

# Anti-inflammatory Agents: Recommendations for Use in Fracture Surgery

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17<sup>th</sup> Annual International San Francisco  
Orthopaedic Trauma Course

# Disclosures

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# Objectives

- Can I use anti-inflammatory agents in the setting of an acute fracture?
- Can I use anti-inflammatory agents in the setting of a nonunion?
- Does aspirin impact fracture healing?

# Objectives

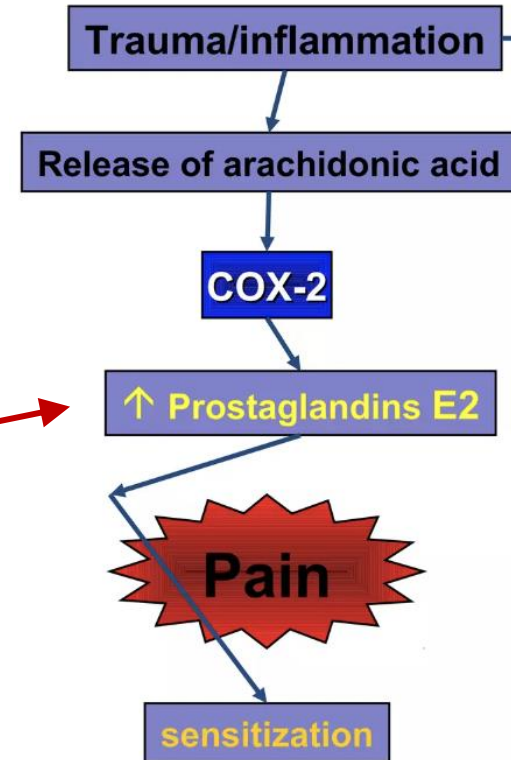


# Objectives



# Mechanism of Action

- Common NSAIDs: Ibuprofen, Aspirin, Naproxen, Ketorolac
- NSAID primary mechanism of action: Inhibition of the enzyme cyclooxygenase (COX)<sup>1,2,3</sup>
  - Prevent conversion of arachidonic acid into thromboxanes, prostaglandins, and prostacyclins
  - Dampen peripheral pain response
  - Anti-Inflammatory, analgesic action



• Prostaglandins (PGE<sub>2</sub>) play a role in bone metabolism & healing<sup>4, 5</sup>

1. WJ Philips Journal of the AAOS 2004  
 2. JR Vane Thrombosis Research 2003  
 3. JR Vane Nat Rev Biol 1971  
 4. AL Symons Arch Oral Biol 2012  
 5. CM Lee J Bone Mineral Metab 2010

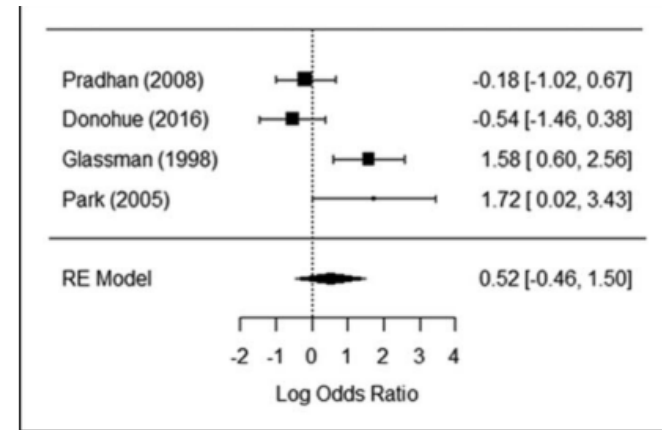
# Pre-clinical Research

- Animal Studies – mice, rat, and rabbit fracture models<sup>1-4</sup>
  - Early-stage fracture healing and osteogenesis inhibition
    - Timing, duration, and dose-dependent
    - Studies suggest this process is COX-2-specific
  - Post-operative NSAIDs inhibit spinal fusion in the rat<sup>5</sup>
  - NSAIDs delay ulna fracture healing in the rat<sup>6</sup>

1. RJ O'Keefe Ann N Y Acad Sci. 2006
2. P. Geusens P Curr Opin Rheumatology 2013
3. LC Gerstenfeld Expert Opin Drug Saf 2004
4. BH Mullis Injury 2006
5. JR Dimar Spine 1996
6. LJ Kidd J Orthopaedic Res 2013

# Clinical Research – Acute Fractures

- Meta-analysis of 16 studies (JAAOS, 2019)<sup>1</sup>
  - NSAID exposure increased delayed union or nonunion
    - (OR = 2.07; CI = 1.19 to 3.61)
  - No effect was noted in pediatrics
    - (OR = 0.58; CI = 0.27 to 1.21)
  - No effect in low dose/short duration
    - (OR = 1.68; CI = 0.63 to 4.46)





# Clinical Research – Acute Fractures

## The effect of NSAIDs on postfracture bone healing: a meta-analysis of randomized controlled trials

Humaid Al Farii, MD, MRCS (Ir)\*, Leila Farahdel, MD, Abbey Frazer, MD, Ali Salimi, MD, Mitchell Bernstein, MD, FRCSC



- 6 RCTs (n=609 patients)
- Overall analysis:
  - NSAID use had increased risk for nonunion (OR = 3.47)
- NSAIDs for a short period (<2 weeks) did not have increased risk for nonunion
- Longer-term NSAID use (>4 weeks), demonstrated increased risk for nonunion

# Clinical Research - Nonunion

- Impact of NSAID use in the setting of nonunion is still unclear<sup>1</sup>
  - Considerations: dosage, class, timing, and comorbidities, type of nonunion
  - Important implications in offsetting opioid usage



1. AP Kurmis J Bone Joint Surg 2012

# What About Aspirin?

- Aspirin usage in rat osteoporotic fracture model<sup>3</sup>
  - Accelerated healing of new callus, increased bone density
  - Promoted overall fracture healing
- Aspirin and clinical fracture healing
  - Does not appear delay healing & union in operatively treated ankle fractures<sup>1</sup>
- Post-operative aspirin delayed radiographic healing in tibial fractures (n=35; retrospective review)<sup>2</sup>

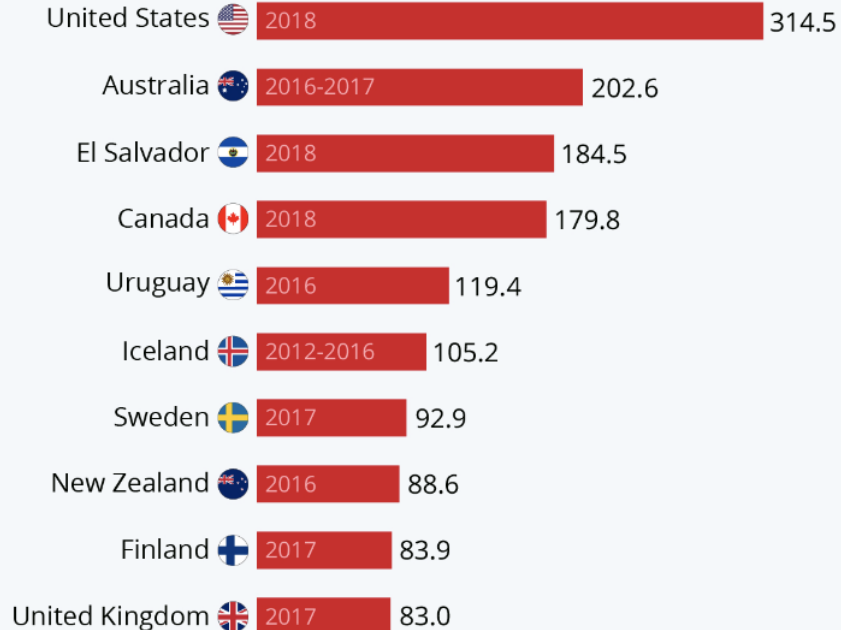


1. AM Hunter Injury 2020
2. D Dombroski U Penn Ortho J 2010
3. JS Wei Asian Pac J Trop Med 2014

# Impact of NSAID Use on Opioid Requirements

## The Deadly Toll of America's Opioid Crisis

Countries with the highest estimated number of drug-related deaths per million persons aged 15-64



# Impact of NSAID Use on Opioid Requirements

- Postoperative NSAID use reduces the requirement for opioid use<sup>1</sup>
  - Multimodal analgesia strategy; opioid-sparing
  - NSAID use did not compromise pain control
- Ibuprofen demonstrated opioid-sparing effects following ambulatory surgery<sup>2</sup> and posterior lumbar body fusion surgery<sup>3</sup>
  - Reduced need for morphine usage post-operatively in adult patients<sup>4,5</sup>
- Ketorolac demonstrates opioid-sparing effects post-operatively<sup>6, 7</sup>

1. L Martinez Clin Ther 2019
2. PF White Anesth Analg 2011
3. HU Pinar Pain Res Manag 2017
4. N Singla Pain Med 2010
5. AG Martinez PLoS One 2016
6. R Alexander J Clin Anesth 2002
7. MS Cepeda Anesthesiology 2005

# Current Guidelines

- **Clinical practice guidelines on NSAID use:**
  - NSAIDs recommended for post-operative pain management<sup>1,2</sup>
    - Reduce opioid usage
    - Minimal risk of nonunion
  - AAOS NSAID guidelines
    - NSAIDs in combination with opioids
    - Ibuprofen, Naproxen & Aspirin
  - NICE NSAID guidelines
    - Topical NSAID as first line treatment before oral NSAID

# Ongoing Research

- NSAIDs RCT
- 1,000 patients planned across 14 METRC sites
- Study Design
  - IM nail for acute diaphyseal tibia fracture
  - Randomized to control or treatment group
  - **Treatment:** 600mg Ibuprofen x3 daily for up to 6 weeks
  - **Control:** No NSAIDs, standard of care regimen
  - Follow for 12 months



# Ongoing Research

- Primary Outcome Measure
  - Rates of surgery to promote union in control vs treatment group
- Secondary Outcome Measures
  - Opioid usage
  - Levels of pain, functional outcomes
  - Rates of radiographic union



# Objectives

- Can I use anti-inflammatory agents in the setting of an acute fracture?
  - Yes, but consider low dose and short duration
- Can I use anti-inflammatory agents in the setting of a nonunion?
  - Limited evidence to provide guidance
- Does aspirin impact fracture healing?
  - Data supports minimal risk





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