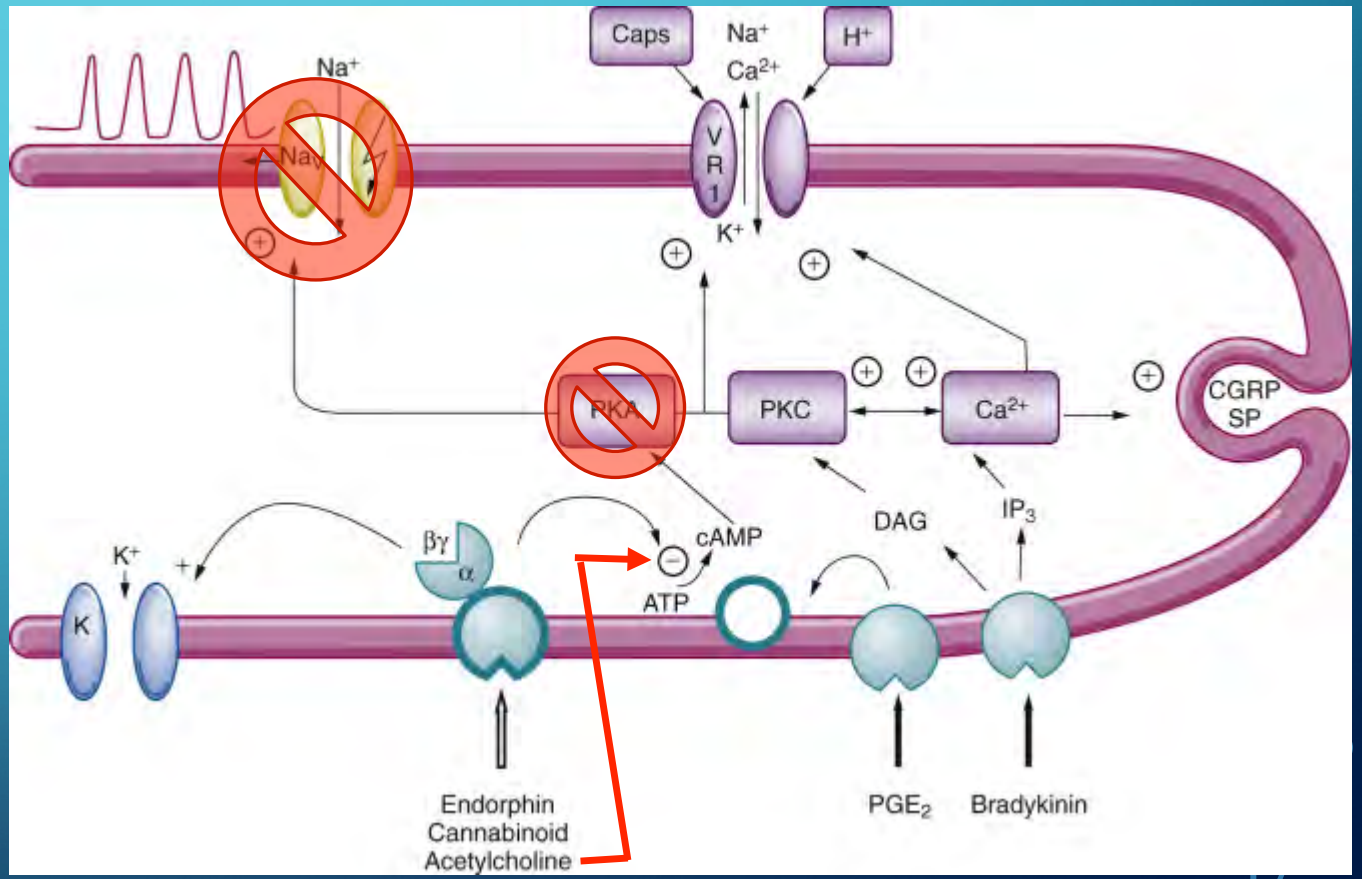
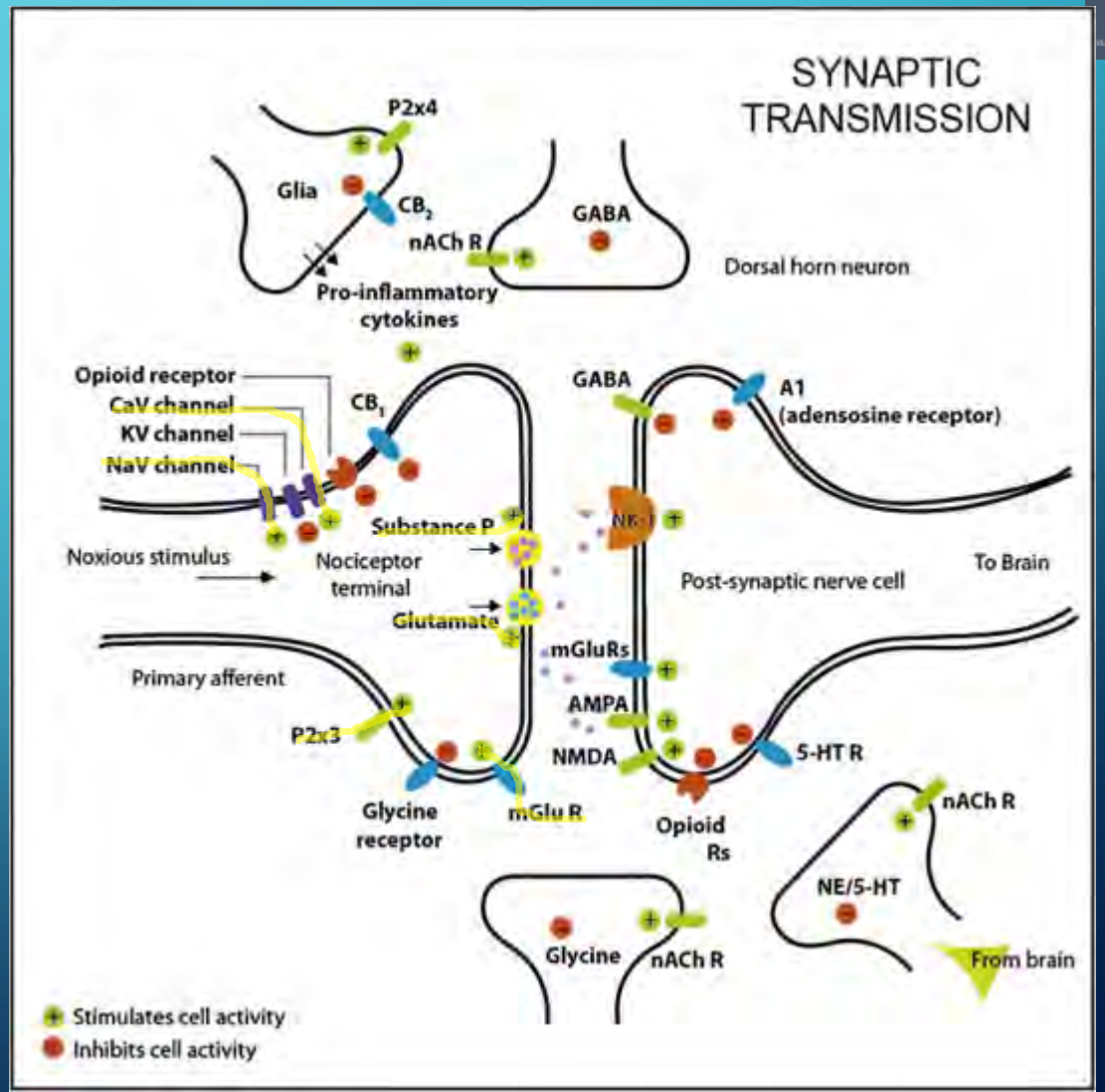


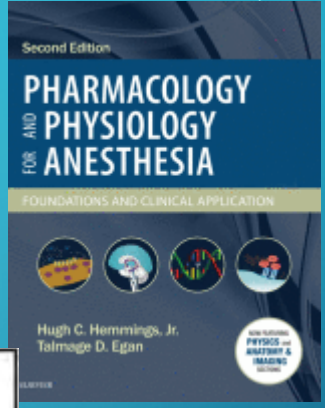
- Vanilloid 1 receptor (VR1)
  - Noxious heat, capsaicin, H^+ ions
- (–) by endorphins, ACh, and endocannabinoids
  - K^+ outflow opposes depolarization
  - Inhibits adenylate cyclase (↓ cAMP formation), thus inactivating PKA



PAIN TRANSMISSION

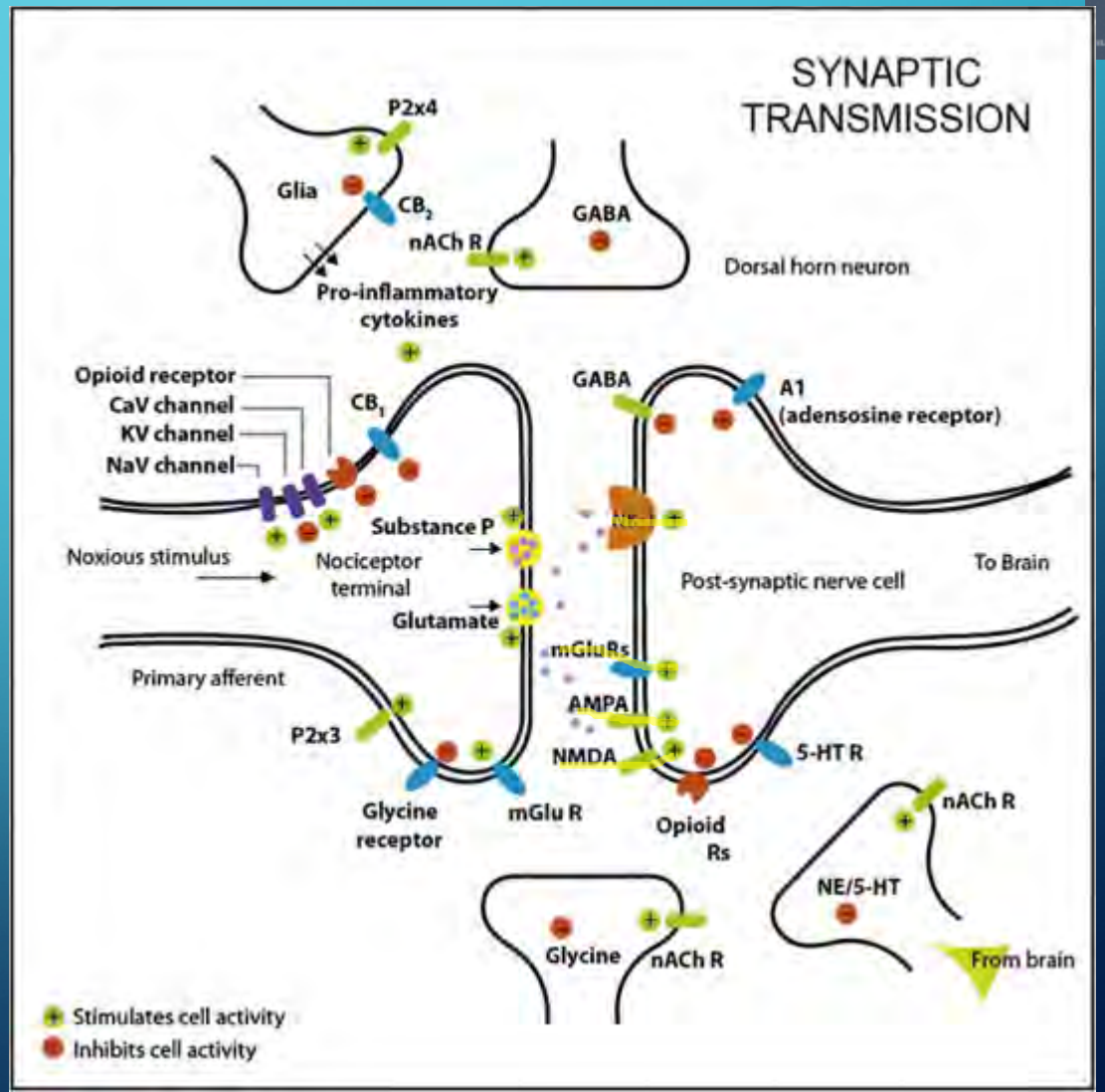
- Pre-synaptic (+)
  - NaV and CaV channels
  - Substance P
  - Glutamate and mGluR

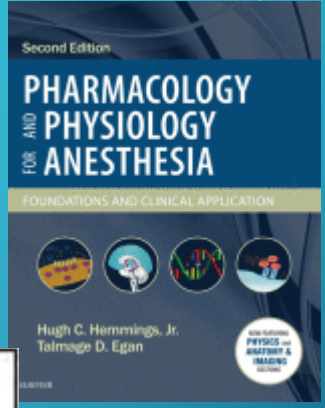




PAIN TRANSMISSION

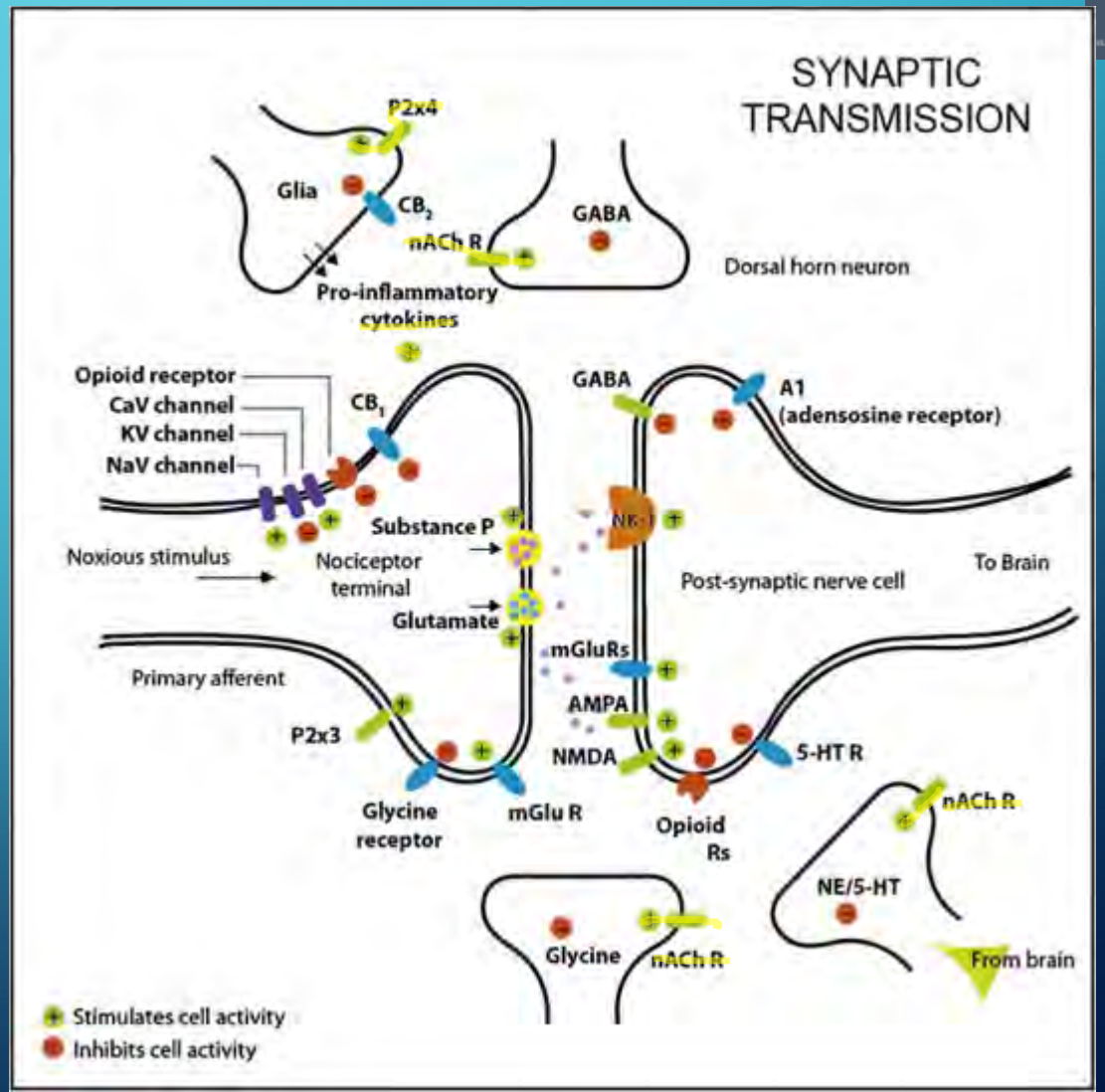
- Pre-synaptic (+)
  - NaV and CaV channels
  - Substance P
  - Glutamate and mGluR
- Post-synaptic (+)
  - NK-1, AMPA, glutamate, and NMDA receptors

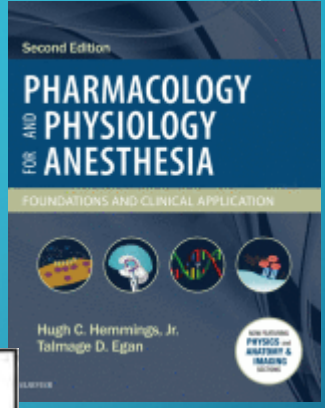




PAIN TRANSMISSION

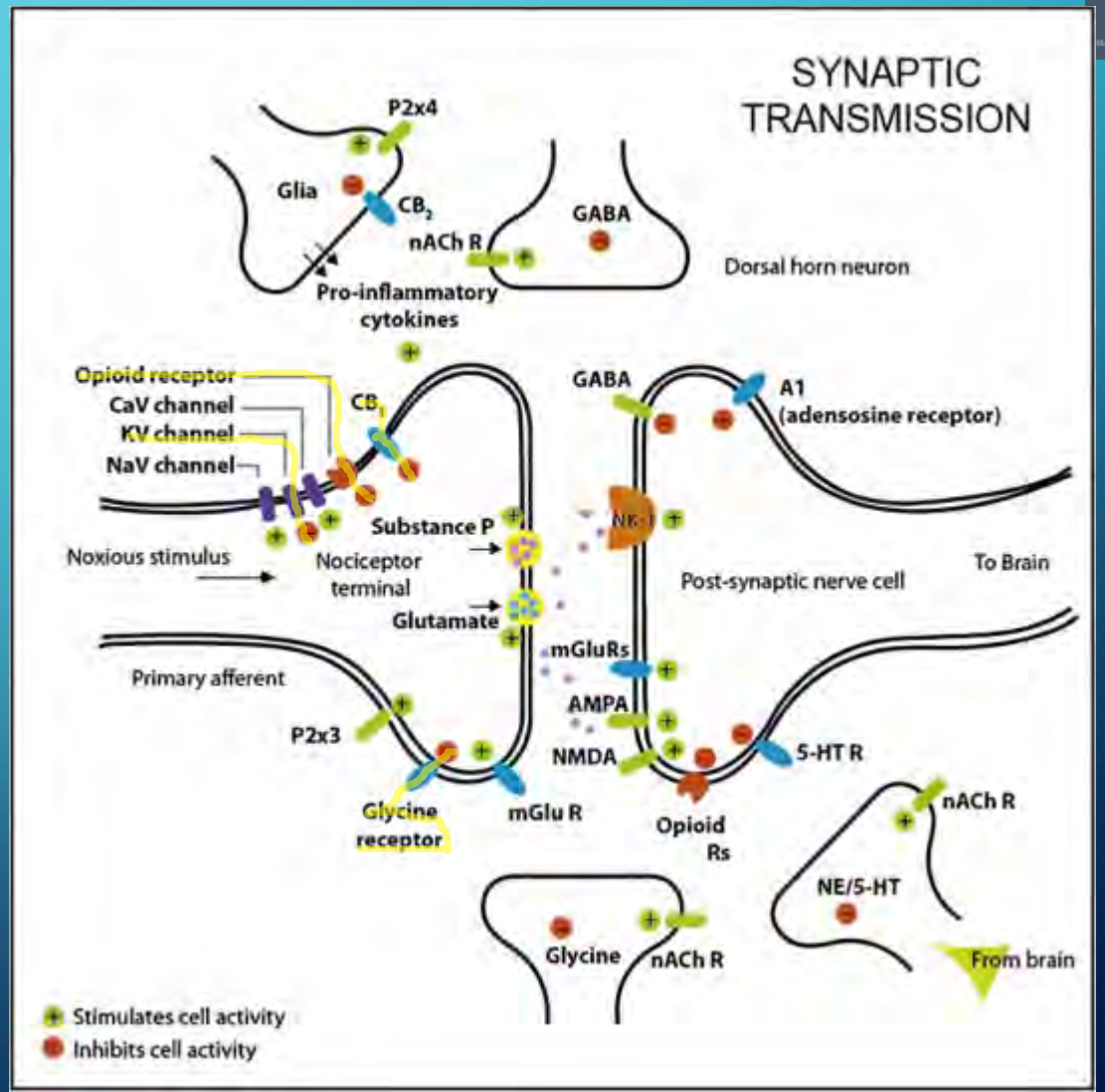
- Pre-synaptic (+)
  - NaV and CaV channels
  - Substance P
  - Glutamate and mGluR
- Post-synaptic (+)
  - NK-1, AMPA, glutamate, and NMDA receptors
- Peri-synaptic (+)
  - Substance P, cytokines
  - nAChR

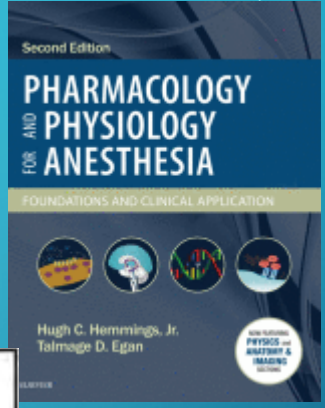




PAIN TRANSMISSION

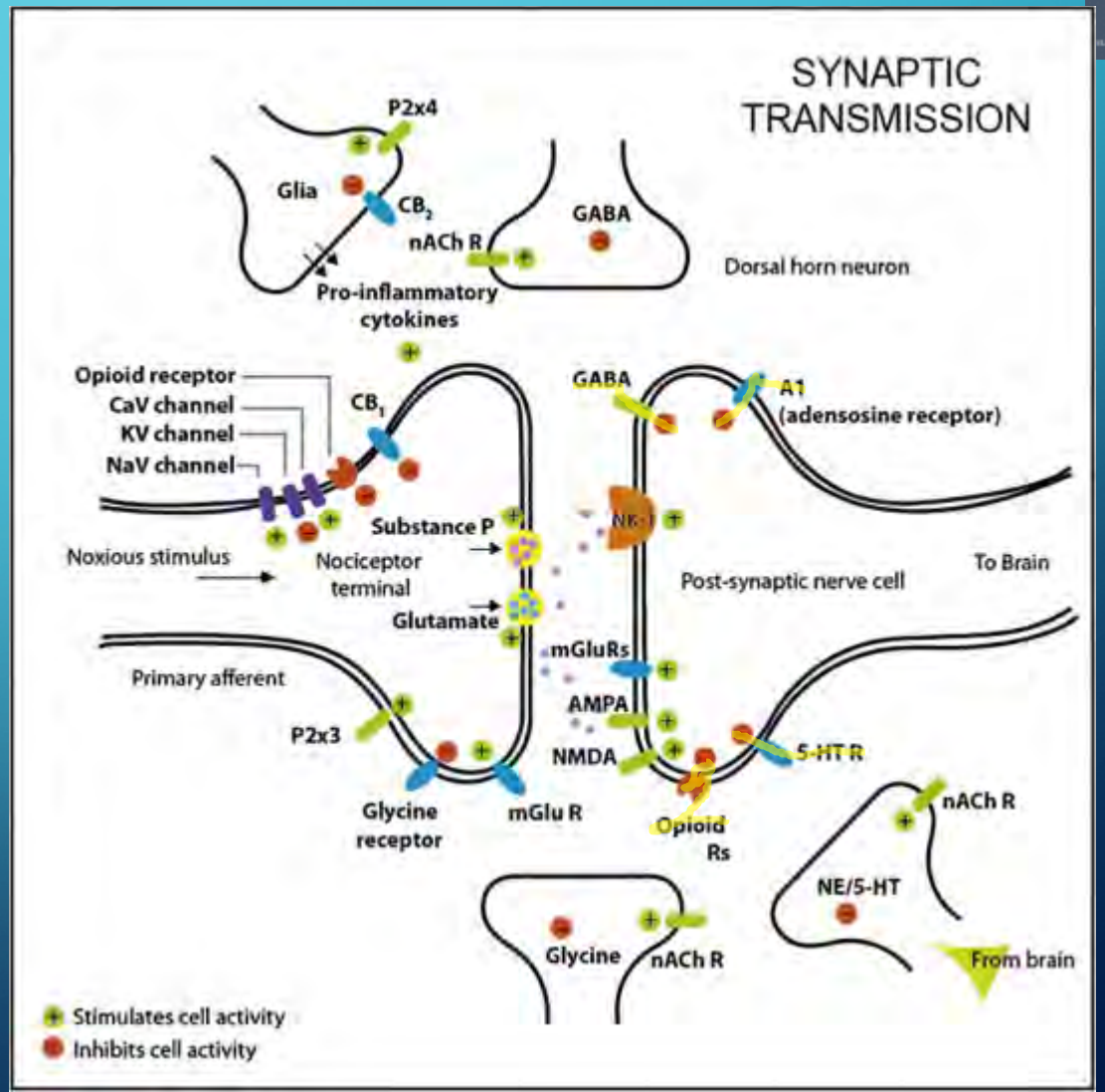
- Pre-synaptic (–)
  - CB1 receptor
  - KV channel, opioid, glycine

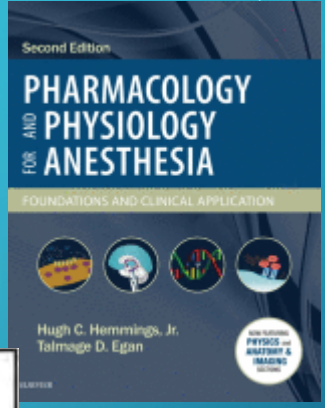




PAIN TRANSMISSION

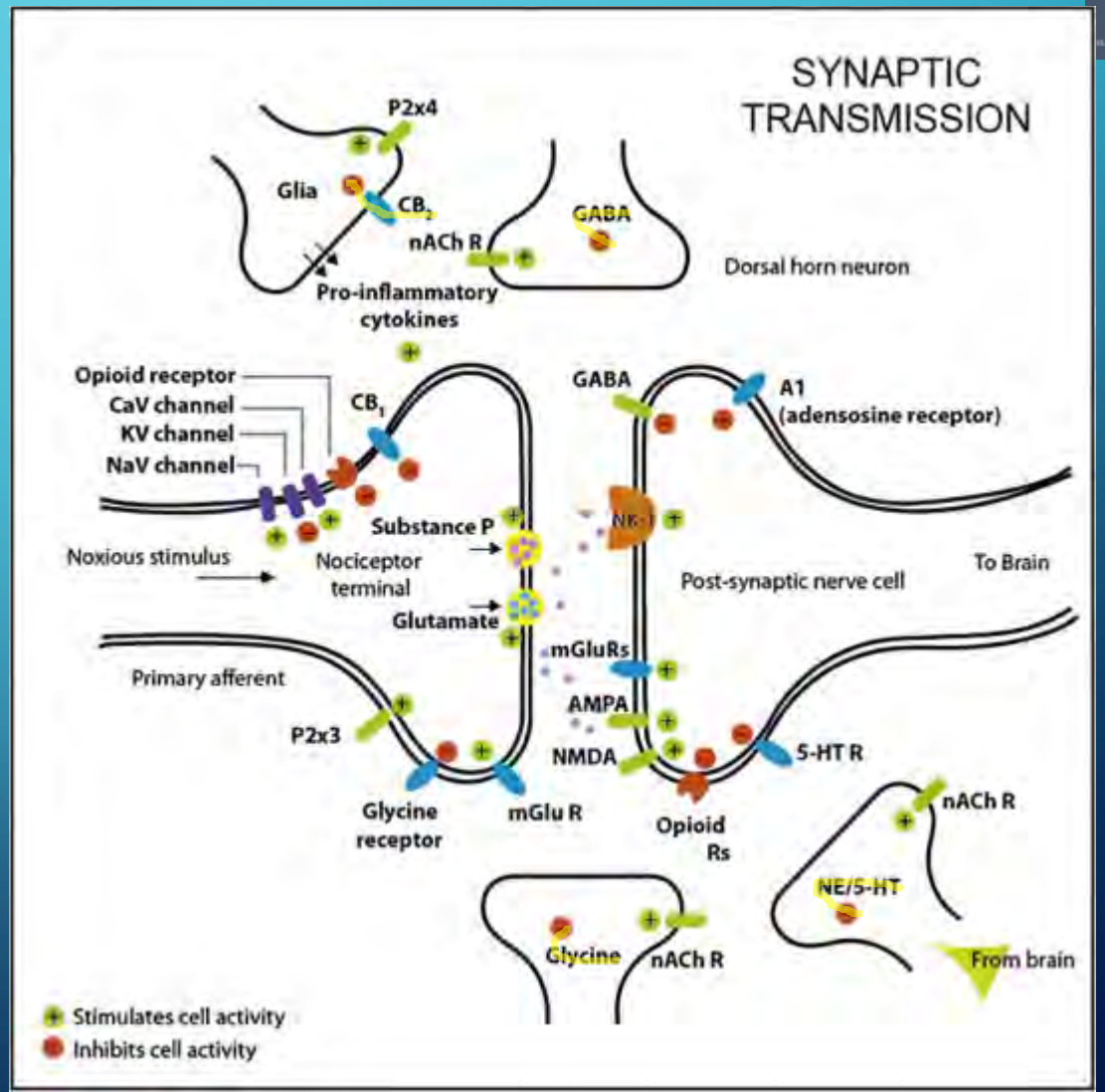
- Pre-synaptic (–)
  - CB1 receptor
  - KV channel, opioid, glycine
- Post-synaptic (–)
  - GABA, adenosine, opioid, 5-HT

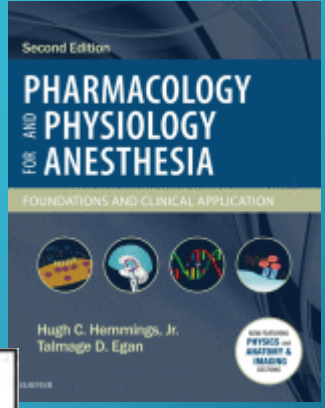




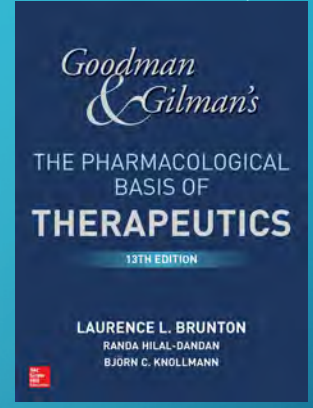
PAIN TRANSMISSION

- Pre-synaptic (–)
  - CB1 receptor
  - KV channel, opioid, glycine
- Post-synaptic (–)
  - GABA, adenosine, opioid, 5-HT
- Peri-synaptic (–)
  - CB2 receptor
  - 5-HT, NE, GABA, glycine





ACETAMINOPHEN



- Antipyretic
  - Inhibits endogenous pyrogens, thus directly affecting hypothalamus
- Analgesic - mechanism unknown
  - COX-1 and COX-2 inhibition in CNS (non-competitive and reversible)
  - Serotonergic pathways
  - Endogenous cannabinoid potentiation
  - COX-3 inhibition (brain, SC, heart)
- No anti-inflammatory effects
- Hepatic metabolism
  - 90% CYP450 → inactive metabolites
  - <10% oxidation → NAPQI
    - Further conjugated by glutathione
- Analgesic dose = 15 mg/kg (max 1,000 mg) q6h scheduled
- Available IV, PO, PR

Anesthesiology 2005; 102:822–31

Efficacy and Safety of Single and Repeated Administration of 1 Gram Intravenous Acetaminophen Injection (Paracetamol) for Pain Management after Major Orthopedic Surgery

Raymond S. Sinatra, M.D., Ph.D., Jonathan S. Jahr, M.D.,† Lowell W. Reynolds, M.D.,‡ Eugene R. Viscusi, M.D.,§ Scott B. Groudine, M.D.,‖ Catherine Payen-Champenois, M.D.#*

Background: **Intravenous acetaminophen injection (paracetamol) is marketed in Europe for the management of acute pain. A repeated-dose, randomized, double-blind, placebo-controlled, three–parallel group study was performed to evaluate the analgesic efficacy and safety of intravenous acetaminophen as compared with its prodrug (propacetamol) and placebo. Propacetamol has been available in many European countries for more than 20 yr.**

Methods: **After orthopedic surgery, patients reporting moderate to severe pain received either 1 g intravenous acetaminophen, 2 g propacetamol, or placebo at 6-h intervals over 24 h. Patients were allowed "rescue" intravenous patient-controlled analgesia morphine. Pain intensity, pain relief, and morphine use were measured at selected intervals. Safety was monitored through adverse event reporting, clinical examination, and laboratory testing.**

Results: **One hundred fifty-one patients (intravenous acetaminophen: 49; propacetamol: 50; placebo: 52) received at least one dose of study medication. The intravenous acetaminophen and propacetamol groups differed significantly from the placebo group regarding pain relief from 15 min to 6 h ($P < 0.05$) and median time to morphine rescue (intravenous acetaminophen: 3 h; propacetamol: 2.6 h; placebo: 0.8 h). Intravenous acetaminophen and propacetamol significantly reduced morphine consumption over the 24-h period: The total morphine doses received over 24 h were 38.3 ± 35.1 mg for intravenous acetaminophen, 40.8 ± 30.2 mg for propacetamol, and 57. 4 ± 52.3 mg for placebo, corresponding to decreases of −33% (19 mg) and −29% (17 mg) for intravenous acetaminophen and propacetamol, respectively. Drug-related adverse events were reported in 8.2%, 50% (most of them local), and 17.3% of patients treated with intravenous acetaminophen, propacetamol, and placebo, respectively.**

Conclusion: **Intravenous acetaminophen, 1 g, administered over a 24-h period in patients with moderate to severe pain after orthopedic surgery provided rapid and effective analgesia and was well tolerated.**

EFFECTIVE pain management is an important component of postsurgical care. Many patients, however, continue to experience inadequate pain relief.[1] Despite improvements in analgesic delivery, including patient-controlled analgesia (PCA) and sustained-release opioids, several recent surveys have found that up to 80% of patients report moderate to severe pain after surgery.[2–4] The ideal postoperative analgesic treatment should provide rapid and effective pain relief, have a low incidence of adverse effects, and have minimal impact on major organ systems or no significant interaction with other pharmacologic agents.

Opioids remain the agents of choice for severe pain; however, this class of analgesics is associated with dose-dependent adverse effects and negative postoperative outcomes.[5,6] Nonopioid analgesics are commonly used alone or as adjuncts to opioid-based analgesia to treat moderate to severe pain. Perioperative administration of acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) has been advocated to provide "multimodal"

REVIEW

Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making

Farah Jibril, Sherif Sharaby, Ahmed Mohamed, and Kyle J Wilby

- Why was this conclusion **not** a surprise?
  - 70-90% oral bioavailability
  - AUC same PO vs. IV (despite higher C_0)
  - Peak serum concentration occurs in < 2 hours after PO administration

Can J Hosp Pharm. 2015;68(3):238-47

ABSTRACT

Background: Intravenous (IV) acetaminophen is increasingly used around the world for pain control for a variety of indications. However, it is unclear whether IV administration offers advantages over oral administration.

Objective: To identify, summarize, and critically evaluate the literature comparing analgesic efficacy, safety, and pharmacokinetics for IV and oral dosage forms of acetaminophen.

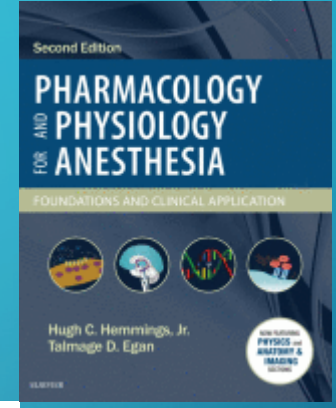
Data Sources: A literature search of the PubMed, Embase, and International Pharmaceutical Abstracts databases was supplemented with keyword searches of Science Direct, Wiley Library Online, and Springer Link databases for the period 1948 to November 2014. The reference lists of identified studies were searched manually.

Study Selection and Data Extraction: Randomized controlled trials comparing IV and oral dosage forms of acetaminophen were included if they assessed an efficacy, safety, or pharmacokinetic outcome. For each study, 2 investigators independently extracted data (study design, population, interventions, follow-up, efficacy outcomes, safety outcomes, pharmacokinetic outcomes, and any other pertinent information) and completed risk-of-bias assessments.

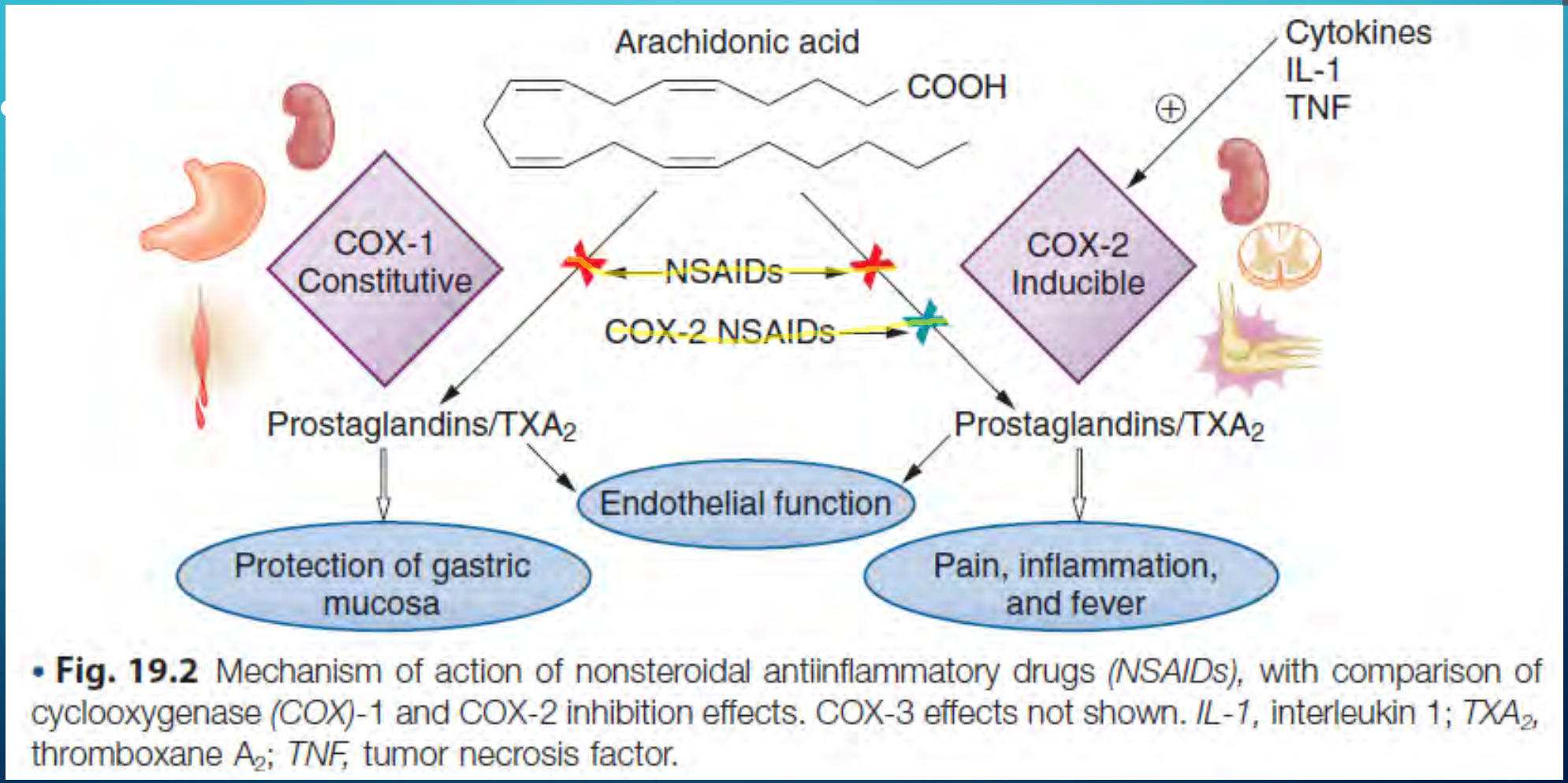
Data Synthesis: Six randomized clinical trials were included. Three of the studies reported outcomes pertaining to efficacy, 4 to safety, and 4 to pharmacokinetics. No clinically significant differences in efficacy were found between the 2 dosage forms. Safety outcomes were not reported consistently enough to allow adequate assessment. No evidence was found to suggest that increased bioavailability of the IV formulation enhances efficacy outcomes. For studies reporting clinical outcomes, the results of risk-of-bias assessments were largely unclear.

Conclusions: For patients who can take an oral dosage form, no clear indication exists for preferential prescribing of IV acetaminophen. Decision-making must take into account the known adverse effects of each dosage form and other considerations such as convenience and cost. Future studies should assess multiple-dose regimens over longer periods for patients with common pain indications such as cancer, trauma, and surgery.

Keywords: acetaminophen, paracetamol, intravenous, analgesia, pain



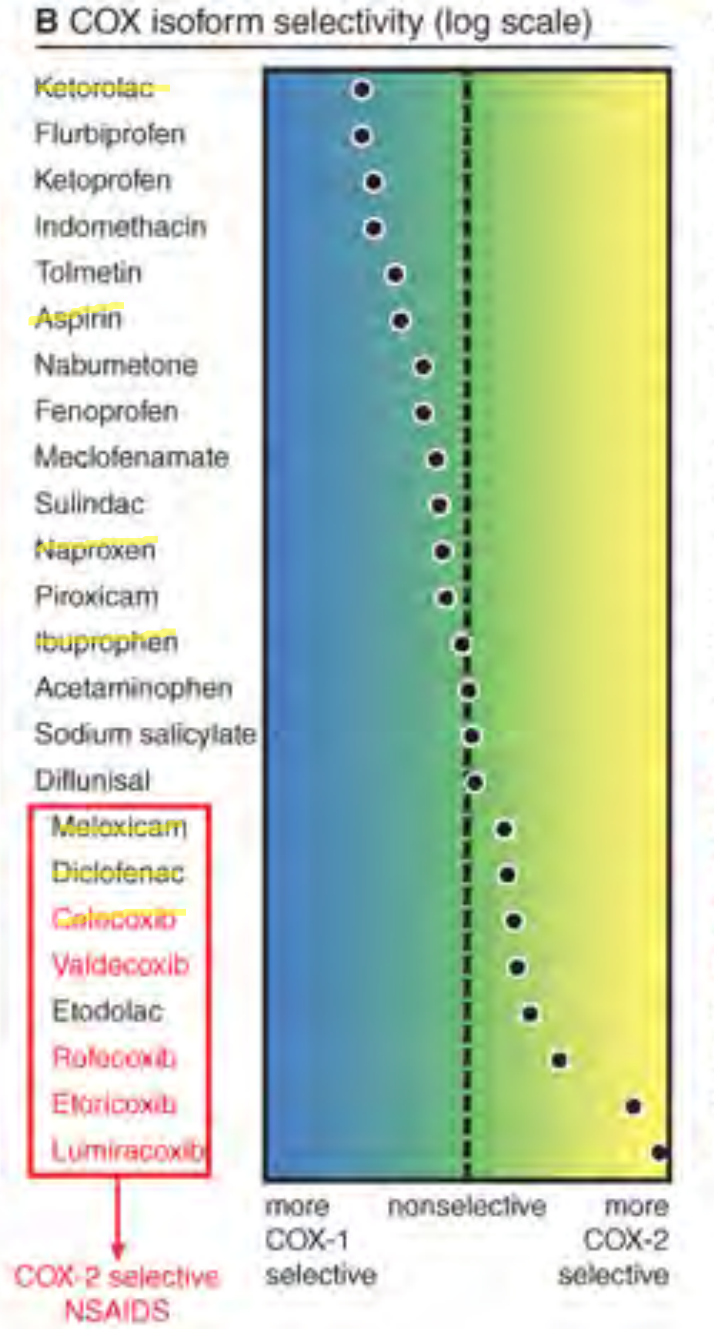
NSAIDS & COX-2 INHIBITORS



• **Fig. 19.2** Mechanism of action of nonsteroidal antiinflammatory drugs *(NSAIDs)*, with comparison of cyclooxygenase *(COX)*-1 and COX-2 inhibition effects. COX-3 effects not shown. *IL-1*, interleukin 1; *TXA_2*, thromboxane A_2; *TNF*, tumor necrosis factor.

NSAIDS & COX-2 INHIBITORS

- Prostaglandins have important functions
  - Mediation of inflammatory response
  - Transduction of pain signals
  - Central pyretic effect
- 90% eliminated by CYP450 system
- Weak base (pKa < 5)
- Highly protein bound (albumin)



NSAIDS & COX-2 INHIBITORS

Non-selective

- Ketorolac 15 mg IV q6h
  - Max dose 120 mg/day
- Naproxen 375 mg PO q12h
  - Max dose 1,000 mg/day
- Ibuprofen 600 mg PO q6h
  - Max dose 3,200 mg/day

Selective COX-2

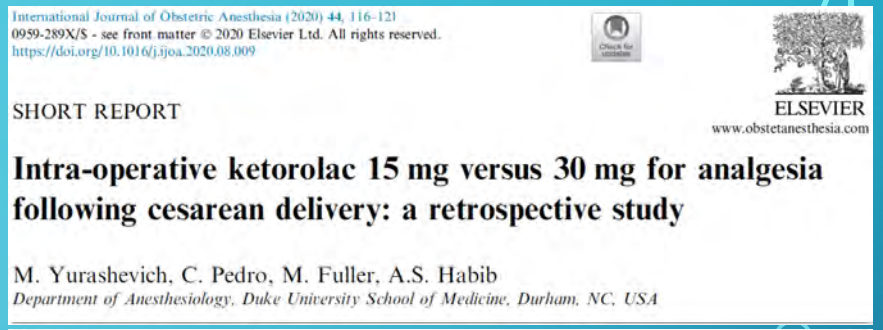
- Celecoxib 200 mg PO q12h
- Meloxicam 15 mg PO daily

PAIN MANAGEMENT AND SEDATION/ORIGINAL RESEARCH

Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

Sergey Motov, MD*; Matthew Yasavolian, MD; Antonios Likourezos, MA, MPH; Illya Pushkar, MPH; Rukhsana Hossain, MPH; Jefferson Drapkin, BS; Victor Cohen, PharmD; Nicholas Filk, PharmD; Andrew Smith, PharmD; Felix Huang, MD; Bradley Rockoff, MD; Peter Homel, PhD; Christian Fromm, MD

*Corresponding Author. E-mail: smotov@maimonidesmed.org, Twitter: @PainFreeED.



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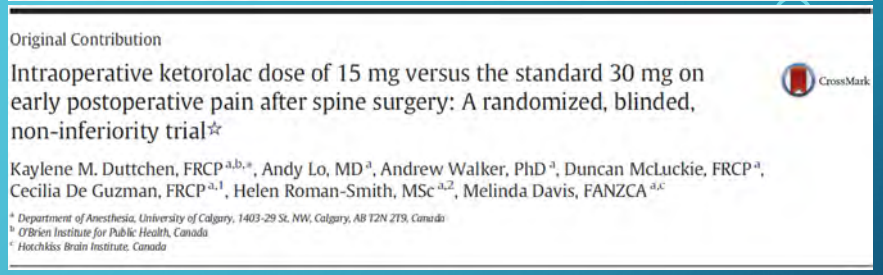
0959-289X/$ - see front matter © 2020 Elsevier Ltd. All rights reserved.
https://doi.org/10.1016/j.ijoa.2020.08.009

SHORT REPORT

ELSEVIER
www.obstetanesthesia.com

Intra-operative ketorolac 15 mg versus 30 mg for analgesia following cesarean delivery: a retrospective study

M. Yurashevich, C. Pedro, M. Fuller, A.S. Habib
Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA

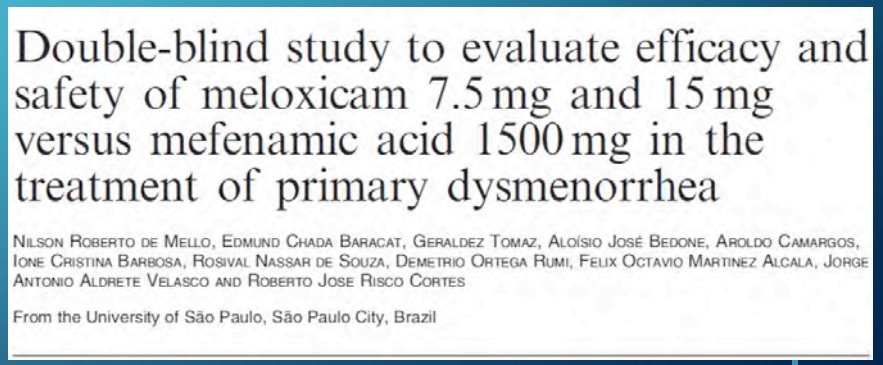


Original Contribution

Intraoperative ketorolac dose of 15 mg versus the standard 30 mg on early postoperative pain after spine surgery: A randomized, blinded, non-inferiority trial☆

Kaylene M. Duttchen, FRCP[a,b,*], Andy Lo, MD[a], Andrew Walker, PhD[a], Duncan McLuckie, FRCP[a], Cecilia De Guzman, FRCP[a,1], Helen Roman-Smith, MSc[a,2], Melinda Davis, FANZCA[a,c]

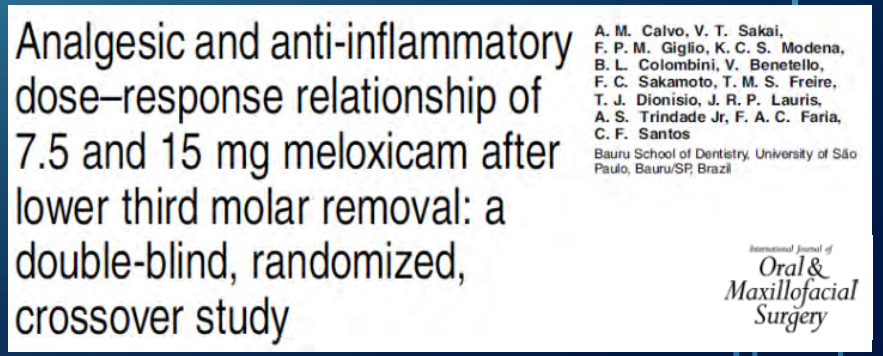
[a] Department of Anesthesia, University of Calgary, 1403-29 St. NW, Calgary, AB T2N 2T9, Canada
[b] O'Brien Institute for Public Health, Canada
[c] Hotchkiss Brain Institute, Canada



Double-blind study to evaluate efficacy and safety of meloxicam 7.5 mg and 15 mg versus mefenamic acid 1500 mg in the treatment of primary dysmenorrhea

Nilson Roberto de Mello, Edmund Chada Baracat, Geraldez Tomaz, Aloísio José Bedone, Aroldo Camargos, Ione Cristina Barbosa, Rosival Nassar de Souza, Demetrio Ortega Rumi, Felix Octavio Martinez Alcala, Jorge Antonio Aldrete Velasco and Roberto Jose Risco Cortes

From the University of São Paulo, São Paulo City, Brazil

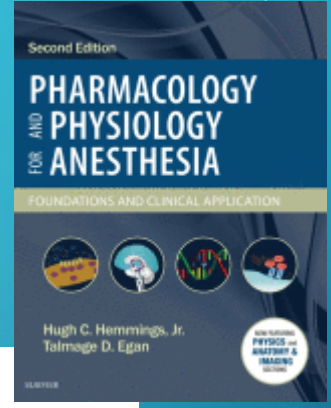


Analgesic and anti-inflammatory dose–response relationship of 7.5 and 15 mg meloxicam after lower third molar removal: a double-blind, randomized, crossover study

A. M. Calvo, V. T. Sakai, F. P. M. Giglio, K. C. S. Modena, B. L. Colombini, V. Benetello, F. C. Sakamoto, T. M. S. Freire, T. J. Dionisio, J. R. P. Lauris, A. S. Trindade Jr, F. A. C. Faria, C. F. Santos

Bauru School of Dentistry, University of São Paulo, Bauru/SP, Brazil

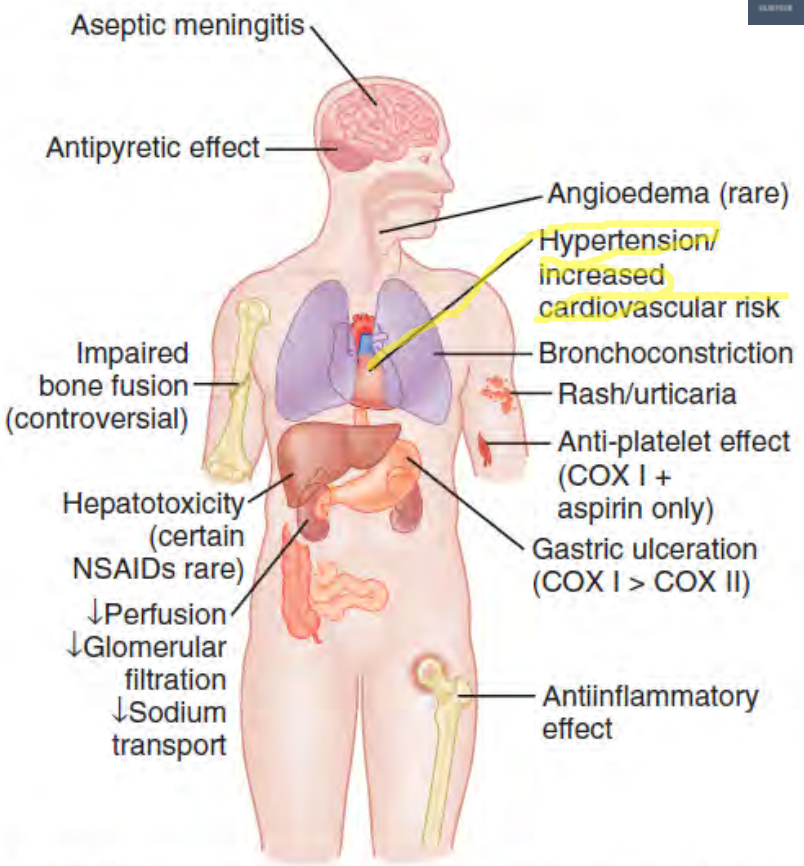
International Journal of Oral & Maxillofacial Surgery



NSAIDS & COX-2 INHIBITORS

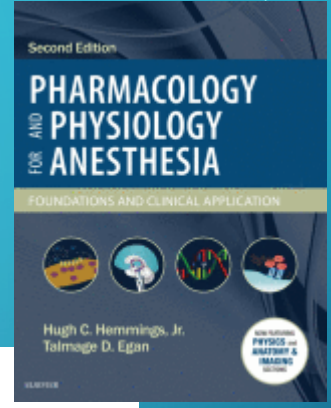
CONSIDERATIONS

- HTN / CV risk



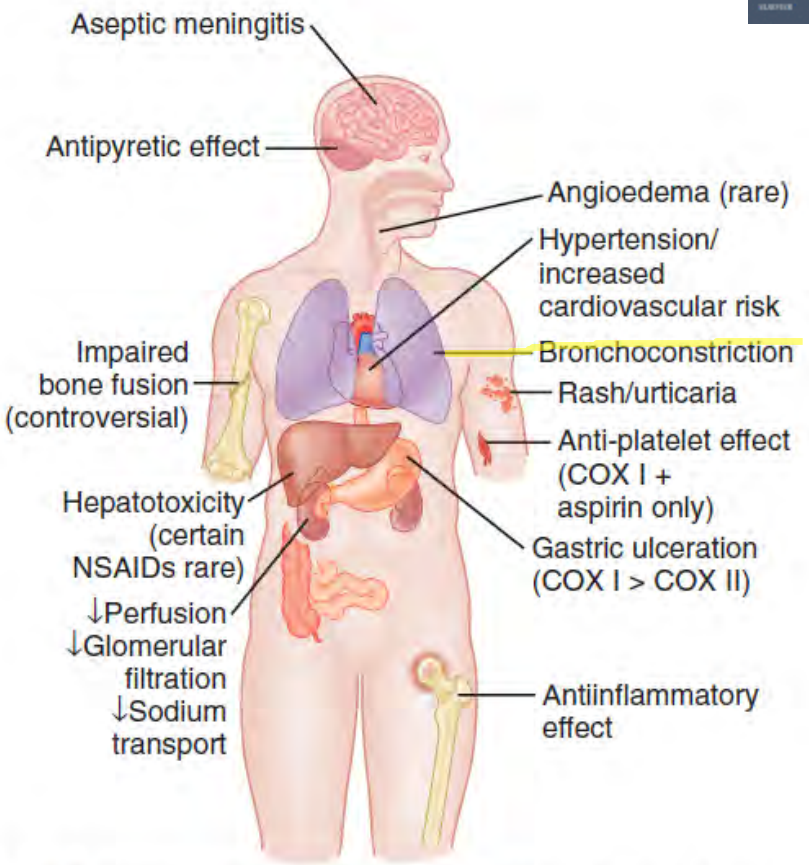
• **Fig. 19.3** Overview of the common pharmacokinetic and pharmacodynamic effects of nonsteroidal antiinflammatory agents. *COX*, Cyclooxygenase; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

NSAIDS & COX-2 INHIBITORS



CONSIDERATIONS

- HTN / CV risk
- Asthma



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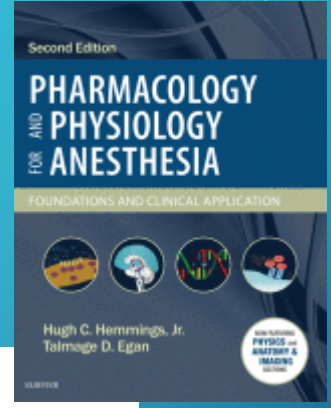
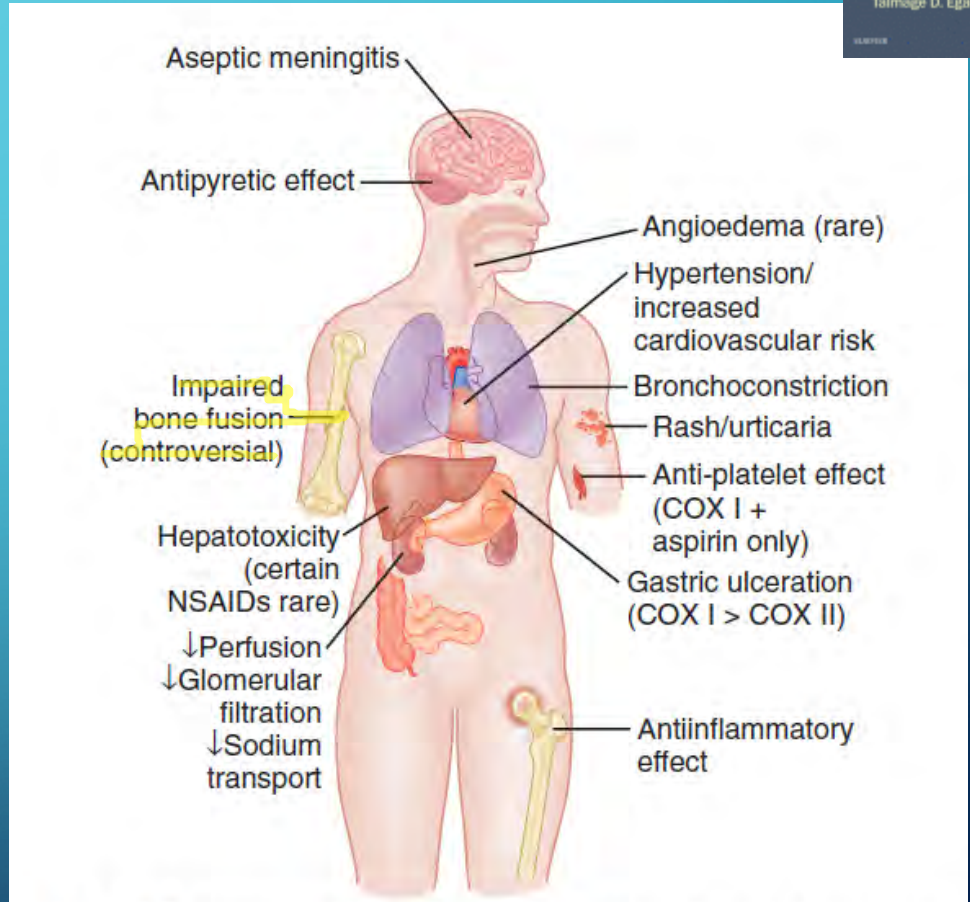
NSAIDS & COX-2 INHIBITORS



CONSIDERATIONS

- HTN / CV risk
- Asthma
- Bone healing



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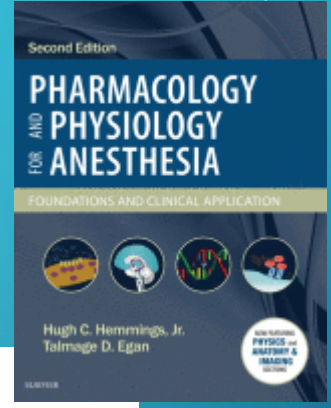
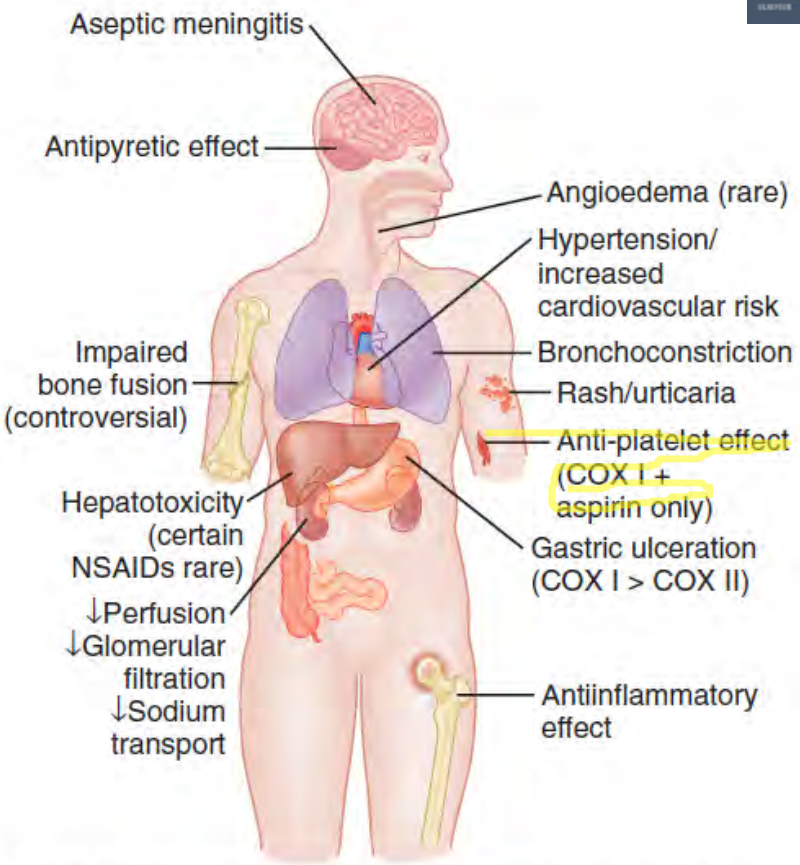
NSAIDS & COX-2 INHIBITORS



CONSIDERATIONS

- HTN / CV risk
- Asthma
- Bone healing
- Bleeding



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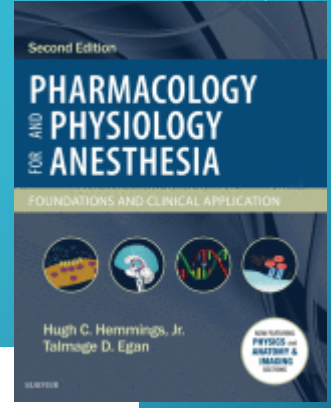
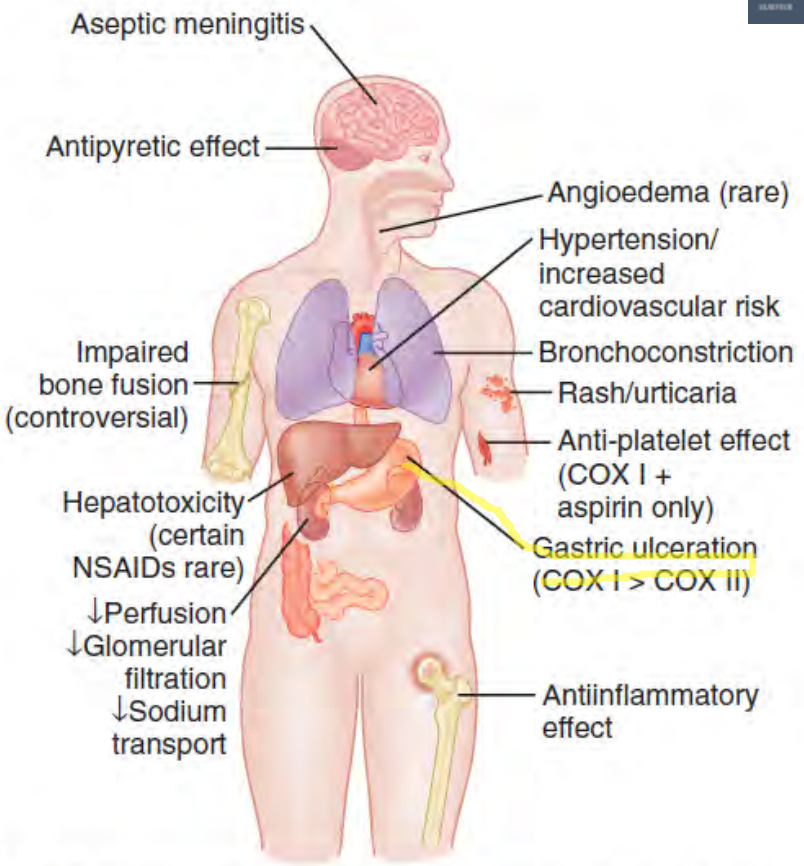
NSAIDS & COX-2 INHIBITORS



CONSIDERATIONS

- HTN / CV risk
- Asthma
- Bone healing
- Bleeding
- GI healing



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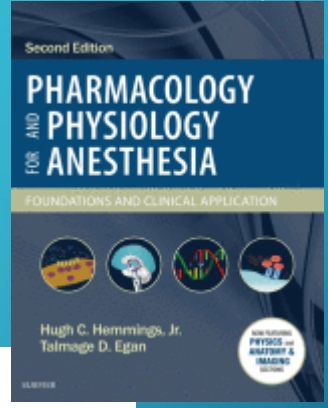
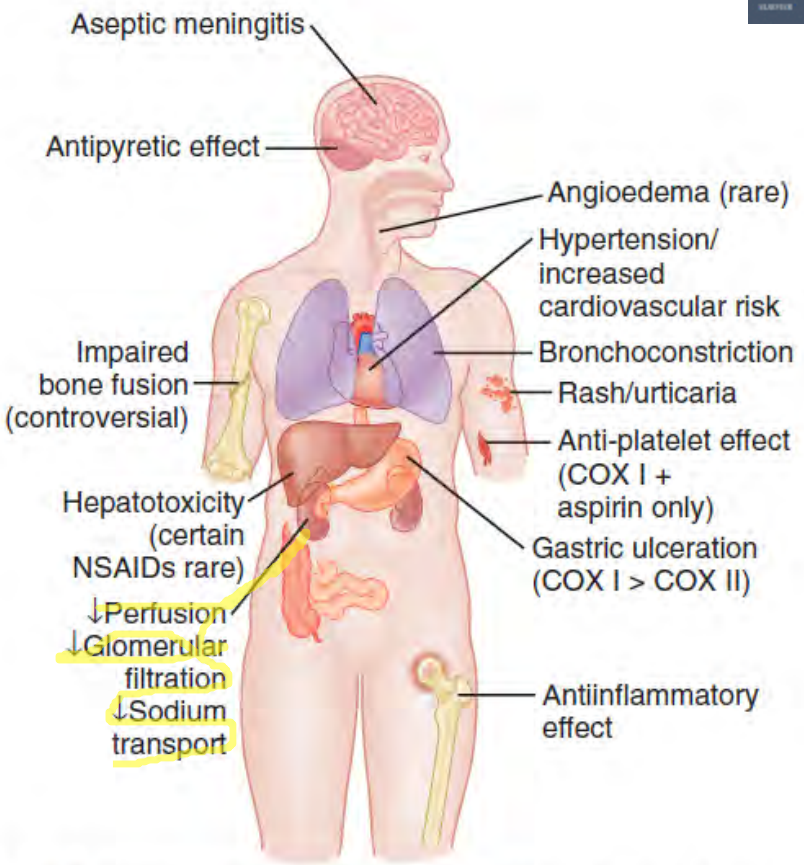
NSAIDS & COX-2 INHIBITORS



CONSIDERATIONS

- HTN / CV risk
- Asthma
- Bone healing
- Bleeding
- GI healing
- CKD / AKI



• **Fig. 19.3** Overview of the common pharmacokinetic and pharmacodynamic effects of nonsteroidal antiinflammatory agents. *COX*, Cyclooxygenase; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

Perioperative use of nonsteroidal anti-inflammatory drugs and the risk of anastomotic failure in emergency general surgery

Nadeem N. Haddad, MD, Brandon R. Bruns, MD, Toby M. Enniss, MD, David Turay, MD, Joseph V. Sakran, MD, MPH, MPA, Alisan Fathalizadeh, MD, Kristen Arnold, MD, Jason S. Murry, MD, Matthew M. Carrick, MD, Matthew C. Hernandez, MD, Margaret H. Lauerman, MD, Asad J. Choudhry, MBBS, David S. Morris, MD, Jose J. Diaz, MD, Herb A. Phelan, MD, Martin D. Zielinski, MD, *and* **NSAIDs SHAPES Workgroup**, *Rochester, Minnesota*

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesic and anti-inflammatory adjuncts. Nonsteroidal anti-inflammatory drug administration may potentially increase the risk of postoperative gastrointestinal anastomotic failure (AF). We aim to determine if perioperative NSAID utilization influences gastrointestinal AF in emergency general surgery (EGS) patients undergoing gastrointestinal resection and anastomosis.

METHODS: *Post hoc* analysis of a multi-institutional prospectively collected database was performed. Anastomotic failure was defined as the occurrence of a dehiscence/leak, fistula, or abscess. Patients using NSAIDs were compared with those without. Summary, univariate, and multivariable analyses were performed.

RESULTS: Five hundred thirty-three patients met inclusion criteria with a mean (±SD) age of 60 ± 17.5 years, 53% men. Forty-six percent (n = 244) of the patients were using perioperative NSAIDs. Gastrointestinal AF rate between NSAID and no NSAID was 13.9% versus 10.7% ($p = 0.26$). No differences existed between groups with respect to perioperative steroid use (16.8% vs. 13.8%; $p = 0.34$) or mortality (7.39% vs. 6.92%, $p = 0.84$). Multivariable analysis demonstrated that perioperative corticosteroid (odds ratio, 2.28; 95% confidence interval, 1.04–4.81) use and the presence of a colocolonic or colorectal anastomoses were independently associated with AF. A subset analysis of the NSAIDs cohort demonstrated an increased AF rate in colocolonic or colorectal anastomosis compared with enteroenteric or enterocolonic anastomoses (30.0% vs. 13.0%; $p = 0.03$).

CONCLUSION: Perioperative NSAID utilization appears to be safe in EGS patients undergoing small-bowel resection and anastomosis. Nonsteroidal anti-inflammatory drug administration should be used cautiously in EGS patients with colon or rectal anastomoses. Future randomized trials should validate the effects of perioperative NSAIDs use on AF. (*J Trauma Acute Care Surg.* 2017;83: 657–661.

LEVEL OF EVIDENCE: Therapeutic study, level III.

KEY WORDS: Nonsteroidal anti-inflammatory drugs; anastomotic failure; anastomosis; emergency general surgery.

Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence after colorectal surgery: a meta-analysis

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Key words
anastomosis, colorectal surgery, dehiscence, leakage, nonsteroidal anti-inflammatory, risk.

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Abstract

Background: Enhanced recovery after surgery protocols supports the post-operative use of nonsteroidal anti-inflammatory drugs (NSAIDs) to minimize the use of opioids. However, there is an increasing concern on the impaired wound healing of anastomosis associated with NSAID use, potentially causing a higher risk of anastomotic leakage. The aim was to conduct a meta-analysis to evaluate the association of NSAIDs with anastomotic leakage after colorectal surgery.

Methods: A literature search was conducted using the MEDLINE, PubMed, Cochrane Library and Clinicaltrial.gov. Studies identified were appraised with standard selection criteria. Data points were extracted and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results: Seventeen studies comprising of 26 098 patients were examined. The analysis of all studies showed a significantly lower rate of anastomotic dehiscence in the no-NSAID group (pooled odds ratio (OR) = 2.00, 95% confidence interval (CI) = 1.48–2.71, $P < 0.00001$). The analysis of randomized controlled trials (RCTs) demonstrates similar dehiscence rates between both groups ($P = 0.17$). In subgroup analysis, non-selective NSAIDs was associated with a higher risk of anastomotic dehiscence (pooled OR = 2.02, 95% CI = 1.62–2.50, $P < 0.00001$). However, there was no difference in the incidence of anastomotic leakage between no-NSAID group and selective NSAID group ($P = 0.05$).

Conclusion: Use of NSAIDs after colorectal surgery may be associated with a higher risk of anastomotic leakage. It is important to balance between the benefits of faster post-operative recovery and potential adverse effects of NSAIDs. Selective NSAIDs may be safer than non-selective ones. More RCTs are warranted to further evaluate the relationship between anastomotic leakage and use of NSAIDs, especially selective ones.

Table 1

Studies of Nonsteroidal Anti-inflammatory Drugs for Pain Management in Patients Undergoing Spine Surgery

Study	Study Design (Procedure)	No. of Patients	Intervention	Results	Level of Evidence[a]
Glassman et al[11]	Retrospective review (lumbar fusion)	288	Intramuscular ketorolac and opioid analgesics	Nonunion rates were higher in patients who received intramuscular ketorolac than in patients who did not receive NSAIDs.	III
Jirarattanaphochai et al[15]	Randomized controlled trial (lumbar diskectomy, decompression, or fusion)	120	Parecoxib (40 mg preoperatively and every 12 hr for 48 hr postoperatively) and morphine	Patients receiving parecoxib had 39% reduction in morphine use, reduced pain at rest, and greater satisfaction.	I
Jirarattanaphochai and Jung[16]	Meta-analysis of 17 randomized controlled trials (lumbar spine surgery)	789	NSAIDs and opioid analgesics	Lower pain scores and lower opioid use in patients receiving NSAIDs and opioids than in patients receiving opioids alone.	II
Li et al[13]	Meta-analysis of five retrospective comparative studies (spinal fusion)	1,403	High-dose ketorolac defined as >120 mg/d, diclofenac >150 mg/d, celecoxib >600 mg/d, rofecoxib >50 mg/d	Increased risk of nonunion with high-dose ketorolac. No detrimental effects of short-term use of NSAIDs (ketorolac, diclofenac, celecoxib, or rofecoxib [removed from market]) at normal doses.	IV

[a] Levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine criteria.[10]

Kurd MF, et al. The Role of Multimodal Analgesia in Spine Surgery. J Am Acad Orthop Surg 2017;25: 260-268.

Eur Spine J (2017) 26:2719–2728
DOI 10.1007/s00586-017-5021-y

REVIEW ARTICLE

The effect of NSAIDs on spinal fusion: a cross-disciplinary review of biochemical, animal, and human studies

Ahilan Sivaganesan[1] · Silky Chotai[1,4] · Gabrielle White-Dzuro[2] · Matthew J. McGirt[3] · Clinton J. Devin[1,4]

Abstract

Purpose Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in postoperative pain management. However, their use in the setting of spine fusion surgery setting has long been a topic of controversy. In this review we examined relevant research, including in vivo, animal, and clinical human studies, with the aim of understanding the effect of NSAIDs on spinal fusion.

Study design/setting Systematic review of study designs of all types from randomized controlled trials and meta-analyses to single-institution retrospective reviews.

Methods A search of PubMed and Embase was conducted using the keywords: "spine," "spinal fracture," NSAIDs, anti-inflammatory non-steroidal agents, bone, bone healing, fracture, fracture healing, yielding a total of 110 studies. Other 28 studies were identified by cross-referencing, resulting in total 138 studies.

Results There is no level I evidence from human studies regarding the use of NSAIDs on spinal fusion rates. The overall tone of the spine literature in the early 2000s was that NSAIDs increased the rate of non-union; however, nearly all human studies published after 2005 suggest that short-term (<2 weeks) postoperative use have no such effect. The dose dependency that is seen with a 2-week postoperative course is not present when NSAIDs are only used for 48 h after surgery.

Conclusions NSAID appear to have dose-dependent and duration-dependent effects on fusion rates. The short-term use of low-dose NSAIDs around the time of spinal fusion surgery is reasonable. Spine surgeons can consider the incorporation of NSAIDs into pain control regimens for spinal fusion patients with the goal of improving pain control and reducing the costs and complications associated with opioids.

Keywords NSAID · Spine · Fusion · Dose · Duration · Surgery

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in postoperative pain management. Countless studies have demonstrated their effectiveness following surgeries of all types [1–5], leading to their inclusion in

THE BONE & JOINT JOURNAL EST. 1948

■ SYSTEMATIC REVIEW: HIP

Non-steroidal anti-inflammatory drugs for heterotopic ossification prophylaxis after total hip arthroplasty

A SYSTEMATIC REVIEW AND META-ANALYSIS

M. Joice,
G. I. Vasileiadis,
D. F. Amanatullah

From Stanford Hospital and Clinics, Stanford, California, United States

Aims
The aim of this study was to assess the efficacy of non-selective and selective non-steroidal anti-inflammatory drugs (NSAIDs) in preventing heterotopic ossification (HO) after total hip arthroplasty (THA).

Methods
A thorough and systematic literature search was conducted and 29 studies were found that met inclusion criteria. Data were extracted and statistical analysis was carried out generating forest plots.

Results
Non-selective NSAIDs showed a significant decrease in the odds for forming HO after THA (odds ratio (OR) -1.35, confidence interval (CI) -1.83 to -0.86) when compared with placebo. Selective NSAIDs also showed a significant decrease in the odds for forming HO after THA when compared with placebo (OR -1.58, CI -2.41 to -0.75). When comparing non-selective NSAIDs with selective NSAIDs, there was no significant change in the odds for forming HO after THA (OR 0.22, CI -0.36 to 0.79).

Conclusion
Our meta-analyses of all available data suggest that both non-selective and selective NSAIDs are effective HO prophylaxis and can be used routinely after THA for pain control as well as prevention of HO. Indomethacin may serve as the benchmark among non-selective NSAIDs and celecoxib among selective NSAIDs. There was no difference in the incidence of HO between non-selective and selective NSAIDs, allowing physicians to choose either based on the clinical scenario and patient-specific factors.

Cite this article: ***Bone Joint J*** 2018;100-B:915–22.

NSAIDS & COX-2 INHIBITORS

- Long bone fracture & nonunion risk at 60 days post-fracture (multiple Rxs)
  - Nonselective NSAIDs = no difference
  - COX-2 inhibitors = ↑ risk
- NSAID or COX-2 inhibitor use within 30 days of fracture is associated with increased risk of nonunion

Risk of Nonunion with Nonselective NSAIDs, COX-2 Inhibitors, and Opioids

George MD, Baker JF, Leonard CE, Mehta S, Miano TA, Hennessy S. *J Bone Joint Surg Am.* 2020;102:1230-8. doi: 10.2106/JBJS.19.01415.

Selection and summary by Jerry Jones, MD.

Background: The incidence of nonunion is approximately 2-10% after long bone fracture and is influenced by fracture location, energy of injury, comorbidities, and other factors. Cyclooxygenase-2 (COX-2) is important in fracture healing, and some animal studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDS), particularly selective COX-2 inhibitors, may impair bone healing enough to increase the risk of nonunion. To date, the safety and clinical relevance of these medications with regards to the risk of nonunion has not been elucidated from human studies. The recognized risks of opioids increase the need to further evaluate the relative risks of utilizing COX-2 inhibitors and nonselective NSAIDS for patients at risk for nonunion.

Using a national private health insurance claims database, 339,864 episodes from 326,876 patients with an ICD-9 diagnosis of an isolated long bone extremity or clavicle fracture that met inclusion criteria were identified retrospectively. Patients with multiple fractures, fracture within the previous year, bone cancer or cancer metastatic to bone, history of malunion/nonunion, malunion/nonunion <90 days after fracture, and those with <1 year follow up or <6 months of prior records were excluded. Filled prescriptions for nonselective NSAIDS, COX-2 inhibitors, and opioids prior to and within 30 days after the fracture were analyzed along with any ICD-9 diagnosis of nonunion between 91 and 365 days after the fracture.

Results: A diagnosis of nonunion occurred in 1.6% of patients, and a procedure to treat the nonunion occurred in 0.9% of patients. Filling a single nonselective NSAID prescription after an isolated long bone fracture was not associated with a greater risk of nonunion (OR=1.07; 1.08 with procedure). Filling a prescription for a COX-2 inhibitor (OR=1.48; 1.84 with procedure) or opioid (OR=1.53; 1.69 with procedure) after an isolated long bone fracture was associated with a greater risk of nonunion. Filling a prescription in the 90 days prior to an isolated long bone fracture was associated with an increased risk of nonunion for nonselective NSAIDS (OR=1.36; 1.44 with procedure) or COX-2 inhibitors (OR=1.76; 1.60 with procedure) but not for opioids. Patients filling multiple prescriptions for nonselective NSAIDS, COX-2 inhibitors, or opioids in the 60 days after the fracture had higher nonunion rates.

Key points: Short term use of nonselective NSAIDS after an isolated long bone fracture is not associated with a greater risk of nonunion. Short term use of COX-2 inhibitors or opioids after an isolated long bone fracture is associated with an increased risk of nonunion. Prior exposure to NSAIDS or COX-2 inhibitors increases the risk of nonunion. Multiple prescriptions after a fracture may reflect increased injury severity which might be a confounding factor. Generalizing these results to other patient populations may not be appropriate as this population has a relatively low risk of nonunion.

The Efficacy and Safety of Nonsteroidal Anti-Inflammatory Drugs in Total Joint Arthroplasty: Systematic Review and Direct Meta-Analysis

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[a] Department of Orthopaedic Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH
[b] Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL
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[d] Department of Research, Quality, and Scientific Affairs, American Academy of Orthopaedic Surgeons, Rosemont, IL
[e] Anderson Orthopedic Research Institute, Alexandria, VA

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pain management
total hip arthroplasty
total knee arthroplasty

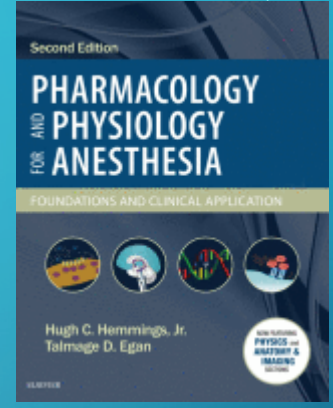
ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have become widely used to manage perioperative pain following total joint arthroplasty (TJA). The purpose of our study is to evaluate the efficacy and safety of NSAIDs in support of the combined clinical practice guidelines of the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Management.

Methods: Databases including MEDLINE, EMBASE, and the Cochrane Central Registry of Controlled Trials were searched for studies published prior to November 2018 on NSAIDs in TJA. Studies included after a systematic review evaluated through direct comparisons and/or meta-analysis, including qualitative and quantitative heterogeneity testing, to evaluate effectiveness and safety of NSAIDs.

Results: After critical appraisal of 2921 publications, 25 articles represented the best available evidence for inclusion in the analysis. Oral selective cyclooxygenase (COX)-2 and non-selective NSAIDs and intravenous ketorolac safely reduce postoperative pain and opioid consumption during the hospitalization for primary TJA. Administration of an oral selective COX-2 NSAID reduced postoperative opioid consumption after discharge from TKA.

Conclusion: Strong evidence supports the use of an oral selective COX-2 or non-selective NSAID and intravenous ketorolac as adjunctive medications to manage postoperative pain during the hospitalization for TJA. Although no safety concerns were observed, prescribers need to remain vigilant when prescribing NSAIDs.

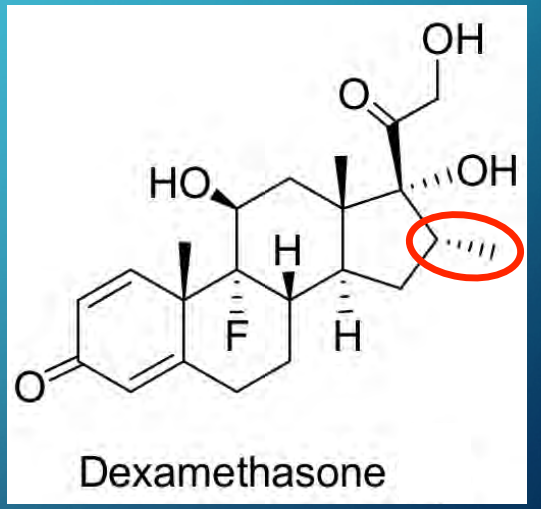


GLUCOCORTICOIDS

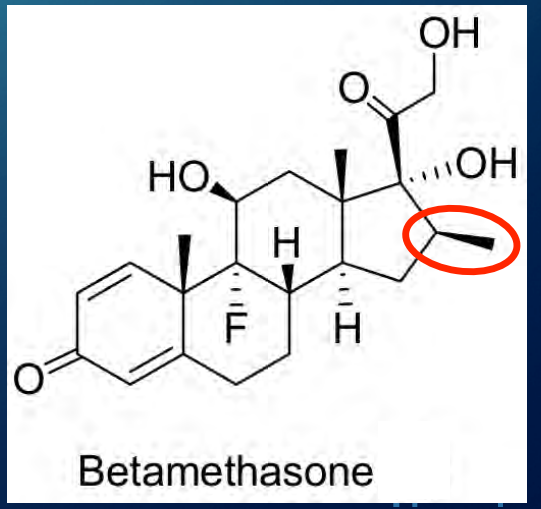
TABLE 36.4 Pharmacokinetics and Pharmacodynamics of Commonly Used Steroids

Steroid	Antiinflammatory Potency	Equivalent Dose (mg)	Elimination Half-Time (hr)	Duration of Action (hr)	Sodium-Retaining Potency
Cortisol	1	20	1.5–3.0	8–12	1
Cortisone	0.8	25	0.5	8–36	0.8
Prednisolone	4	5	2–4	12–36	0.8
Prednisone	4	5	2–4	12–36	0.8
Methylprednisolone	5	4	2–4	12–36	0.5
Betamethasone	25	0.75	5	36–54	0
Dexamethasone	25	0.75	3.5–5.0	36–54	0
Triamcinolone	5	4	3.5	12–36	0
Fludrocortisone	10	2		24	250
Aldosterone	0				3000

E, Epidural; *IA*, intraarticular; *IM*, intramuscular; *IV*, intravenous; *O*, oral; *T*, topical.
From Elisha S, Ouellette RG, Joyce J. *Pharmacology for Nurse Anesthesiology*. Sudbury, MA: Jones and Bartlett Learning; 2011. Table 18.3.



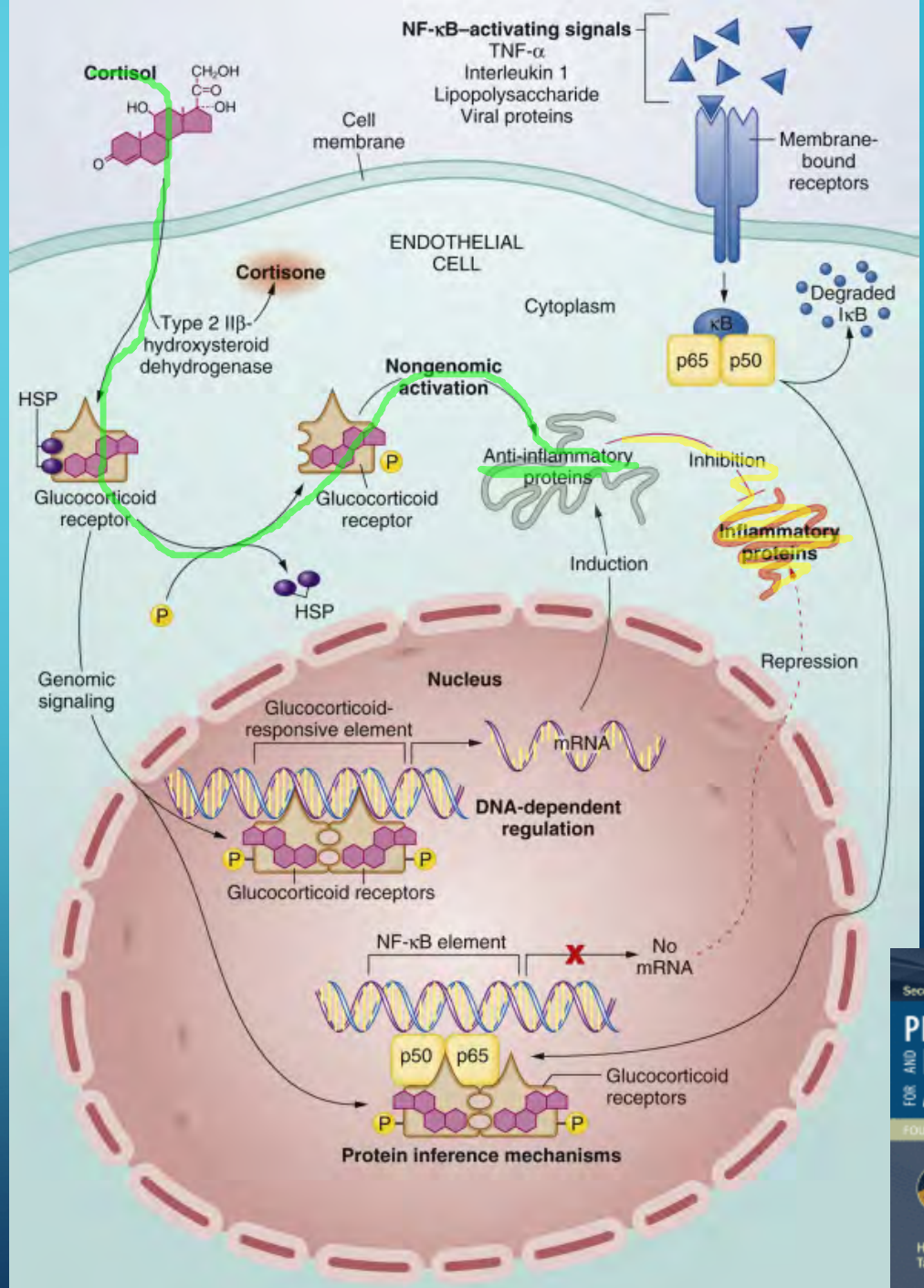
Dexamethasone

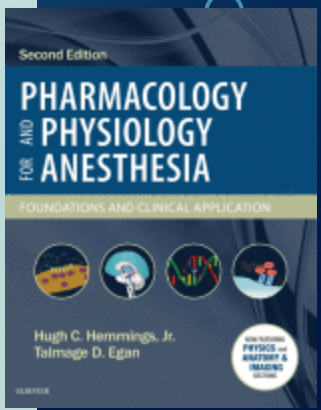


Betamethasone

GLUCOCORTICOIDS

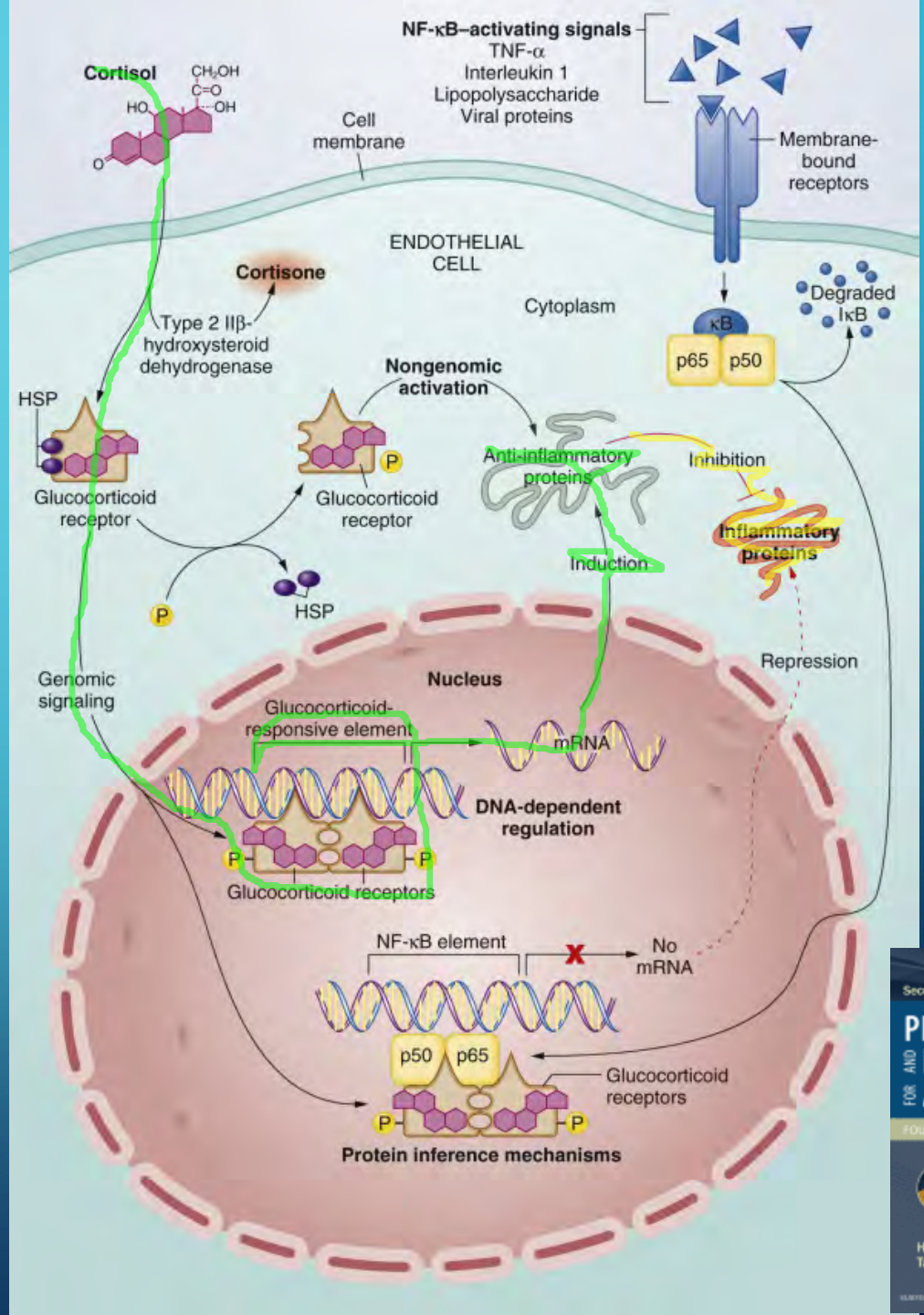
- Anti-inflammatory & analgesic MOA
  - Activation of anti-inflammatory proteins in the cytoplasm

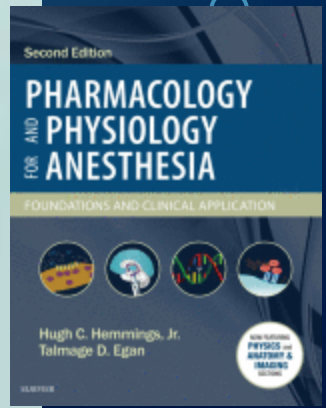




GLUCOCORTICOIDS

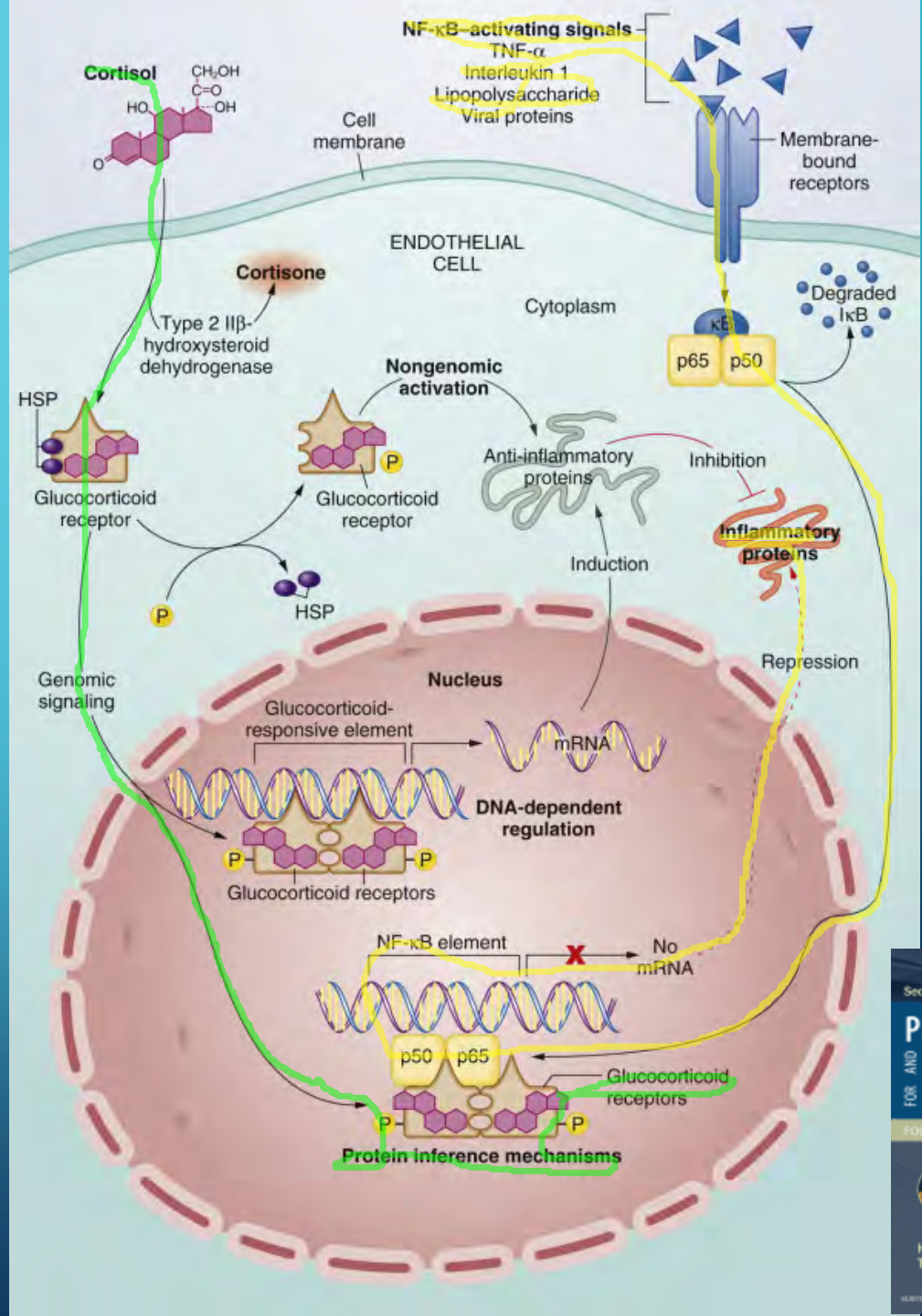
- Anti-inflammatory & analgesic MOA
  - Activation of anti-inflammatory proteins in the cytoplasm
  - Induction of anti-inflammatory protein production

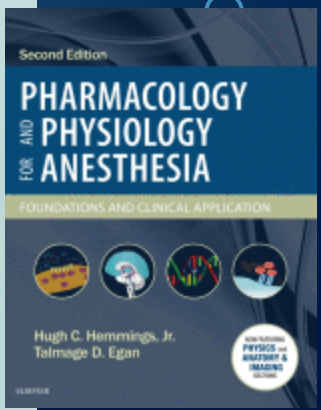




GLUCOCORTICOIDS

- Anti-inflammatory & analgesic MOA
  - Activation of anti-inflammatory proteins in the cytoplasm
  - Induction of anti-inflammatory protein production
  - Repression of pro-inflammatory protein production and inhibiting downstream signaling by inflammatory cytokines
- Net effect: ↓ PLA2, etc.





Perioperative Single Dose Systemic Dexamethasone for Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

Gildàsio S. De Oliveira, Jr., M.D.,* Marcela D. Almeida, M.D.,† Honorio T. Benzon, M.D.,‡ Robert J. McCarthy, Pharm.D.§

Anesthesiology 2011; 115:575–88.

ABSTRACT

Background: Dexamethasone is frequently administered in the perioperative period to reduce postoperative nausea and vomiting. In contrast, the analgesic effects of dexamethasone are not well defined. The authors performed a meta-analysis to evaluate the dose-dependent analgesic effects of perioperative dexamethasone.

Methods: We followed the PRISMA statement guidelines. A wide search was performed to identify randomized controlled trials that evaluated the effects of a single dose systemic dexamethasone on postoperative pain and opioid consumption. Meta-analysis was performed using a random-effect model. Effects of dexamethasone dose were evaluated by pooling studies into three dosage groups: low (less than 0.1 mg/kg), intermediate (0.11–0.2 mg/kg) and high (≥0.21 mg/kg).

Results: Twenty-four randomized clinical trials with 2,751 subjects were included. The mean (95% CI) combined effects favored dexamethasone over placebo for pain at rest (≤4 h, −0.32 [0.47 to −0.18], 24 h, −0.49 [−0.67 to −0.31]) and with movement (≤ 4 h, −0.64 [−0.86 to −0.41], 24 h, −0.47 [−0.71 to −0.24]). Opioid consumption was decreased to a similar extent with moderate −0.82 (−1.30 to −0.42) and high −0.85 (−1.24 to −0.46) dexamethasone, but not decreased with low-dose dexamethasone −0.18 (−0.39–0.03). No increase in analgesic effectiveness or reduction in opioid use could be demonstrated between the high- and intermediate-dose dexamethasone. Preoperative administration of dexamethasone appears to produce a more consistent analgesic effect compared with intraoperative administration.

Conclusion: Dexamethasone at doses more than 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption after surgery. The preoperative administration of the drug produces less variation of effects on pain outcomes.

What We Already Know about This Topic

- Dexamethasone is often used to prevent postoperative nausea and vomiting, but its effects on pain are less well studied

What This Article Tells Us That Is New

- In a meta-analysis of approximately 2,500 patients, dexamethasone, >0.1 mg/kg, reduced postoperative pain and opioid consumption

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BJA

Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis

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Editor's key points

- Dexamethasone appears to have some analgesic effects in the postoperative period.
- Meta-analysis of 45 studies found lower pain scores and lower opioid requirement at 2 and 24 h.
- While the effect was statistically significant, the clinical benefit is less clear.
- Blood glucose was raised after operation, but there was no apparent increase in adverse effects.

Background. The analgesic efficacy and adverse effects of a single perioperative dose of dexamethasone are unclear. We performed a systematic review to evaluate the impact of a single i.v. dose of dexamethasone on postoperative pain and explore adverse events associated with this treatment.

Methods. MEDLINE, EMBASE, CINAHL, and the Cochrane Register were searched for randomized, controlled studies that compared dexamethasone *vs* placebo or an antiemetic in adult patients undergoing general anaesthesia and reported pain outcomes.

Results. Forty-five studies involving 5796 patients receiving dexamethasone 1.25–20 mg were included. Patients receiving dexamethasone had lower pain scores at 2 h [mean difference (MD) −0.49 [95% confidence interval (CI): −0.83, −0.15]) and 24 h [MD −0.48 (95% CI: −0.62, −0.35)] after surgery. Dexamethasone-treated patients used less opioids at 2 h [MD −0.87 mg morphine equivalents (95% CI: −1.40 to −0.33)] and 24 h [MD −2.33 mg morphine equivalents (95% CI: −4.39, −0.26)], required less rescue analgesia for intolerable pain [relative risk 0.80 (95% CI: 0.69, 0.93)], had longer time to first dose of analgesic [MD 12.06 min (95% CI: 0.80, 23.32)], and shorter stays in the post-anaesthesia care unit [MD −5.32 min (95% CI: −10.49 to −0.15)]. There was no dose–response with regard to the opioid-sparing effect. There was no increase in infection or delayed wound healing with dexamethasone, but blood glucose levels were higher at 24 h [MD 0.39 mmol litre^{-1} (95% CI: 0.04, 0.74)].

Conclusions. A single i.v. perioperative dose of dexamethasone had small but statistically significant analgesic benefits.

Keywords: analgesics, opioid; dexamethasone; glucocorticoids; hyperglycaemia; pain, postoperative; surgical wound infection

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Review

The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: A systematic review and meta-analysis

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ARTICLE INFO

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Meta-analysis
Total knee arthroplasty
VAS score
Nausea

ABSTRACT

Background: Total knee arthroplasty (TKA) is gradually emerging as the treatment of choice for end-stage osteoarthritis. In the past, Perioperative dexamethasone treatment is still a controversial subject in total knee arthroplasty. Therefore, we write this systematic review and meta-analysis to evaluate the efficacy of dexamethasone on pain and recovery after Total knee Arthroplasty.

Materials and methods: Embase, Pubmed, and Cochrane Library were comprehensively searched. Randomized controlled trials, cohort studies were included in our meta-analysis. Eight studies that compared dexamethasone groups with placebo groups were included in our meta-analysis. The research was reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. Randomized controlled trials were included in our meta-analysis.

Results: Our study demonstrated that the dexamethasone group was more effective than the placebo group in term of VAS score at 24 h($P < 0.00001$), 48 h($P = 0.0002$); Opioid consumption ($P < 0.00001$); postoperative nausea ($P < 0.00001$); and Inflammatory factors of CPR at 24 h ($P = 0.003$).

Conclusion: Our meta-analysis demonstrated that dexamethasone decreased postoperative pain, the incidence of POVN, and total opioid consumption effectively which played a critical role in rapid recovery to TKA. However, we still need large sample size, high quality studies to explore the relationship between complications and dose response to give the final conclusion.

International Journal of Surgery 52 (2018) 149–155.

The efficacy of dexamethasone on pain and recovery after total hip arthroplasty

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Total hip arthroplasty (THA) perioperative dexamethasone treatment is still a controversial subject. We write this systematic review and meta-analysis to evaluate the efficacy of dexamethasone on pain and recovery after THA.

Methods: Two researchers searched the relevant studies from Pubmed, Cochrane, and Embase. The research was reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. Randomized controlled trials (RCTs) were included in our meta-analysis. At the same time, the assessment of the risk of bias was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions version. The pooled data are processed by software RevMan 5.3.

Result: In accordance with inclusion and exclusion, 3 studies with 207 patients were eligible and accepted into this meta-analysis. For RCTs, the risk of bias was evaluated by Cochrane Collaboration tool. Only one study did not have detection bias. Our study demonstrated that the dexamethasone group was more effective than the placebo group in term of visual analogue scale (VAS) score at 24 hours ($P < .001$), 48 hours ($P = .04$); opioid consumption ($P < .001$); length of stay (LOS, $P < .001$); and postoperative nausea ($P = .001$).

Conclusion: Dexamethasone not only reduces postoperative pain scores and postoperative opioids consumption within 48 hours, but also reduces postoperative vomiting and effectively reduces LOS. However, we still need large sample size and high quality studies to explore the relationship between complications and dose response to give the final conclusion.

Abbreviations: LOS = length of stay, RCT = randomized controlled trial, THA = total hip arthroplasty, VAS = visual analogue scale.

Keywords: dexamethasone, meta-analysis, nausea, total hip arthroplasty, VAS score

Preoperative dexamethasone reduces acute but not sustained pain after lumbar disk surgery: a randomized, blinded, placebo-controlled trial

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Abstract

Glucocorticoids have attracted increasing attention as adjuvants in the treatment of acute postoperative pain. Furthermore, anecdotal reports may support glucocorticoids for preventing sustained postoperative pain. We explored preoperative dexamethasone combined with paracetamol and ibuprofen on acute and sustained pain after lumbar disk surgery. In this blinded study, 160 patients undergoing lumbar disk surgery were randomly assigned to 16 mg IV dexamethasone or placebo. All patients received perioperative paracetamol and ibuprofen, and postoperative IV patient-controlled analgesia with morphine. Primary outcome was pain during mobilization (visual analog scale) 2 to 24 hours postoperatively. Secondary outcomes were acute pain at rest, morphine consumption, nausea, vomiting, ondansetron consumption, sedation, and quality of sleep. Patients were followed up by written questionnaire 3 months postoperatively. Acute pain during mobilization (weighted average area under the curve, 2-24 hours) was significantly reduced in the dexamethasone group: 33 (22) mm vs placebo 43 (18) mm, (95% confidence interval [CI] 3-16) $P = 0.005$. Vomiting 0 to 24 hours postoperatively was reduced in the dexamethasone group (17 episodes) vs placebo (51 episodes) $P = 0.036$. No other differences were observed. However, 6.5% (95% CI 2-15) in the dexamethasone group vs placebo 0% had an antibiotically treated wound infection ($P = 0.13$). Sixteen percent (95% CI 7-26) vs 8% (95% CI 0-17) reported new weakness/paralysis of the legs in the dexamethasone and placebo groups, respectively, 3 months postoperatively ($P = 0.20$). In conclusion, preoperative dexamethasone significantly reduced pain during mobilization and vomiting, after lumbar disk surgery. No significant effects were observed 3 months postoperatively.

Keywords: Pain postoperative, Analgesia postoperative, Dexamethasone, Spine

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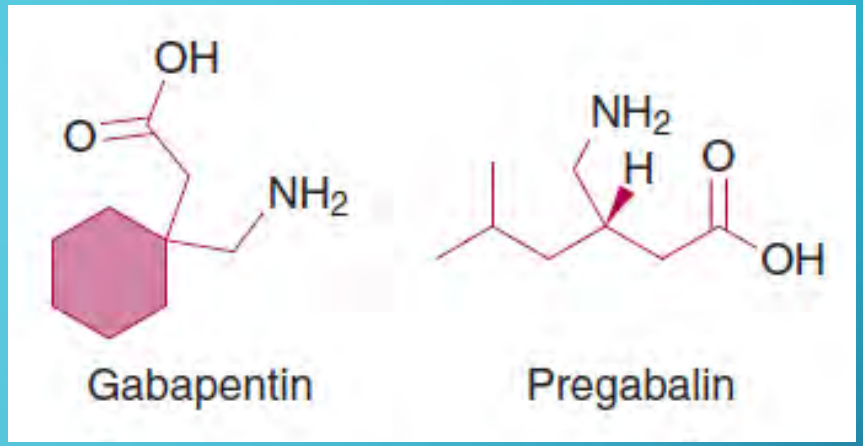
Source	Study design	Sample size (N)	Dexamethasone dose	Results
De Oliveira et al,[3] 2011	Meta-analysis	2,751	Patients were separated into subgroups receiving dexamethasone at dosages < 0.1 mg/kg, 0.11-0.2 mg/kg, or > 0.2 mg/kg	Dexamethasone at dosages more than 0.1 mg/kg resulted in lower pain scores at 4 hours and 24 hours, and resulted in a reduction in the required morphine equivalent units required after surgery. No difference was seen in the intermediate-dose group vs the high-dose group.
Jokela et al,[13] 2009	Blinded RCT	129	Patients were randomly assigned to receive a placebo or dexamethasone, 5 mg, 10 mg, or 15 mg	Dexamethasone, 10 mg and 15 mg, results in decreased oxycodone consumption during the first 2 hours after surgery. Dexamethasone, 15 mg, reduces the amount of oxycodone required for the first 24 hours after laparoscopic hysterectomy
Kardash et al,[7] 2008	Double-blinded RCT	50	Patients received either a placebo or dexamethasone, 40 mg	Dexamethasone, 40 mg, has a prolonged suppressive effect on the inflammatory response and decreases dynamic pain 24 hours after total hip arthroplasty
Kim et al,[8] 2016	Blinded RCT	59	Patients received either a placebo or dexamethasone, 10 mg	Dexamethasone, 10 mg, resulted in lower pain scores at 12 and 24 hours following uterine artery embolization
Samona et al,[10] 2017	Retrospective chart review	102	Patients received either a placebo or dexamethasone, 8 mg	Dexamethasone, 8 mg, resulted in decreased pain scores 24 hours after total knee arthroplasty, as well as decreased oral narcotic consumption
Szucs et al,[9] 2016	Double-blinded RCT	30	Patients received either a placebo or dexamethasone, 0.1 mg/kg	Pain scores at rest were lower at 6 hours following operative fixation of a fractured femur neck, and cumulative morphine consumption was lower 24 hours after surgery
Waldron et al,[6] 2013	Meta-analysis	5,796	Patients were separated into subgroups receiving dexamethasone, either 4-5 mg or 8-10 mg	Pain scores were lower in patients who received dexamethasone, 8-10 mg, postoperatively at 2 and 24 hours, and a reduction of morphine equivalent units at 2 and 24 hours

Table 1. Study Design, Sample Size, Dexamethasone Dose, and Results for Studies Evaluating Analgesic Effects of Intravenous Dexamethasone
Abbreviation: RCT, randomized controlled trial.

Source	Adverse effect examined	Sample size (N)	Study design	Results
Bolac et al,[16] 2013	Surgical site infection, wound cellulitis, wound separation, fascial dehiscence	431	Retrospective chart review	No difference demonstrated in rates of surgical site infection, wound cellulitis, wound separation, or fascial dehiscence in patients who received dexamethasone compared with those who did not
De Oliveira et al,[3] 2011	Wound healing, wound infection rate, blood glucose levels	2,751	Meta-analysis	No difference found in wound healing, rates of wound infection, or postoperative glucose levels between the group receiving dexamethasone and the group that did not
Gali et al,[17] 2012	Wound infection rate	574	Retrospective chart review	No difference found in the rate of postoperative wound infection rates in patients who received dexamethasone compared with patents who did not
Hans et al,[14] 2006	Blood glucose levels in diabetic and nondiabetic patients	63	Prospective nonrandomized trial	Blood glucose levels were found to be marginally higher postoperatively in diabetic patients who received dexamethasone, although the clinical significance of this is debatable
Richardson et al,[18] 2016	Periprosthetic joint infection rate	6,294	Retrospective chart review	No difference was found in the rate of periprosthetic joint infections in patients who received an intraoperative dose of dexamethasone compared with those who did not
Tien et al,[15] 2016	Blood glucose levels in diabetic and nondiabetic patients	85	Randomized controlled trial	Dexamethasone increases postoperative blood glucose levels, but no difference was found in the level of increase between diabetic and nondiabetic patients
Waldron et al,[6] 2013	Wound healing, wound infection rates, and blood glucose levels	5,796	Meta-analysis	No difference was seen in wound healing or wound infection rates between the control and treatment groups. Blood glucose levels were found to be higher in the treatment group 24 hours postoperatively.

Table 2. Study Design, Sample Size, and Results of Studies Evaluating the Potential Adverse Effects of Dexamethasone Administration

GABAPENTINOIDS



- MOA = binds to $\alpha_2\delta$-1 subunit of presynaptic VGCC in CNS
- FDA indications = seizures, neuropathic pain
- Other uses = fibromyalgia, postherpetic neuralgia
- Common SE = dizziness, somnolence, fatigue, ataxia
- Its use in postoperative acute pain is controversial after 2020 review article

ANESTHESIOLOGY

Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain

A Systematic Review and Meta-analysis

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ANESTHESIOLOGY 2020; 133:265–79

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Gabapentinoids such as gabapentin and pregabalin are often included in perioperative multimodal analgesia regimens in an attempt to reduce acute, subacute, and chronic pain after

ABSTRACT

Background: Widely used for acute pain management, the clinical benefit from perioperative use of gabapentinoids is uncertain. The aim of this systematic review was to assess the analgesic effect and adverse events with the perioperative use of gabapentinoids in adult patients.

Methods: Randomized controlled trials studying the use of gabapentinoids in adult patients undergoing surgery were included. The primary outcome was the intensity of postoperative acute pain. Secondary outcomes included the intensity of postoperative subacute pain, incidence of postoperative chronic pain, cumulative opioid use, persistent opioid use, lengths of stay, and adverse events. The clinical significance of the summary estimates was assessed based on established thresholds for minimally important differences.

Results: In total, 281 trials (N = 24,682 participants) were included in this meta-analysis. Compared with controls, gabapentinoids were associated with a lower postoperative pain intensity (100-point scale) at 6 h (mean difference, −10; 95% CI, −12 to −9), 12 h (mean difference, −9; 95% CI, −10 to −7), 24 h (mean difference, −7; 95% CI, −8 to −6), and 48 h (mean difference, −3; 95% CI, −5 to −1). This effect was not clinically significant ranging below the minimally important difference (10 points out of 100) for each time point. These results were consistent regardless of the type of drug (gabapentin or pregabalin). No effect was observed on pain intensity at 72 h, subacute and chronic pain. The use of gabapentinoids was associated with a lower risk of postoperative nausea and vomiting but with more dizziness and visual disturbance.

Conclusions: No clinically significant analgesic effect for the perioperative use of gabapentinoids was observed. There was also no effect on the prevention of postoperative chronic pain and a greater risk of adverse events. These results do not support the routine use of pregabalin or gabapentin for the management of postoperative pain in adult patients.

(ANESTHESIOLOGY 2020; 133:265–79)

Primary outcome

Secondary outcome (an important one!)

Table 1. Summary Estimates from Meta-analyses with the Assessment of the Statistical Heterogeneity and the Quality of the Evidence

Outcomes	Number of Trials	Number of Patients: Gabapentinoids	Number of Patients: Control	Summary Estimate: Mean Difference or Risk Ratio [95% CI]	I^2, %	Quality of the Evidence: Grades of Recommendation, Assessment, Development, and Evaluation Rating
Postoperative acute pain (100-point scale)*						
6 h	129	5,499	4,710	−10 [−12 to −9]	91	Low†
12 h	130	5,871	5,198	−9 [−10 to −7]	90	Low†
24 h	141	6,593	5,481	−7 [−8 to −6]	88	Low†
48 h	59	3,434	2,778	−3 [−5 to −1]	88	Low†
72 h	32	2,410	1,724	−2 [−4 to 0]	76	Low†
Postoperative subacute pain (100-point scale)	18	650	642	−6 [−9 to −3]	98	Low‡
Postoperative chronic pain	27	1,767	1,431	0.89 [0.74 to 1.07]	42	Moderate§
Postoperative opioid administration, mg of IV morphine equivalent‖						
24 h	117	4,807	4,253	−7.90 [−8.82 to −6.98]	98	Very low#
48 h	24	808	692	−9.79 [−12.81 to −6.78]	93	Very low#
72 h	4	200	173	−29.18 [−46.89 to −11.47]	94	Very low#
Length of stay (h)						
Postanesthesia care unit	10	512	383	−0.01 [−0.09 to 0.07]	73	Low†
Intensive care unit	6	184	184	0.14 [−3.49 to 3.78]	0	Low†
Hospital	17	1,359	1,104	2.96 [0.28 to 5.63]	62	Moderate§
Adverse events						
Ataxia or fall	14	1,228	1,107	1.31 [0.88 to 1.95]	40	Moderate**
Delirium	4	452	454	1.12 [0.85 to 1.47]	0	Low††
Visual disturbance	54	2,494	2,143	1.89 [1.53 to 2.33]	0	Moderate‡‡
Respiratory depression	42	2,251	2,108	0.79 [0.46 to 1.35]	0	Low§§
Nausea and/or vomiting	187	9,337	7,808	0.77 [0.72 to 0.82]	44	Moderate‡‡
Dizziness	134	6,645	5,409	1.25 [1.12 to 1.39]	39	Low‖‖

*Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h. †One level for potential risk of bias and one level for inconsistency. ‡One level for inconsistency and one level for imprecision. §One level for potential publication bias. ‖Intervals considered for the time point: 24 h, 0 to 24 h; 48 h, 0 to 48 h; and 72 h, 0 to 72 h. #One level for potential risk of bias, one level for indirectness, one level for inconsistency, and one level for potential publication bias. **One level for imprecision. ††Two levels for imprecision. ‡‡One level for potential risk of bias. §§One level for potential risk of bias and one level for imprecision. ‖‖One level for potential risk of bias and one level for potential publication bias.

The Efficacy and Safety of Gabapentinoids in Total Joint Arthroplasty: Systematic Review and Direct Meta-Analysis

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ABSTRACT

Background: Gabapentinoids are commonly used as an adjunct to traditional pain management strategies after total joint arthroplasty (TJA). The purpose of this study is to evaluate the efficacy and safety of gabapentinoids in primary TJA to support the combined clinical practice guidelines of the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society, and the American Society of Regional Anesthesia and Pain Management.

Methods: The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched for studies published prior to November 2018 on gabapentinoids in TJA. All included studies underwent qualitative and quantitative homogeneity testing followed by a systematic review and direct comparison meta-analysis to assess the efficacy and safety of gabapentinoids.

Results: In total, 384 publications were critically appraised to provide 13 high-quality studies regarded as the best available evidence for analysis. In the perioperative period prior to discharge, pregabalin reduces postoperative opioid consumption, but gabapentinoids do not reduce postoperative pain. After discharge, gabapentin does not reduce postoperative pain or opioid consumption, but pregabalin reduces both postoperative pain and opioid consumption.

Conclusion: Moderate evidence supports the use of pregabalin in TJA to reduce postoperative pain and opioid consumption. Gabapentinoids should be used with caution, however, as they may lead to an increased risk of sedation and respiratory depression especially when combined with other central nervous system depressants such as opioids.

GABAPENTINOIDS

$$TI = \frac{TD50}{ED50}$$

Gabapentin	CHARACTERISTICS	Pregabalin
Logarithmic (saturable)	Absorption	Linear
Small Intestine only	Location	SI to Ascending Colon
30-80%	Bioavailability	90%
Three hours	Tmax	One hour
75% urine, 25% feces	Excretion	98% urine
Narrow	Therapeutic Index	Wide
3600 mg	Max Daily Dose	900 mg

GABAPENTINOIDS

- How have these 2020 review articles changed my practice?
  - No more gabapentin, unless home med
  - More selective with pregabalin use
- Reasons why I would use pregabalin:
  - Home med
  - Chronic opioid use
  - Chronic EtOH use
  - Total joint arthroplasty, esp. primary
  - Patient wants to minimize opioids

ANTIDEPRESSANTS

Does improved mood help improve perception of pain?

TRICYCLIC ANTIDEPRESSANTS

- Reuptake inhibitor of 5-HT, DA, NE
- Antagonist at cholinergic, NMDA, & histaminergic (H1) receptors
- Off label uses:
  - Diabetic neuropathy
  - Post-herpetic neuralgia
  - Central pain syndromes
  - Myofascial pain

SEROTONIN-NE REUPTAKE INHIBITOR

- Reuptake inhibitor of 5-HT and NE
- ↑ DA levels in prefrontal cortex via inhibition of NE transporters
- Blocks voltage-gated Na channel
- FDA-approved indications
  - Diabetic neuropathy
  - Post-herpetic neuralgia
  - Chronic musculoskeletal pain

ANTIDEPRESSANTS

TRICYCLIC ANTIDEPRESSANTS

- Amitriptyline: NE > 5-HT > DA
  - High affinity for α, H1, M1 receptors
- Nortriptyline: NE > 5-HT > DA
  - Metabolite of amitriptyline with little affinity for α, H1, M1 receptors

SEROTONIN-NE REUPTAKE INHIBITOR

- Venlafaxine: 5-HT > NE >>> DA
  - PK leads to delayed and unreliable onset of analgesia
- Duloxetine: 5-HT = NE

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[Intervention Review]

Nortriptyline for neuropathic pain in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
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Citation: Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD011209. DOI: 10.1002/14651858.CD011209.pub2.

Authors' conclusions

We found little evidence to support the use of nortriptyline to treat the neuropathic pain conditions included in this review. There were no studies in the treatment of trigeminal neuralgia. The studies were methodologically flawed, largely due to small size, and potentially subject to major bias. The results of this review do not support the use of nortriptyline as a first line treatment. Effective medicines with much greater supportive evidence are available, such as duloxetine and pregabalin.

ANTIDEPRESSANTS

Table 3. Main Results of Pain Outcomes from Included Trials of Antidepressant for Early Postoperative Pain

Antidepressant	First Author, yr	Pain Measure	Time/Duration of Follow-up	Treatment *vs.* Placebo SES‡	Treatment *vs.* Active Comparator Difference
Amitriptyline*	Levine, 1986[43]*†	10 cm VAS	Eight intervals from 10 to 150 min after postoperative morphine administration	No significant differences noted throughout the duration of follow-up	Desipramine superior in efficacy to amitriptyline
Amitriptyline	Kerrick, 1993[42]†	10 cm VAS	8 AM/3 PM on postoperative days 1, 2, and 3	Pain significantly *higher* with amitriptyline from 3 PM on day 1 to 8 AM on day 3	N/A
Amitriptyline	Vahedi, 2010[48]	10 cm VAS	6, 12, 18, and 24 h postoperatively	Pain significantly *lower* with amitriptyline at 24 h only; SES = 0.56	N/A

(ANESTHESIOLOGY 2014; 121:591-608)

Comparison of venlafaxine and duloxetine: measuring clinical impact of time to therapeutic dose (TTD) among patients achieving therapeutic dosing for pain

Abstract

Background: Chronic opioid therapy remains controversial; however, there is consensus among treatment guidelines that adjunct medications should be utilized first. A meta-analysis revealed serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine to be equally efficacious in the treatment of neuropathic pain and recommend them as first-line therapy.1 Although, the therapeutic dosing for pain with both medications is well established there are no head-to-head studies comparing the two medications. The impact of medication selection (TIMS) as measured by percentage of patients achieving therapeutic dose and time to therapeutic dose (TTD) for neuropathic pain with either venlafaxine or duloxetine is not well understood. These outcomes along with adverse effect profiles need to be evaluated to inform clinical decision making.

Materials and Methods: This was a single center, retrospective, observational analysis. New start prescriptions for either venlafaxine or duloxetine between January 1, 2011 and January 1, 2014 were identified. Through data warehouse extraction the following was collected: age, gender, weight, height, race, comorbidities, prescriber and concomitant antidepressants and anticonvulsants on date of initiation. Manual data collection through the Computerized Patient Record System (CPRS) was then utilized to determine veteran eligibility as well as if therapeutic dose was achieved, TTD, as well as discontinuation rates and cause.

Results: 682 charts were reviewed to identify 302 patients, 151 in each group. The duloxetine group had 120 patients achieve therapeutic dose compared to 82 in the venlafaxine group ($p<0.0001$). Median TTD for duloxetine was 7 days (0-44.25, IQR) compared to venlafaxine 31.5 days (10-115, IQR). At study conclusion, 50/151 (33.1%) patients remained on duloxetine compared to 31/151 (20.5%) of those on venlafaxine (p-value 0.0191). Side effects were reported in 37% of patients in venlafaxine group compared to 22% of duloxetine group ($p=0.0053$). Of note, 117 (77%) of the duloxetine patients had a previous trial of venlafaxine therapy.

Conclusion: Patients taking duloxetine are significantly more likely to achieve therapeutic dose, arrive at therapeutic dose more quickly, and remain on the medication compared to venlafaxine. Titration schedule may influence tolerability. Duloxetine should be favored over venlafaxine in treatment algorithms for neuropathic pain.

Keywords: antidepressants, duloxetine, venlafaxine, neuropathic pain, diabetic neuropathy, pain

Atkinson T, Flynn KW, and Baker J. *Pharm Pharmacol Int J*. 2018;6(2):132−136.

Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study

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BACKGROUND: Postsurgical quality of recovery is worse in female than that in male patients. Duloxetine has been used successfully for the treatment of chronic pain conditions, but its use for preventing acute postoperative pain has been limited to a single previous study. More importantly, the effect of preoperative duloxetine on global postoperative quality of recovery has yet to be evaluated. The main objective of the current investigation was to evaluate the effect of perioperative duloxetine on postoperative quality of recovery in women undergoing abdominal hysterectomy.

METHODS: The study was a prospective, randomized, placebo-controlled, double-blinded trial. Female patients undergoing abdominal hysterectomy were randomized to receive duloxetine (60 mg orally 2 hours before surgery and 24 hours after surgery) or an identical placebo pill. The primary outcome was the quality of recovery-40 score at 24 hours. Secondary outcomes included opioid consumption and postoperative pain scores. A *P* value <0.05 was used to reject type I error.

RESULTS: Seventy patients were recruited, and 63 completed the study. The median difference (95% confidence interval) in global recovery scores (quality of recovery-40) at 24 hours after surgery between the duloxetine and the placebo group was 9 (4–20) ($P < 0.001$). Total opioid consumption was reduced at 24 hours in the duloxetine group compared with the placebo group, median (interquartile range) of 1 (0–5) mg IV morphine compared with 5.5 (0.5–9) mg IV morphine ($P = 0.004$). Nausea, vomiting, and time to postanesthesia care unit discharge were not significantly reduced in the duloxetine group compared with placebo.

CONCLUSIONS: Duloxetine improves postoperative quality of recovery after abdominal hysterectomy. In addition, duloxetine reduces postoperative opioid consumption, even in the presence of a robust multimodal analgesic strategy. Duloxetine seems to be a viable pharmacologic strategy to improve postoperative quality of recovery in female patients undergoing abdominal hysterectomy. (Anesth Analg 2016;122:98–104)

Duloxetine as an Analgesic Reduces Opioid Consumption After Spine Surgery

A Randomized, Double-Blind, Controlled Study

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Objectives: Multimodal analgesia is widely advocated for the control of perioperative pain in an effort to reduce the use of opioid. Duloxetine is a selective inhibitor of serotonin and norepinephrine reuptake with efficacy for chronic pain conditions. The primary objective of this study was to evaluate the efficacy of two 60 mg oral doses of duloxetine in terms of fentanyl consumption during the postoperative period in patients undergoing elective spine surgery.

Materials and Methods: This study was prospective, double-blind, randomized, and placebo controlled. Patients received either 60 mg duloxetine or an identical placebo 1 hour before surgery and again the following morning. The study participants were allocated into 2 groups: Group C (control) participants received the placebo and Group D (duloxetine) participants received 60 mg duloxetine. The total consumption of fentanyl 48 hours after surgery was measured. Secondary end points were pain scores and the presence or absence of adverse effects, such as headache, nausea, vomiting, itching, dizziness, and drowsiness.

Results: Demographic characteristics did not differ between groups. There was a significant difference in fentanyl consumption in the first 24 hours between Groups C and D (mean difference, 223.11 ± 39.32 μg; $P < 0.001$). Fentanyl consumption also differed between Groups C and D after 48 hours (mean difference, 179.35 ± 32.55 μg; $P < 0.000$). The pain scores over 48 hours did not significantly differ between groups. The incidence of side-effects was similar in both groups.

Discussion: Duloxetine was effective as an adjunct for postoperative analgesia and reduced opioid consumption.

Key Words: pain, postoperative, analgesia, duloxetine, spinal fusion

(*Clin J Pain* 2017;33:865–869)

to noxious stimuli, such as the metabolic endocrine response to surgical trauma, autonomic reflexes with adverse effects on physiological functions, muscle spasms, and other undesirable results.[1] Adequate control of postoperative pain is also important and, along with the intensity of acute postoperative pain, has been cited as a risk factor for chronic postoperative pain.[2]

Multimodal analgesia is the main concept used for postoperative pain management. This type of analgesia uses either various analgesics with different mechanisms of action or multiple simultaneous treatment techniques administered through different routes to provide analgesia at lower doses of each drug or with fewer repetitions of the same technique and with fewer adverse effects.[1] Multimodal analgesic regimens have been specifically recommended for the treatment of postoperative pain.[1] Opioids remain necessary to treat moderate to severe pain, but their use increases the risk of side-effects and hyperalgesia.[1] Adjuvants have thus been used to reduce the need for opioids in the postoperative period. In particular, ketamine and gabapentinoids have been found to improve postoperative pain scores and reduce the need for opioids as well as opioid side-effects, such as postoperative nausea and vomiting.[2,3]

Recently, selective serotonin and norepinephrine reuptake inhibitor antidepressants have been reported to produce varying degrees of pain relief in several persistent and chronic pain syndromes in humans, including diabetic neuropathy, postherpetic neuralgia, and fibromyalgia.[4] Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that has been approved by the Food and Drug Administration to treat major depressive disorder

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KJP

Original Article

Perioperative duloxetine as part of a multimodal analgesia regime reduces postoperative pain in lumbar canal stenosis surgery: a randomized, triple blind, and placebo-controlled trial

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The 20th Society of Anaesthesiologists of Nepal Annual Conference (SANCON 2019), 14-16th Mar. 2019, Kathmandu, Nepal.

Background: Duloxetine is an antidepressant that is also useful in chronic neuropathic and central origin pain. In this study, the role of duloxetine in decreasing acute postoperative pain after lumbar canal stenosis surgery is explored.
Methods: In this single center, triple blinded, and placebo-controlled trial, 96 patients were randomized for statistical analysis. The intervention group received oral duloxetine 30 mg once a day (OD) for 2 days before surgery, 60 mg OD from the day of surgery to the postoperative second day and 30 mg OD for the next 2 days (a total duration of 7 days). A placebo capsule was given in the other group for a similar time and schedule. The same standard perioperative analgesia protocols were followed in both groups.
Results: Total morphine consumption up to 24 hours was significantly decreased in the duloxetine group ($P < 0.01$). The time to the first analgesia requirement was similar in both groups but the time to the second and third dose of rescue analgesia increased significantly in the duloxetine group. The time to ambulation was decreased significantly ($P < 0.01$) in the duloxetine group as compared to the placebo group. Pain scores remained similar during most of the time interval. No significant difference was observed in the complication rate and patient satisfaction score recorded.
Conclusions: Duloxetine reduces postoperative pain after lumbar canal stenosis surgery with no increase in adverse effects.

Key Words: Acute Pain; Analgesia; Antidepressive Agents; Duloxetine Hydrochloride; Humans; Morphine; Pain Management; Pain, Postoperative; Patient Satisfaction; Walking

Perioperative duloxetine for acute postoperative analgesia: a meta-analysis of randomized trials

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ABSTRACT

Background Multimodal analgesia is a fundamental part of modern surgery and enhanced recovery pathways. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has been validated for the treatment of chronic neuropathic pain. The evidence for duloxetine as an adjunct for the treatment of acute postoperative pain remains controversial. We conducted a meta-analysis to determine the efficacy of duloxetine in the acute perioperative setting.

Methods A literature search was conducted in the major databases (PubMed, EMBASE and Google Scholar) for randomized controlled trials (RCTs) evaluating duloxetine compared with placebo control for acute postoperative pain. The primary outcome was postoperative pain assessed at 2, 4, 6, 24 and 48 hours time frames. Secondary outcomes included postoperative opioid administration, as well as side effects, such as postoperative nausea/vomiting (PONV), pruritus, dizziness and headache.

Results 574 patients (n=9 RCTs) were included in the analysis, divided between duloxetine (n=285 patients) and placebo (n=289 patients). Duloxetine use was associated with a significant reduction in pain scores as early as 4 (mean difference (MD) −0.9, 95% CI −1.33 to −0.47) and as late as 48 (MD −0.94, 95% CI −1.56 to −0.33) hours postoperatively compared with placebo. In addition, duloxetine was associated with a significant reduction in opioid administration at 24 (standardized MD (SMD) −2.24, 95% CI −4.28 to −0.19) and 48 (SMD −2.21, 95% CI −4.13 to −0.28) hours as well as a significant reduction in PONV (risk ratio 0.69, 95% CI 0.49 to 0.95, p=0.03) compared with placebo. There was no difference between groups in other side effects.

Conclusion Duloxetine, a non-opioid neuromodulator, may provide efficacy for the treatment of acute perioperative pain. Additional prospective studies are required to establish optimal perioperative dosing regimens, role in the setting of a comprehensive multimodal analgesic plan and impact on chronic postsurgical pain.

PROSPERO registration number CRD42019121416

Duloxetine for the treatment acute postoperative pain in adult patients: A systematic review with meta-analysis

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ABSTRACT

Background: Duloxetine administered during the acute perioperative period has been associated with lesser postoperative pain and analgesic consumption.

Study objectives: The study aimed to quantify the pooled effects of duloxetine on postoperative pain, analgesic consumption, and side-effects in the first 48 postoperative (PO) hours.

Design: Systematic review with meta-analysis.

Setting: Postoperative pain management.

Patients: Adult patients undergoing elective surgery.

Search strategy and study selection. Medline, Cochrane, EMBASE, CENTRAL, and Web of Science were searched without language restrictions for prospective, parallel randomized controlled trials comparing duloxetine to placebo for the management of postoperative pain in adult patients.

Measurements: Pain scores (11-point scales), opioid consumption (i.v. morphine equivalents), and frequency of side-effects were compared between duloxetine and placebo. Effect sizes were summarized as mean differences (MD), standardized mean differences (SMD) or risk ratios (RR) with the respective 95% confidence intervals (95% CI). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were used to classify the quality of evidence.

Results: Thirteen studies were included. Duloxetine decreased pain at 24 h (MD = −0.66 points; 95% CI = −1.14 to −0.19 points; SMD = −0.59; 95% CI = −1.06 to −0.12; p = 0.01; I2 = 88%), and at 48 PO hours (MD = −0.90 points; 95% CI = −1.54 to −0.26 points; SMD = −0.66; 95% CI = −0.94 to −0.38; p = 0.01; I2 = 93%); and opioid consumption at 24 PO hours (MD = −8.21 mg; 95% CI = −13.32 mg to −3.10 mg; SMD = −2.17; 95% CI = −3.10 to −1.24; p < 0.001; I2 = 95%), and at 48 PO hours (MD = 7.71 mg; 95% CI = −13.86 mg to −1.56 mg; SMD = −2.13; 95% CI = −3.51 to −0.75; p = 0.02; I2 = 97%). Duloxetine did not affect the prevalence of postoperative nausea and/or vomiting (PONV) pruritus, headache or dizziness. High inter-study heterogeneity and within-study bias resulted in very-low quality of evidence for the primary outcomes.

Conclusions: Although statistically significant effects of duloxetine were found on postoperative pain and opioid consumption during the first 48 postoperative hours, the effect sizes were below the expected minimal clinically relevant differences. Also, high risk-of-bias and inter-study heterogeneity caused the very-low quality of evidence (GRADE). We conclude that the currently available evidence does not support the clinical use of duloxetine for the management of acute postoperative pain.

MUSCLE RELAXANTS

- Cyclobenzaprine
  - TCA-like chemical structure
  - CNS depressant → SC
  - Approved for acute pain from spasms
- Methocarbamol
  - Anticholinergic inhibition of the RAS leads to ↓ reflexes and ↓ muscle tone
  - Approved for muscle spasm
- Tizanidine
  - Alpha-2 agonist → ↓ release of NT in presynaptic neurons of SC and brain
  - Approved for muscle spasm & spasticity
  - Implied class effect; neuropathic pain
- Baclofen
  - GABA analogue → ↓ release of NT in presynaptic neurons of SC and brain
  - Approved for muscle spasticity

MUSCLE RELAXANTS

- Diazepam
  - Benzodiazepine → synergy with opioids for respiratory depression
  - Allosteric binding to GABA receptors
    - SC = muscle relaxation
    - Brain = anxiolysis, sedation
  - Approved for anxiety, seizures, muscle spasm & spasticity
  - Other uses include sedation and EtOH withdrawal

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SAGE

Efficacy of Methocarbamol for Acute Pain Management in Young Adults With Traumatic Rib Fractures

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Abstract

Background: Rib fractures account for more than one-third of blunt thoracic injuries and are associated with serious complications. Use of nonopioid adjunctive agents such as methocarbamol for pain control has increased considerably. **Objective:** This study aimed to assess the impact of methocarbamol addition to the pain control regimen on daily opioid requirements for young adults with rib fractures. **Methods:** This observational, retrospective study included patients aged 18 to 39 years with 3 or more rib fractures who were admitted to a level I trauma center between July 2014 and July 2018. Patients were dichotomized based on admission before and after methocarbamol addition to the institutional rib fracture protocol. The primary outcome was to determine the impact of methocarbamol on daily opioid requirements. Secondary outcomes included hospital length of stay (LOS) and diagnosis of pneumonia. **Results:** A total of 50 patients were included, with 22 and 28 patients in the preprotocol and postprotocol groups, respectively. All patients in the latter group received methocarbamol, whereas no patient in the preprotocol group received methocarbamol. Cumulative opioid exposure was significantly less for patients admitted after methocarbamol addition to the protocol (219 vs 337 mg oral morphine equivalents; $P = 0.01$), and hospital LOS was also decreased (4 vs 3 days; $P = 0.03$). No significant differences in the incidence of pneumonia or adverse effects were observed. **Conclusion and Relevance:** This is the first study to evaluate the impact of methocarbamol on reducing opioid requirements. Given the risks associated with opioids, use of methocarbamol as an analgesia-optimizing, opioid-sparing multimodal agent may be reasonable.

Keywords

trauma, muscle relaxants, pain management, pharmaceutical care, skeletal muscle relaxants, trauma medicine

NMDA RECEPTOR ANTAGONISTS

MAGNESIUM

- Competitive Ca^{++} channel blocker
- Inhibits catecholamine release
- Potentiates ND-NMBDs

MEMANTINE

- Uncompetitive, low-affinity, open-channel blockade of Glutamate-specific NMDA receptors
- Antagonist to 5-HT3 & nACh receptors

DEXTROMETHORPHAN

- No direct effect at opioid receptor
- Antagonist to nACh receptors
- Inhibitor of VGCC and transporters of both 5-HT and NE

ASA NEWS

"Oh Mg!" Magnesium: A Powerful Tool in the Perioperative Setting

August 2018 Issue

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- MMA + Mg = no benefit
- PNB + Mg = no benefit
- TEA + Mg = no benefit

- Placebo vs. Mg = Mg better
  - Intraop or PACU MME
  - NRS pain scores
  - # of patients requesting opioid

RESEARCH ARTICLE

Memantine before Mastectomy Prevents Post-Surgery Pain: A Randomized, Blinded Clinical Trial in Surgical Patients

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Competing Interests: The authors declare that they have no conflict of interest.

Abstract

Background

Neuropathic pain following surgical treatment for breast cancer with or without chemotherapy is a clinical burden and patients frequently report cognitive, emotional and quality of life impairment. A preclinical study recently showed that memantine administered before surgery may prevent neuropathic pain development and cognitive dysfunction. With a translational approach, a clinical trial has been carried out to evaluate whether memantine administered before and after mastectomy could prevent the development of neuropathic pain, the impairment of cognition and quality of life.

Method

A randomized, pilot clinical trial included 40 women undergoing mastectomy in the Oncology Department, University Hospital, Clermont-Ferrand, France. Memantine (5 to 20 mg/day; n = 20) or placebo (n = 20) was administered for four weeks starting two weeks before surgery. The primary endpoint was pain intensity measured on a (0–10) numerical rating scale at three months post-mastectomy.

Results

Data analyses were performed using mixed models and the tests were two-sided, with a type I error set at $\alpha = 0.05$. Compared with placebo, patients receiving memantine showed at three months a significant difference in post-mastectomy pain intensity, less rescue analgesia and a better emotional state. An improvement of pain symptoms induced by cancer chemotherapy was also reported.

Conclusions

This study shows for the first time the beneficial effect of memantine to prevent post-mastectomy pain development and to diminish chemotherapy-induced pain symptoms. The lesser analgesic consumption and better well-being of patients for at least six months after treatment suggests that memantine could be an interesting therapeutic option to diminish the burden of breast cancer therapy.

Perioperative Dextromethorphan as an Adjunct for Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: *N*-methyl-D-aspartate receptor antagonists have been shown to reduce perioperative pain and opioid use. The authors performed a meta-analysis to determine whether the use of perioperative dextromethorphan lowers opioid consumption or pain scores.

Methods: PubMed, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Pubget, and EMBASE were searched. Studies were included if they were randomized, double-blinded, placebo-controlled trials written in English, and performed on patients 12 yr or older. For comparison of opioid use, included studies tracked total consumption of IV or intramuscular opioids over 24 to 48 h. Pain score comparisons were performed at 1, 4 to 6, and 24 h postoperatively. Difference in means (MD) was used for effect size.

Results: Forty studies were identified and 21 were eligible for one or more comparisons. In 848 patients from 14 trials, opioid consumption favored dextromethorphan (MD, −10.51 mg IV morphine equivalents; 95% CI, −16.48 to −4.53 mg; $P = 0.0006$). In 884 patients from 13 trials, pain at 1 h favored dextromethorphan (MD, −1.60; 95% CI, −1.89 to −1.31; $P < 0.00001$). In 950 patients from 13 trials, pain at 4 to 6 h favored dextromethorphan (MD, −0.89; 95% CI, −1.11 to −0.66; $P < 0.00001$). In 797 patients from 12 trials, pain at 24 h favored dextromethorphan (MD, −0.92; 95% CI, −1.24 to −0.60; $P < 0.00001$).

Conclusion: This meta-analysis suggests that dextromethorphan use perioperatively reduces the postoperative opioid consumption at 24 to 48 h and pain scores at 1, 4 to 6, and 24 h. (ANESTHESIOLOGY 2016; 124:696-705)

LIDOCAINE

- Analgesia unrelated to VGSC effects
- Systemic lidocaine effects include:
  - Modulation of neuropathways
    - Ca^{++} channels, NMDA receptor
    - K^{+} channels, glycine system, GPCR
  - Decreases levels of cytokines
    - IL-1δ, TNF-α, COX-2, PGE2
  - Inhibits migration & adhesion of PMNs
    - ICAM-1, PAF, LPA
- After discontinuation of infusion, the clinical benefit exceeds $t_{1/2}$ by > 5-12x

Lidocaine	Pharmacokinetics
Analgesic dose	LD = up to 1.5 mg/kg MD = 0.5 to 3 mg/kg/hr
Onset	45 to 90 seconds
Half-life	90 to 120 minutes
Metabolism	Hepatic CYP450
Active metabolites	MEGX = cardiotoxic GX = competitive antagonist to lidocaine; renal clearance
Therapeutic concentration	1.5 to 5 mcg/mL at steady state
Adverse reactions	Dizziness, tinnitus, hypotension, QRS prolongation, dysrhythmias

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REVIEW OF THERAPEUTICS

Intravenous Lidocaine for Acute Pain: A Systematic Review

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Table 4. Use of Intravenous Lidocaine in Observational Studies and RCTs

Study design	Cause of pain	Intervention	Comparator	Results
RCT[23]	Acute radicular low back pain	Lidocaine 100 mg IV over 2 min as single dose	Ketorolac 30 mg IV over 2 min as single dose	N=41 Lidocaine VAS decreased from 8.3 to 0.8 (95% CI 0–23, p=0.003) Ketorolac VAS decreased from 7.4 to 1.4 (CI 0–28, p=0.007) No difference in degree of reduction between groups (p=0.835)
RCT[19]	Renal colic	Lidocaine 1.5 mg/kg IV as single dose	Morphine 0.1 mg/kg IV as single dose	N=240 Lidocaine VAS reduced from 9.6 to 1.1; morphine VAS reduced from 9.7 to 2.2 (p=0.0001) 90% of lidocaine group responded successfully compared with 70% in the morphine group (p=0.0001)
RCT[22]	Critical limb ischemia	Lidocaine 2 mg/kg IV over 5 min as single dose	Morphine 0.1 mg/kg IV over 5 min as single dose	N=40 Lidocaine VAS was 7.5 at 0 min, 5.75 at 15 min, and 4.25 at 30 min Morphine VAS was 7.65 at 0 min, 7 at 15 min, and 6.5 at 30 min (95% CI 1.218–3.282)

CI = confidence interval; CPZ = chlorpromazine; DHE = dihydroergotamine; ICU = intensive care unit; IV, intravenous; NRS = Numeric Rating Scale; RCT = randomized controlled trial; VAS = Visual Analog Scale; VRS = Verbal Rating Scale.

Comparison of intravenous lidocaine versus epidural anesthesia for traumatic rib fracture pain: a retrospective cohort study

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ABSTRACT

Background Effective analgesia is essential in managing traumatic rib fractures. Intravenous lidocaine (IVL) is effective in treating perioperative pain, acute pain in the emergency department, cancer pain in hospice, and outpatient chronic neuropathic pain. Our study examined the associations between IVL versus epidural analgesia (EA) and pain for the treatment of acute rib fracture in the inpatient setting.

Methods We performed a retrospective study involving adults admitted to an academic level I trauma center from June 1, 2011 to June 1, 2016 with consults to the pain service for acute rib fracture pain. Eighty-nine patients were included in the final analysis (54 IVL and 35 EA patients). Both groups had usual access to opioid medications. The primary outcome was absolute change in numeric pain scores during 0–24 and 24–48 hours after initiating IVL or EA, compared with baseline. Secondary outcomes include opioid consumption, incentive spirometry, supplemental oxygens, pneumonia, endotracheal intubation and length of hospital stay.

Results Numeric pain scores differed at baseline (mean 5.6 for IVL vs 4.5 for EA, p=0.01), while age, injury severity, and number of fractured ribs were similar. IVL and EA were associated with similar reductions in numeric pain scores within 0–24 and 24–48 hours (mean −2.9 for IVL vs −2.3 for EA during both periods, p=0.19 and p=0.17 respectively) . There was greater non-neuraxial opioid consumption with IVL compared with EA (98.6 vs 22.3 mg morphine equivalents (MME) at 0–24 hours, p=0.0005; 105.6 vs 18.9 MME at 24–48 hours, p<0.0001). When epidural opioids were analyzed, the EA group was exposed to higher total MME at 0–24 hours (655.2 vs 98.6 MME, p<0.0001) and 24–48 hours (586 vs 105.6 MME, p=0.0001), suggesting an opioid sparing effect of IVL.

Conclusion Our results suggest that IVL is similar to EA in numeric pain score reduction, and that IVL may have an opioid sparing effect when taking neuraxial opioids into account. IVL may be an effective alternative to epidurals for the treatment of rib fracture pain. It should be considered for patients who have contraindications to epidurals or are unable to receive an epidural in a timely manner.

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RESEARCH ARTICLE

Intravenous lidocaine as a non-opioid adjunct analgesic for traumatic rib fractures

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Abstract

Introduction

Pain management is the pillar of caring for patients with traumatic rib fractures. Intravenous lidocaine (IVL) is a well-established non-opioid analgesic for post-operative pain, yet its efficacy has yet to be investigated in trauma patients. We hypothesized that IVL is associated with decreased inpatient opioid requirements among patients with rib fractures.

Methods

We retrospectively evaluated adult patients presenting to our Level 1 trauma center with isolated chest wall injuries. After 1:1 propensity score matching patients who received vs did not receive IVL, we compared the two groups' average daily opioid use, opioid use in the last 24 hours of admission, and pain scores during admissions hours 24–48. We performed multivariable linear regression for these outcomes (with sensitivity analysis for the opioid use outcomes), adjusting for age as a moderating factor and controlling for hospital length of stay and injury severity.

Results

We identified 534 patients, among whom 226 received IVL. Those who received IVL were older and had more serious injury. Compared to propensity-score matched patients who did not receive IVL, patients who received IVL had similar average daily opioid use and pain scores, but 40% lower opioid use during the last 24 hours of admission ($p = 0.002$). Multivariable regression–with and without sensitivity analysis–did not show an effect of IVL on any outcomes.

Conclusion

IVL was crudely associated with decreased opioid requirements in the last 24 hours of admission, the time period associated with opioid use at 90 days post-discharge. However, we did not observe beneficial effects of IVL on multivariable adjusted analyses; we are conducting a randomized control trial to further evaluate IVL's opioid-sparing effects for patients with rib fractures.

THE END.

QUESTIONS?