PainWeek®

NSAID Counterattack, Baby We're Back!

Timothy J Atkinson, PharmD, BCPS

Title and Affiliation

Timothy J Atkinson, PharmD, BCPS, CPE
Clinical Pharmacy Practitioner, Pain Management
Director, PGY2 Pain Management & Palliative Care Residency Program
Pain Representative, National VA Pharmacy Residency Advisory Board
VA Tennessee Valley Healthcare System
Nashville, TN

Disclosure

- Consulting Fee (e.g., Advisory Board): Purdue Pharma LP

Learning Objectives

- Discuss evidence supporting FDA class effect warnings
- Describe guideline updates to NSAID utilization
- Outline strategies to deliver NSAID therapy and overcome treatment obstacles
- Compare non-traditional NSAID formulations

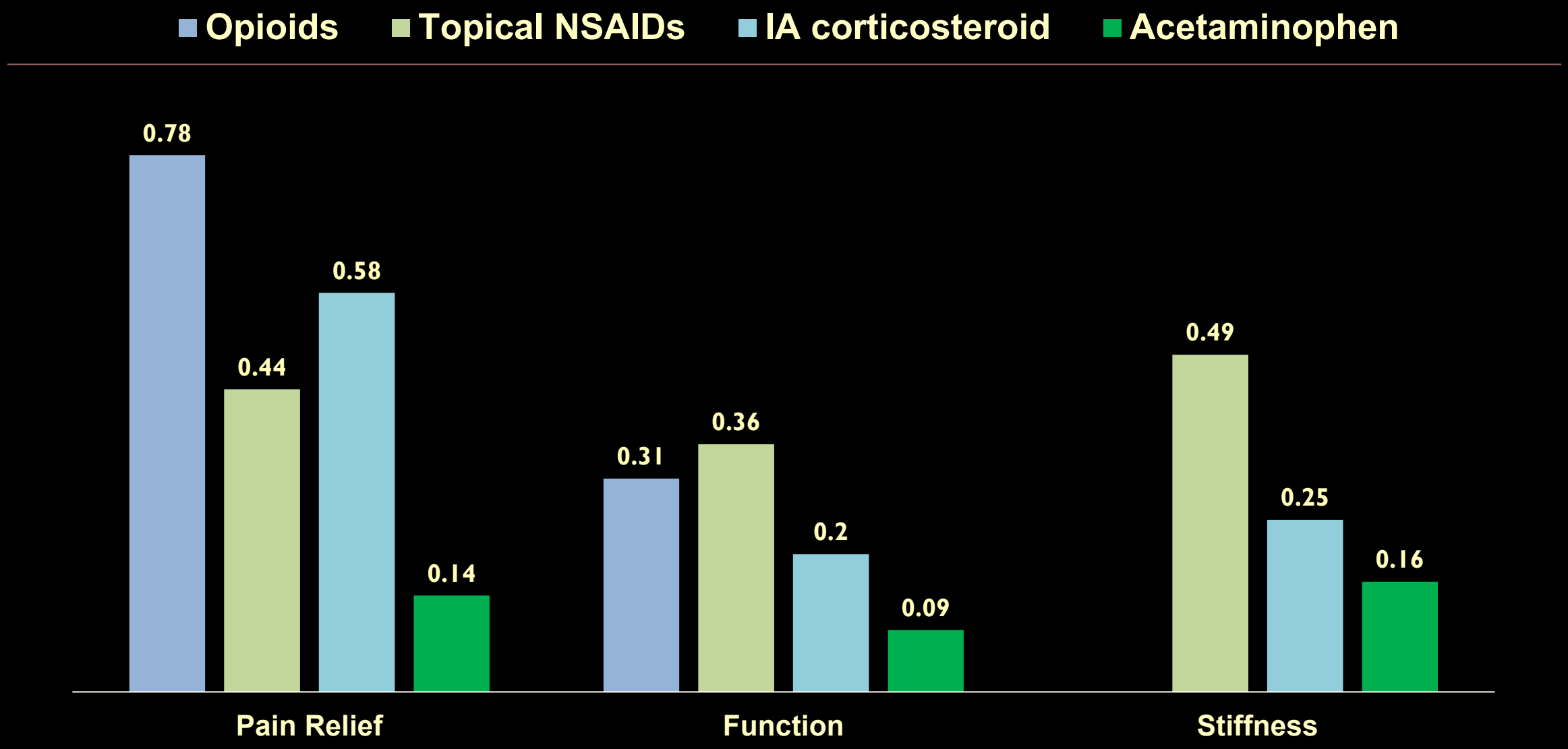
Why are we getting excited about NSAIDs?

Historical Perspective

- 1828: **Johann Bűchner**, a professor of pharmacy, isolated bitter-tasting crystals from willow bark and named it “salicin.”
- 1838: Italian chemist **Rafael Piria** produced salicylic acid (SA) by hydrolysis and oxidation to a more active and pure form.
- 1858: French chemist **Francis Gerhardt** buffered SA with sodium and acetyl chloride creating acetyl salicylic acid (ASA)
  - Abandoned his research, as he didn’t recognize improved GI tolerability.
- 1870(s): Scientists demonstrated that ASA could successfully treat rheumatoid arthritis, rheumatic fever, and gout.
- 1897: **Felix Hoffman** created a more stable form of ASA.
- 1899: ASA was first marketed as a powder.
- 1900: ASA tablets became available by the **Bayer Company**
  - Aspirin®
- 1900: Aspirin quickly became the most popular painkiller worldwide used for backache, headache, and arthritis.

Ugurlucan M, M Caglar I, N Turhan Caglar F, Ziyade S, Karatepe O, Yildiz Y, Zencirci E, Gungor Ugurlucan F, H Arslan A, Korkmaz S, Filizcan U. Aspirin: from a historical perspective. Recent patents on cardiovascular drug discovery. 2012 Apr 1;7(1):71-6.

Effect Size of Rx Interventions in Knee OA



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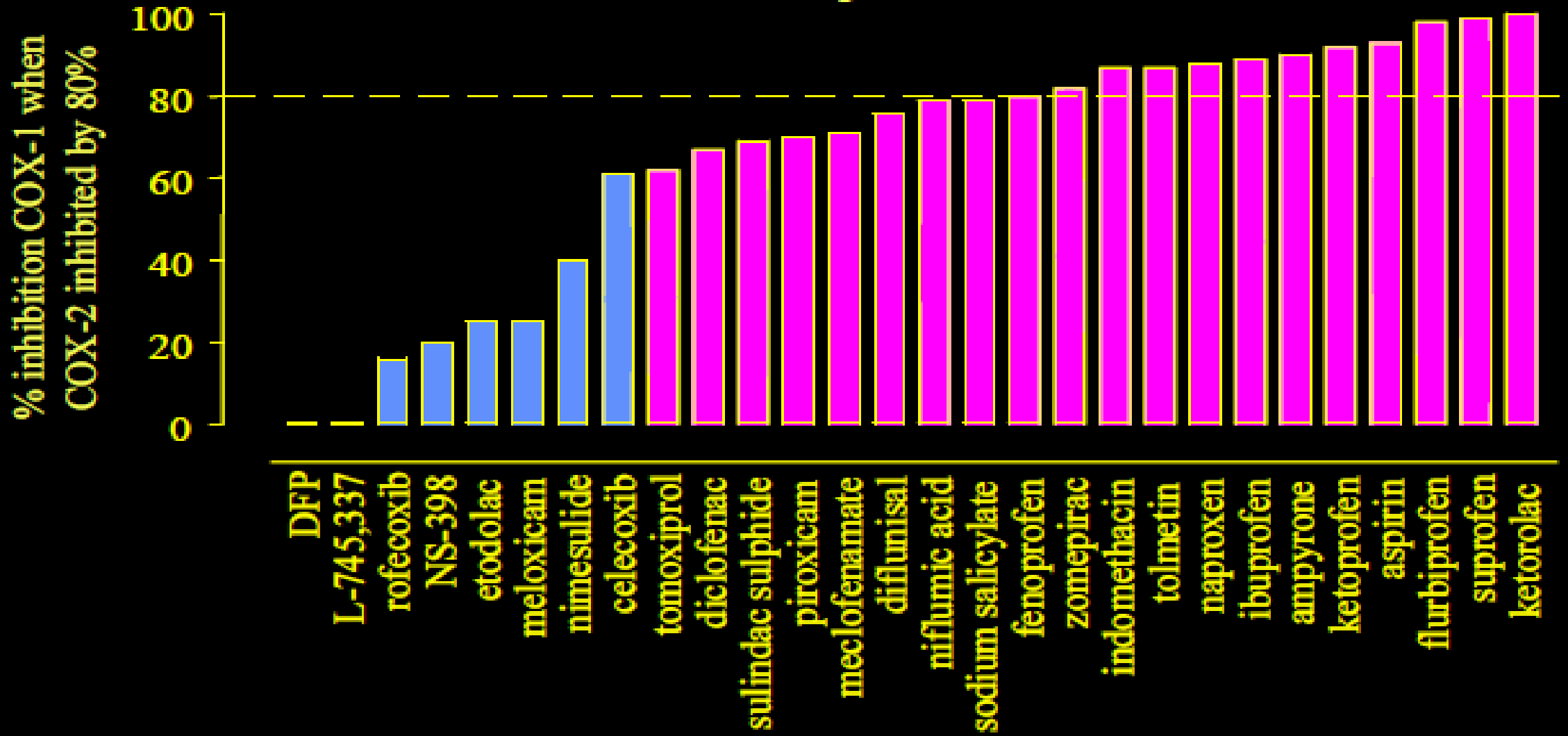
SOURCE: OARSI 2010

Relationship between 80% ('therapeutic') inhibition of COX-2 and inhibition of COX-1 in an in vitro human whole blood assay



Warner et al, PNAS 1999; 96:7563–7568

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis (PRECISION)

- Randomized, multi-center, double-blind, non-inferiority trial
- Included patients at increased cardiovascular risk and had rheumatoid arthritis or osteoarthritis (majority)
- **Doses evaluated:**
  - Celecoxib: 100-200mg BID (mean: 209±37 mg)
  - Naproxen: 375-500mg BID (mean: 852±103 mg)
  - Ibuprofen 600-800mg TID (mean: 2045±246 mg)
- **Preventative measures:**
  - Esomeprazole 20-40mg provided to all patients
  - Investigators encouraged to provide cardiovascular preventative management

Nissen SE, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016; 2519-2529.

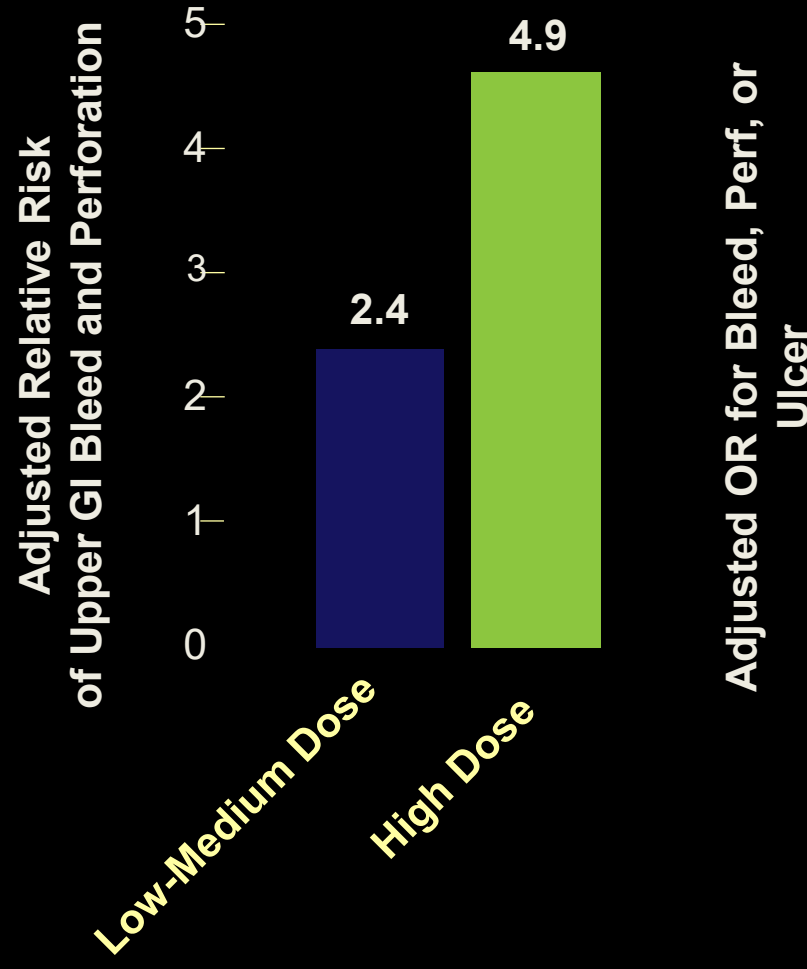
Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis (PRECISION)

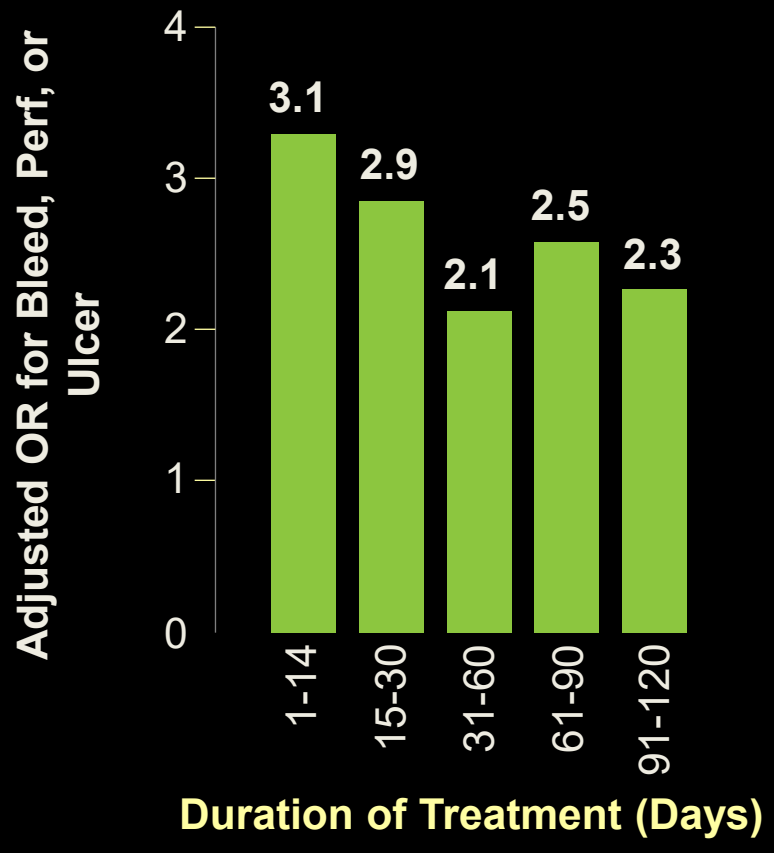
- Results:

	Hazard Ratio (95% Confidence Interval)
–Primary Outcomes (cardiovascular)	
• Celecoxib vs Naproxen	**0.90 (0.71 – 1.15)**
• Celecoxib vs Ibuprofen	**0.81 (0.65 – 1.02)**
–Clinically Significant GI Events	
• Celecoxib vs Naproxen	**0.51 (0.32 – 0.81)**
• Celecoxib vs Ibuprofen	**0.43 (0.27 – 0.68)**
–Renal Events	
• Celecoxib vs Naproxen	**0.66 (0.44 – 0.97)**
• Celecoxib vs Ibuprofen	**0.54 (0.37 – 0.80)**
–Death from Any Cause	
• Celecoxib vs Naproxen	**0.65 (0.46 – 0.92)**
• Celecoxib vs Ibuprofen	**0.68 (0.48 – 0.97)**

Nissen SE, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016; 2519-2529.

Risks of Serious GI Complications Related to NSAID Dose[1] & Duration[2]





Clinical Pearls:

- Strong dose-dependent
- Moderately decreased risk over time

Research Questions:

- GI prophylaxis success
- # GI bleeds vs # deaths
  - Related to NSAIDs

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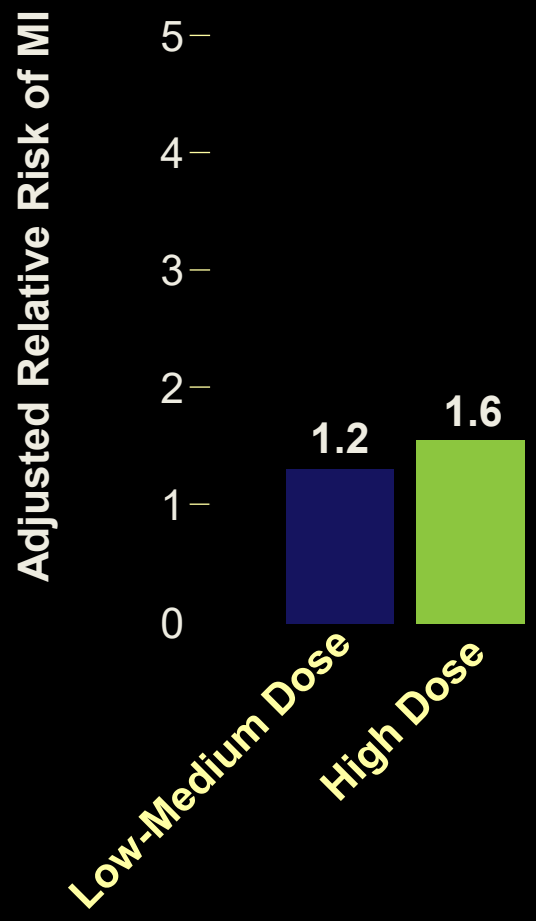
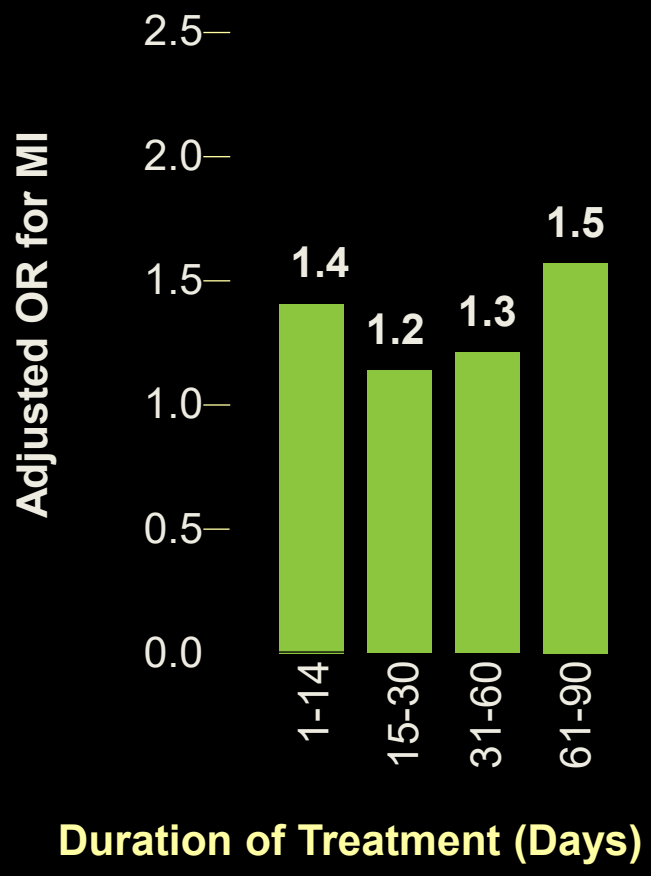
GI, gastrointestinal. Perf, perforation; OR, odds ratio; RR, relative risk.

References: 1. Garcia Rodriguez LA, Hernandez-Diaz S. *Epidemiology*. 2001;12(5):570-576. 2. **Adapted from:** 1. Helin-Salmivaara A, et al. *Scand J Gastroenterol.* 2007;42(8):923-932.

Risks of Serious Cardiovascular (CV) Complications Related to NSAID Dose[1] & Duration[2]





Clinical Pearls:

- Not dose-dependent
- No cumulative treatment effects

Research Questions:

- CVA, CV risk (dose & duration)
- CV Risk index to predict CV complications before starting NSAIDs

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CV, cardiovascular; MI, myocardial infarction; OR, odds ratio; RR, relative risk.

References: 1. Garcia Rodriguez LA, et al. *J Am Coll Cardiol.* 2008;52(120):1628-1636. 2. Helin-Salmivaara A, et al. *Eur Heart J.* 2006;27(14):1657-1663.

Relative Cardiovascular Risk With NSAIDs (Pooled Data from Meta-Analysis)

- Oral Diclofenac
  - Highest CV risk

Drug	MI	Stroke	CV Death	Death from any cause
Naproxen	0.82 (0.37 – 1.67)	1.76 (0.91-3.33)	0.98 (0.41-2.37)	1.23 (0.71-2.12)
Ibuprofen	1.61 (0.5 – 5.77)	**3.36* (1-11.6)**	2.39 (0.69-8.64)	1.77 (0.73-4.3)
Diclofenac	0.82 (0.29-2.20)	**2.86* (1.09-8.36)**	**3.98* (1.48-12.7)**	**2.31* (1-4.95)**
Celecoxib	1.35 (0.71- 2.39)	1.12 (0.6-2.06)	2.07 (0.98-4.55)	1.5 (0.96-2.54)
Etoricoxib	0.75 (0.23- 2.39)	2.67 (0.82-8.72)	**4.07* (1.23-15.7)**	2.29 (0.94-5.71)
Rofecoxib	**2.12* (1.26-3.56)**	1.07 (0.6-1.82)	1.58 (0.88-2.84)	**1.56* (1.04-2.23)**
Lumaricoxib	2 (0.71-6.21)	**2.81* (1.05-7.48)**	1.89 (0.64-7.09)	1.75((0.78-4.17)

*indicates statistical significance

Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. B*MJ*. 2011; 342:c7086.

Re-Examine Cardiovascular Risk with COX-2 Inhibition

- Meta-analysis in 2017
  - Determine if COX-2 selectivity increases CV Risk
- Primary Endpoints:
  - Any Myocardial infarction (MI)
  - Any Stroke
  - CV Death
- 26 Studies met inclusion/exclusion criteria
  - Excluded if study duration < 1 month
  - Excluded if CV outcomes not reported
- Included 8 NSAIDs for comparison:
  - Meloxicam, ibuprofen, naproxen, diclofenac, etoricoxib, celecoxib, lumiracoxib, rofecoxib
  - Each compared to placebo
  - Drugs were compared against Coxibs with and without Rofecoxib

Gunter BR, et al. NSAID-Induced CV Adverse Events. *J Clin Pharm Ther.* 2017; 42:27-38.

Results of the Meta-analysis

- Results: (Compares to other NSAIDs)
  - –Composite CV Outcomes

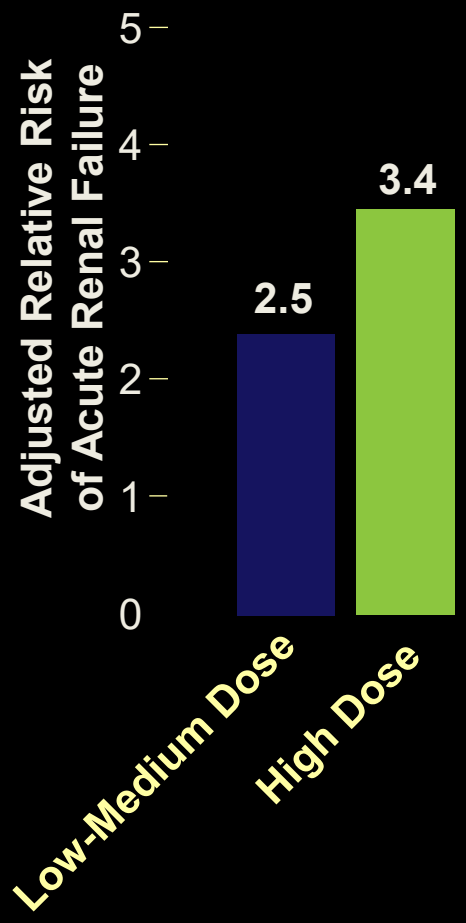
	Hazard Ratio (95% Confidence Interval)
• Celecoxib	**0.81 (0.66 – 0.99)***
• Diclofenac	**1.07 (0.86 – 1.32)**
• Etoricoxib	**0.88 (0.70 – 1.12)**
• Ibuprofen	**1.16 (0.81 – 1.66)**
• Lumiracoxib	**1.20 (0.84 – 1.71)**
• Naproxen	**0.96 (0.74 – 1.26)**
• Rofecoxib	**1.61 (1.31 – 1.98)***

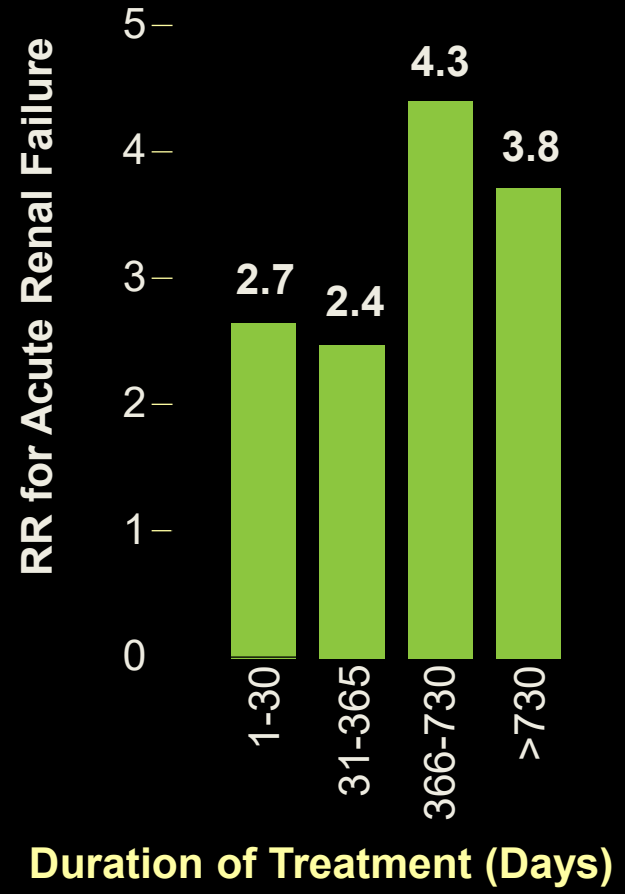
  - –Only Rofecoxib is statistically significant (SS) against placebo
    - Only Rofecoxib is SS against other NSAIDs
- Coxib group no different than non-selective NSAIDs
  - –When Rofecoxib is removed

*Statistical Significance

Gunter BR, et al. NSAID-Induced CV Adverse Events. *J Clin Pharm Ther.* 2017; 42:27-38.

Risks of Serious Renal Complications Related to NSAID Dose & Duration[1]





Clinical Pearls:

- Moderately dose-dependent
- Significant cumulative effect

Research Questions:

- NSAID impact on CKD
- NSAID use in dialysis

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OR, odds ratio; RR, relative risk.

References: Adapted from 1. Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.

Topical Diclofenac Pharmacokinetics

Diclofenac Prescription Dosage Forms						
Brand Name	Form	Strength	Dose	Cmax (ng/mL)	Tmax (hr)	AUC (ng/hr/mL)
Diclofenac (Voltaren, Cataflam, generic)	Tablets	50mg	TID	2270 ± 778	6.5	3890 ± 1710
Voltaren	Gel	1%	48g/day*	53.8 ± 32	10	807 ± 478
Solaraze	Gel	3%	2g TID x 6 days	5 ± 5	4.5 ± 8	9 ± 19
Flector	Patch	1.3%	BID x 5 days	1.3 – 8.8	120	96
Pennsaid	Topical Solution	1.5% w/w	QID x 7 days	19.4 ± 9.3	4 ± 6.5	745.2 ± 374.7
***This is above the maximum daily dose recommended**						

FDA Labeling

Class Effect Warnings?

Topical NSAIDs
- GI Risk
- Cardiac Risk

Is there enough evidence to support labeling?

Fudin J. Should Topical NSAIDs have Strict Heart Risk Warnings? Pharmacy Times. Published July 16, 2015. Available at: http://www.pharmacytimes.com/contributor/jeffrey-fudin/2015/07/should-topical-nsaids-have-strict-heart-risk-warnings

Center for Drug Evaluation and Research. Drugs@FDA Diclofenac Package Inserts.

Adverse Event Reporting & Safety Review

Therapeutic Goods Administration (Australia) Safety Review of Diclofenac (2014)

- Query of EMA's Adverse Drug Reporting System (ADRS)
  - 84 reports of adverse events with topical diclofenac
  - 3 events when oral diclofenac excluded
    - 2 reports of liver function test abnormalities
    - 1 report of GI bleed

- Safety Review Conclusion:
  - Risk/benefit for topical diclofenac remains favorable
  - Paucity of evidence of serious systemic side effects with topical diclofenac

Therapeutic Goods Administration: Safety Review of Diclofenac.

A New IV NSAID Option: Meloxicam

IV Meloxicam

FDA Approved: 2/20/2020

Indication: indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics

- Limitation: delayed onset of analgesia (2-3 hours), not recommended when rapid onset of analgesia is required
- Dose: 30mg once daily administered by intravenous injection over 15 seconds
- Contraindications:
  - Hypersensitivity to meloxicam, aspirin
  - CABG
  - Moderate to severe renal insufficiency at risk of renal failure due to volume depletion

Drugs@FDA. ANJESO Drug Label. Published 4/28/21. Accessed 7/21/21. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

IV Meloxicam

- Parameters
- Pharmacokinetics:
  - C_{max} (ng/mL)
  - T_{max} (h)
  - AUC_{inf} (ng*hr/mL)
  - $T_{1/2}$ (h)

Single-Dose Pharmacokinetics

IV	vs	Oral
5642±1009		1221.9±289
0.12±0.04		6.57±4.12
107508±34443		53988±23207
23.3±9.36		26.4±12.1

- Metabolism:
  - CYP2C9 (60%)
  - CYP3A4 (9%)

- Excretion:
  - Equal excretion into urine/feces
  - Mean half-life ($t_{1/2}$) is approximately 24 hours

Drugs@FDA. ANJESO Drug Label. Published 4/28/21. Accessed 7/21/21. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

IV Meloxicam

What to watch:

- Perioperative utilization and incorporation into ERAS protocols
  - 2 Phase III studies
    - Bunionectomy – started day after surgery, 2 days of treatment
    - Abdominoplasty – started day of surgery, 2 days of treatment
- ER/Urgent Care utilization
  - IV Ketorolac vs IV Meloxicam
    - IV Meloxicam fewer doses and longer duration of action
      - Higher than oral serum levels for 48 hours after 1st injection
- Ambulatory Clinic utilization – clinic med orders
  - Orthopedics
  - Pain Clinics
  - Primary Care

Drugs@FDA. ANJESO Drug Label. Published 4/28/21. Accessed 7/21/21. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

NSAID Updates For Perioperative Pain Management

A New Meta-Analysis for NSAIDs & Perioperative Bleeding

- 2521 articles screened
- 229 selected for detailed assessment
  - Based on title and abstract
- 74 Studies met criteria
- N = 151,031 patients
- 41 Randomized Controlled Trials
- 27 Cohort Studies
- 6 case-control studies
  - Eliminated from meta-analysis
- 29 studies tracked bleeding as primary outcome
  - Rest were tracked as complications

- Studies range from 1987-2019
- 2 in 1980s
- 15 in 1990s
- 18 in 2000s
- 39 in 2010s
  - 10 in 2018 alone

- Perioperative Bleeding Outcomes Defined:
  - Hematoma
  - Return to OR
  - Blood transfusions

Bongiovanni T, Lancaster E, Ledesma Y et al. Systematic Review and Meta-Analysis of the Association Between Non-Steroidal Anti-Inflammatory Drugs and Operative Bleeding in the Perioperative Period. *J Am Coll Surg.* 2021; 232:765-790.

NSAIDs (# studies)

- Ketorolac (41)
- Diclofenac (8)
- Ibuprofen (8)
- Celecoxib (6)
- Ketoprofen (5)
- Parecoxib (4)
- Lornoxicam (3)
- Meloxicam (2)
- Indomethacin (2)
- Flurbiprofen (2)
- Various (1 study each)

Timing of NSAID Administration:

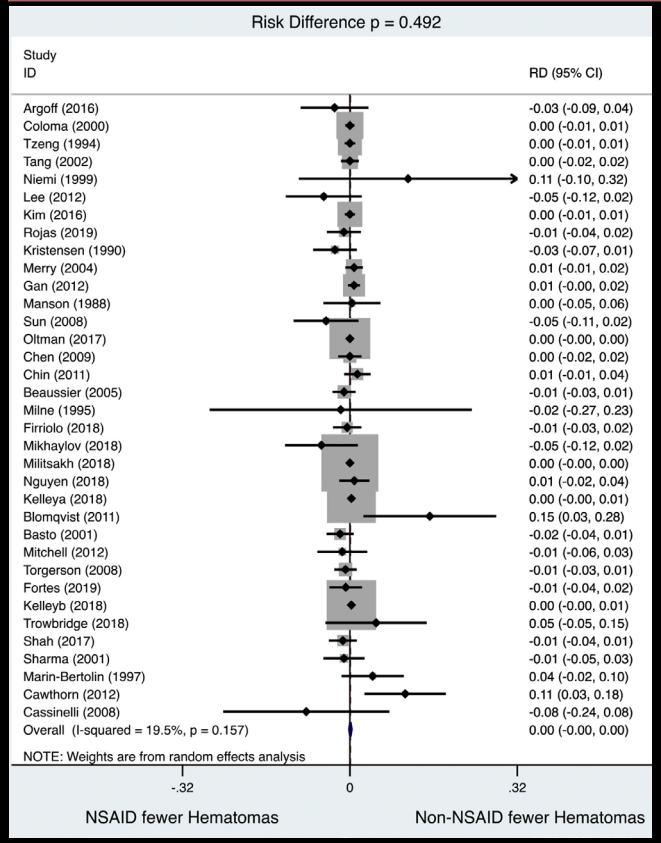
- Pre-operative (13)
- Intra-operative (24)
- Postoperative (56)

Surgery Types (# studies)

- Breast surgery (14)
- Abdominal (10)
  - Open & laparoscopic
- ENT (9)
  - Mostly tonsillectomies
- Orthopedic (9)
- Neurosurgical (4)
- Cosmetic (4)
- Thyroid/parathyroid resection (4)
- Plastic surgery (4)
- OBGYN (4)
- Cardiac (4)
- Perianal (4)
- Dental (4)
- Podiatric (4)
- Endoscopic retrograde cholangiopancreatography (4)

Bongiovanni T, Lancaster E, Ledesma Y et al. Systematic Review and Meta-Analysis of the Association Between Non-Steroidal Anti-Inflammatory Drugs and Operative Bleeding in the Perioperative Period. *J Am Coll Surg.* 2021; 232:765-790.

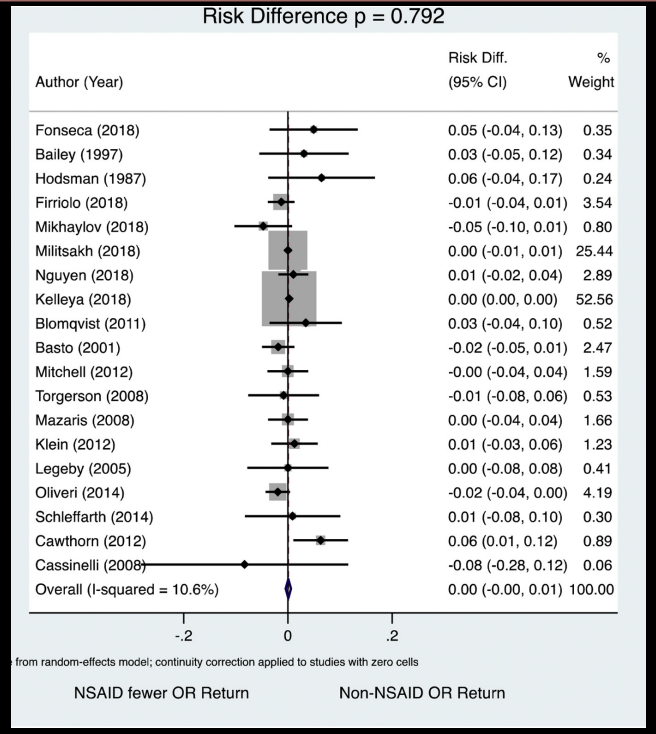
Hematomas



No difference NSAID vs Non NSAID

I^2 = 19.5%, p = 0.157

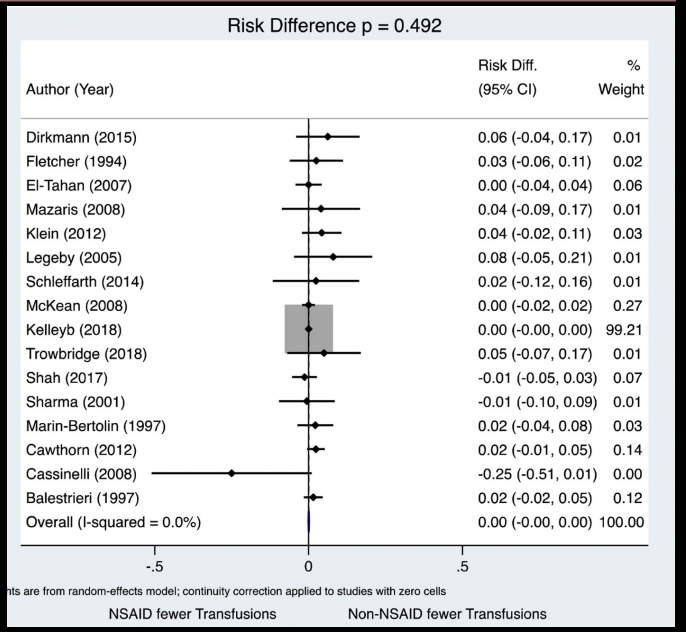
Return to Operating Room



No difference NSAID vs Non NSAID

I^2 = 10.6%, p = 0.318

Blood Transfusions



No difference NSAID vs Non NSAID

I^2 = 19.5%, p = 0.157

Begg's test performed for each individual meta-analysis = no evidence of bias for any of the outcomes

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Bongiovanni T, Lancaster E, Ledesma Y et al. Systematic Review and Meta-Analysis of the Association Between Non-Steroidal Anti-Inflammatory Drugs and Operative Bleeding in the Perioperative Period. *J Am Coll Surg.* 2021; 232:765-790.

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and NSAIDs 2020

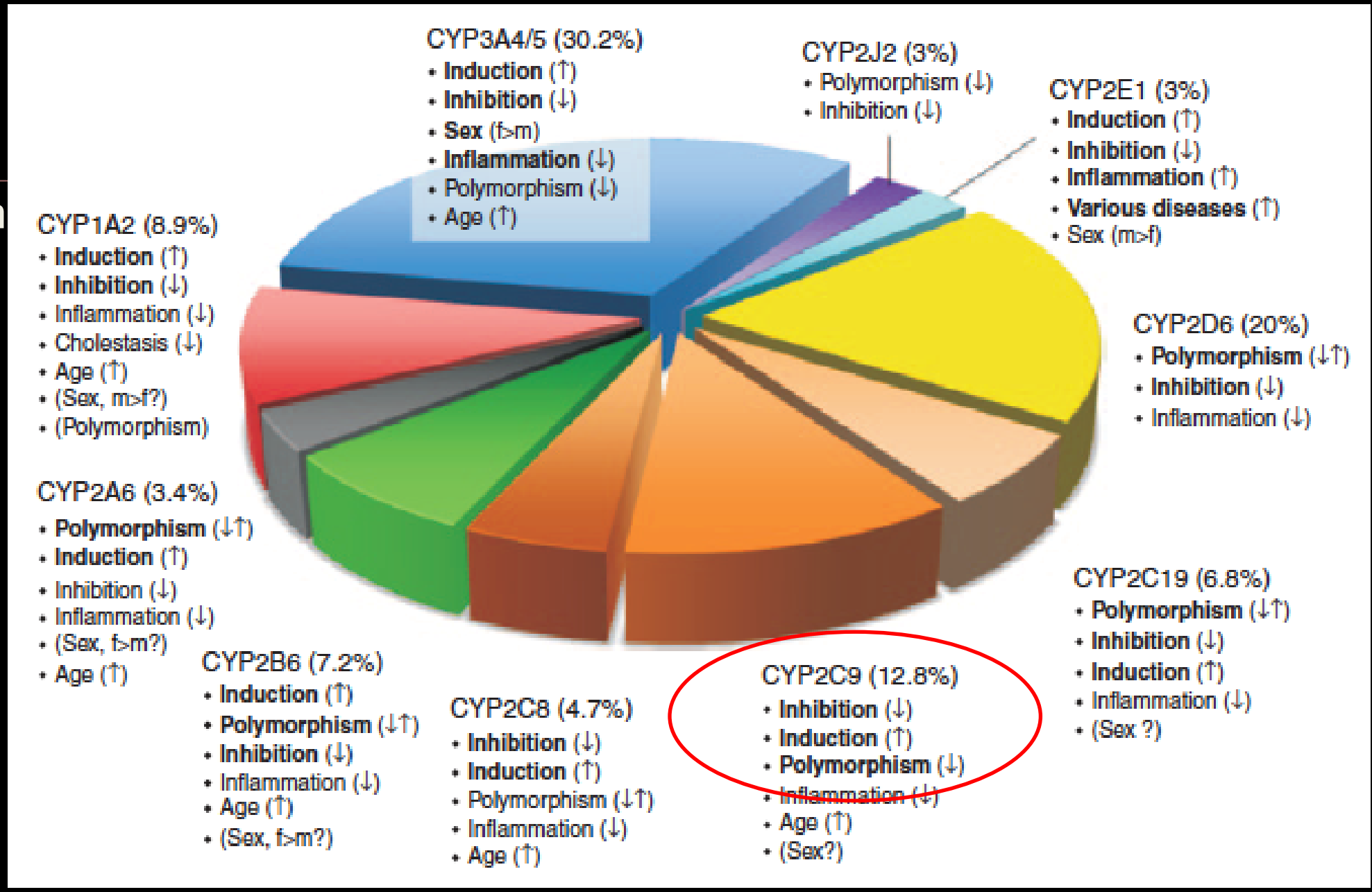
Updates on NSAID Pharmacogenetics

CYP450 Metabolism

- 3A4 (30.2%)
- 2D6 (20%)
- 2C9 (12.8%)

Polymorphism

- 2D6
- 2C19
- 2C8
- 2B6



CYP 450

Ultra Rapid Metabolizer (UM)
- High enzyme activity

Extensive (Normal) Metabolizer (EM)
- Normal enzyme activity

Intermediate Metabolizer (IM)
- Reduced enzyme activity

Poor Metabolizer (PM)
- Dysfunctional or minimal activity

CYP2C9

CYP2C9 is located in cluster of CYP2C genes on chromosome 10
- (CYP2C18, CYP2C19, CYP2C9, CYP2C8)

CYP2C9 Functional Allele Groups
- CYP2C9*1 – Normal function
- CYP2C9*2, *5, *8, *11 – Decreased function
- CYP2C9*3, *6, *13 – No function

CYP2C9*2 has strong linkage disequilibrium with CYP2C8*3
- 80% of individuals carrying CYP2C9*2 also carry CYP2C8*3
- Clinically relevant for NSAIDs that are substrates of both CYP2C8/CYP2C9

Intermediate and Poor Metabolizers of CYP2C9 predisposed:
- Serious bleeding with warfarin
- Increased risk of phenytoin-related toxicities

Theken K, Lee C, Gong L et al. Clinical Pharamcogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. *Clin Pharmacol Therapeutics.* 2020; 108(2):191-200.

NSAID Metabolism and Pharmacogenetic Relevance

NSAID	NSAID Chemical Class	$T_{1/2}$ (h)	Metabolism (Major)	Metabolism (Minor)	PM ↑ Levels	IM ↑ Levels	Relevant
Ibuprofen	Arylpropionic acid	2-4	CYP2C9 (~50%)	CYP2C8	Yes	Yes	Yes
Naproxen	Arylpropionic acid	12-15	Glucuronidation (~60%)	CYP2C9 (~20%)	No	No	No
Diclofenac	Heteroaryl acid	1-2	Glucuronidation (~80%)	CYP2C9 (~20%)	No	No	No
Meloxicam	Enolic acid	15-20	CYP2C9 (40-60%)	CYP3A4	Yes	Yes	Yes
Piroxicam	Enolic acid	30-86	CYP2C9 (~50%)		Yes	Yes	Yes
Indomethacin	Indole & Indene acetic acid	4-6	CYP2C9 (~50%)	Glucuronidation (~20%)	Yes	No	Yes
Sulindac	Indole & Indene acetic acid	7	CYP1A2	CYP3A4	No	No	No
Celecoxib	Diaryl-substituted Pyrazoles	11-16	CYP2C9 (70-90%)	CYP3A4	Yes	No	Yes

$T_{1/2}$ = half-life; PM = Poor Metabolizer; IM Intermediate Metabolizer

CYP 2D6 Phenotypic Expression by Ethnicity

CYP 2D6 Phenotypes	African (%)	Caucasian (%)	Middle Eastern (%)	East Asian (%)	South/Central Asian (%)	Oceanian (%)
Ultrarapid Metabolizer	4.5	3.2	11.1	1.1	2.8	20.5
Normal Metabolizer	71.2	76.8	74.4	85.4	88.5	76.7
Intermediate Metabolizer	12.5	6.9	5.6	8.8	6.9	1.8
Poor Metabolizer	1.9	6.1	1.2	0.9	1.5	0.5

Indeterminate phenotype not included

Source: https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/

CYP 2C9*2 & CYP2C8*3
Linkage Disequilibrium Across Populations

CYP 2C Allele Frequency	CYP2C9*2 (%)	CYP2C8*3 (%)
American Superpopulation	9.9	9.9
Puerto Rican	13.9	14.4
Columbian	12.2	11.7
Mexican	10.1	10.1
Peruvian	2.3	2.3
European Superpopulation	12.4	11.8
Italian	15.4	15.4
North and Western European	15.1	15.1
British	8.7	9.3
Finnish (Finland)	8.1	8.1
Spain	14.0	14.9

CYP 2C Allele Frequency	CYP2C9*2 (%)	CYP2C8*3 (%)
African Superpopulation	0.8	0.8
East Asian Superpopulation	0.1	0.1
Chinese	0.0	0.0
Japanese	0.0	0.0
Vietnamese	0.0	0.0
South Asian Superpopulation	3.4	2.9
Indian	4.8	3.8
Pakistani	5.2	4.6
Bengali (Bangladesh)	1.7	1.7
Sri Lankan	2.9	1.9

To heal or not to heal? That is the question!

Updates on NSAIDs and Bone Healing

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Remember This?

A Medical Madoff: Anesthesiologist Faked Data in 21 Studies

A pioneering anesthesiologist has been implicated in a massive research fraud that has altered the way millions of patients are treated for pain during and after orthopedic surgeries

March 10, 2009 |By Brendan Borrell

Over the past 12 years, anesthesiologist Scott Reuben revolutionized the way physicians provide pain relief to patients undergoing orthopedic surgery for everything from torn ligaments to worn-out hips. Now, the profession is in shambles after an investigation revealed that at least 21 of Reuben's papers were pure fiction, and that the pain drugs he touted in them may have slowed postoperative healing.

Some evidence in animal studies, but not currently in human studies….or is there?

Available at: http://www.scientificamerican.com/article/a-medical-madoff-anesthestesiologist-faked-data/

Bone Healing

- Controversial among surgeons
- Proposed MOA: Prostaglandins may play a critical role in bone metabolism and healing. PGE_2 may control osteoblast behavior through receptors that are regulated by cyclooxygenase (COX) enzymes
- 100,000 fractures result in nonunion each year in the U.S.
- Multifactorial
  - Nonmodifiable risk factors:
    - Age, sex, fracture location, fracture characteristics, pre-existing patient co-morbidities
  - Modifiable risk factors:
    - Alcohol/tobacco consumption, nutritional status, bisphosphonates, and NSAIDs

Wheatley B, Nappo K, Christensen D et al. Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. *J Am Acad Ortho Surg.* 2019; 27:e330-e336.

A Meta-analysis in 2019

- 4,341 studies screened → 26 studies considered → 16 studies in final analysis
- Pooled analysis of 15, 242 bones
  - 3,283 exposed to NSAIDs
  - 11,959 not exposed
- 226/512 cases were exposed to NSAID (All cases)
  - Odds Ratio 2.07 (1.19 to 3.61)
- 13/37 cases were exposed to NSAIDs (Pediatric)
  - Odds Ratio 0.58 (0.27 to 1.21)
- 213/475 cases were exposed to NSAIDs (Adult)
  - Odds Ratio 2.93 (1.61 to 5.33)
- Age significantly associated with nonunion when exposed to NSAIDs

Wheatley B, Nappo K, Christensen D et al. Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. *J Am Acad Ortho Surg.* 2019; 27:e330-e336.

Drilling Down

- 6 Studies of long bones totaling 12,030 bones
  - 89/328 cases were exposed to NSAIDs
    - Odds Ratio 2.34 (1.12 to 4.90)
- 5 Studies of spine included 1,127 patients
  - 106/125 cases were exposed to NSAIDs
    - Odds Ratio 4.90 (1.45 to 16.58)
    - Metaregression did not suggest a significant difference
- 4 studies of low dose/short duration involving 1,109 bones
  - 52/98 cases were exposed to NSAIDs
    - Odds Ratio 1.68 (0.63 to 4.46)
    - Does not markedly increase risk

Wheatley B, Nappo K, Christensen D et al. Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. *J Am Acad Ortho Surg.* 2019; 27:e330-e336.

A New Meta-analysis in 2020

- Confirms nonunion risk in tibia fracture (long bone)
  - 111 studies involving 41,429 patients

Found 15 significant risk factors for nonunion:

- Age > 60 YO
- Male
- Tobacco smoker
- BMI > 40
- Diabetes
- NSAID use
- Opioid use
- Middle or distal tibia fracture
- High-energy fracture
- Open fracture
- Open reduction
- Fixation model
- Infection
- Gustilo-Anderson grade IIIB or IIIC
- Muller AO Classification of fractures C

Tian R, Zheng F, Zhao W et al. Prevalence and influencing factors of nonunion in patients with tibial fracture: systematic review and meta-analysis. *J Ortho Surg Res.* 2020; 15:377.

Spinal Fusion

- NSAIDs appear to have a dose and duration dependent effect on fusion rates[1]
  - Short duration or low dose no significant impact on fusion
    - 48 hours
- Pseudoarthrosis after thoracolumbar posterolateral fusion[2]
  - Ketorolac has dose and duration dependent effect
    - >2 days Odds Ratio 3.44 (1.87 to 6.36)
    - Doses ≥ 120mg/day Odds Ratio 2.93 (1.06 to 8.12)
  - Ketorolac use in smokers was associated with much higher rate of pseudoarthrosis
    - Odds Ratio 8.71 (2.23 to 34.0)

1. Sivaganesan A, Chotai S, White-Dzuro G et al. The effect of NSAIDs on spinal fusion: a cross-disciplinary review of biochemical, animal, and human studies. *Eur Spine J.* 2017: 26:2719-2728.
2. Li J, Ajiboye R, Orden M et al. The Effect of Ketorolac on Thoracolumbar Posterolateral Fusion. *Clin Spine Surg.* 2018; 31:65-72.

Guideline Updates


Low Back Pain

Evidence Map

Chronic Low Back Pain

Pharmacologic

2nd Line

NSAIDs

Tramadol

Strong Opioids

Duloxetine

Buprenorphine Patch

Active

1st Line

Yoga

Tai Chi

Exercise

MCE

Passive

1st Line

Acupuncture

Massage

LLLT

Spinal Manipulation

1st Line

Psychological

Progressive Relaxation

CBT

Biofeedback

Mindfulness-Based Stress Reduction

Qaseem A, Wilt T, Mclean R et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2017; 166:514-530.

Pharmacology & Psychology Treatment of Chronic Low Back Pain

NSAIDs: No difference in pain relief between NSAIDs. No data on COX-2 vs traditional NSAIDs.

Duloxetine:
No difference between TCAs and SSRIs. Only duloxetine had evidence of benefit for pain and function.

Progressive Relaxation:
Compared against wait list controls rather than placebo control group.

Buprenorphine patch:
Consider advantages of dosage form in higher risk patients.

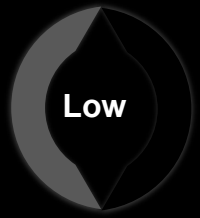
Strong Opioids:
No differences between long-acting opioids. No difference between IR vs ER opioids.

Tramadol:
2nd line pharmacologic option prior to consideration of stronger opioids.

Cognitive Behavioral Therapy:
Combined with other psychological modalities and compared against wait list controls. No benefit for function.

Biofeedback:
Electromyography biofeedback compared against wait list controls. No benefit for function.

Mindfulness-based Stress Reduction:
Benefit persists up to 6-12 months. One study showed no difference between MBSR and CBT.



Quality of Evidence

Moderate Effect Size:
2-5 points on RDQ

Moderate Effect Size:
1-2 points on NRS

Small Effect Size:
1-2 points on RDQ

Small Effect Size:
0.5-1 points on NRS

Slight Effect Size:
0-1 points on RDQ

Slight Effect Size:
0-0.5 points on NRS

Function Effect Size: A mean between group difference on the Roland-Morris Disability Questionnaire scale (0 -11)

Pain Effect Size: A mean between group difference on a numeric rating scale (0 -10)

Qaseem A, Wilt T, Mclean R et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2017; 166:514-530.

Osteoarthritis Guidelines

	American College of Rheumatology (ACR)	Osteoarthritis Research Society International (OARSI)
Hip Osteoarthritis	▪ 1st Line: Oral NSAIDs ▪ 2nd Line: Topical NSAIDs	▪ 1st Line: Oral NSAIDs
Knee Osteoarthritis	▪ 1st Line: Topical NSAIDs ▪ 2nd Line: Oral NSAIDs	▪ 1st Line: Topical NSAIDs ▪ 2nd Line: Oral NSAIDs
Hand Osteoarthritis	▪ 1st Line: Oral NSAIDs ▪ 2nd Line: Topical NSAIDs	

PAINWEEK®

Kolasinski S, Neogi T, Hochberg M et al. 2019 ACR/Arthritis Foundation guideline for Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care & Research.* 2020. 72(2):149-162.
Bannuru R, Osani M, Vaysbrot E et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis & Cartilage.* 2019;(27):1578-1589.

Osteoarthritis Guidelines

American College of Rheumatology (ACR)

- "Unless otherwise specified, recommendations regarding physical therapy, psychosocial, and mind-body approaches assume the patient will be adding the intervention to usual care"
- "Usual care includes the use of maximally recommended or safely tolerated doses of over-the-counter NSAIDs and/or acetaminophen, as has generally been explicitly permitted in clinical trials of nonpharmacologic interventions"

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Kolasinski S, Neogi T, Hochberg M et al. 2019 ACR/Arthritis Foundation guideline for Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care & Research.* 2020. 72(2):149-162.

NSAIDs in Guidelines

NSAIDs are recommended as 1st line Pharmacotherapy for the treatment:

- Endometriosis
- Axial spondyloarthropathy
- Psoriatic Arthritis
- Gout
- Polymyositis
- Tendonitis
- Bursitis
- Diffuse Idiopathic Skeletal Hyperostosis (DISH)
- Inflammatory Bowel Disease (remission)
  - Short-term use, lower doses safer
  - Long-term use in active disease may worsen
- Kawasaki Disease (aspirin)
- Paget's Disease
- Reactive Arthritis

NSAID Pearls of Prevention

NSAIDs have been shown to prevent or improve

Aspirin (ASA)

- Fracture risk (ASA) ↑BMD
- Breast Cancer (ASA)
- Colorectal cancer
  - –Improves overall survival
- Bile Duct Cancer
- Gastric Cancer

NSAIDs

- Bipolar Disorder
  - –Celecoxib improves mania scores
- Dementia
  - –Long-term NSAID use (>6 years)
- Amyotrophic lateral sclerosis (ALS)
  - –NSAIDS & APAP reduced risk of ALS
- Psychotic Disorders
  - –Only as adjunct treatment; alone not significant
- Gastric Cancer

Zheng W et al. J Psychiatric Research. 2017; 92:139-146.
Huang X et al. Oncotarget. 2017; 8(3):4781-4795.
Veettil S et al. BMC Cancer. 2017; 17:763.
Veettil S et al. BMC Gastroenterol. 2021; 21:130.
Lapumnuaypol K et al. QJM. 2019; 421-427.
Bavaresco D et al. CNS & Neurological Disorders. 2019;18.

Lin J et al. BMC Cancer. 2020; 20:638.
Jeppesen R et al. Brain, Behavior, and Immunity. 2020; 90:364-380.
Fortuni F et al. Eur J Prev Cardiology. 2019; 26(15):1677-1679.
Chang M et al. Nature Research. 2020; 10:14759.

Chang K et al. Medicine. 2016; 95(10):e3056.
Cao Y et al. Medicine. 2020; 99:38.
Barker A et al. BMJ Open. 2020: 10:e026876.

Conclusions

- New NSAID formulations provide strategic therapeutic options
- NSAID risk of perioperative bleeding is low, expect use to increase
- NSAID Pharmacogenetics provide insight into NSAID-related adverse effects
- NSAIDs impact long bone healing and increase risk of nonunion
- NSAIDs guideline recommendations are increasing
- NSAIDs appear to prevent or reduce incidence of some types of cancer or severity of psychiatric illness but data is weak and requires additional study.

NSAID Counterattack, Baby We're Back!

Questions?

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