# Use and Complications of NSAIDs

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# Objectives

- Better understand mechanism of action for NSAIDs
- Gain enhanced understanding of NSAID use
- Improve familiarity with complications of NSAIDs

# NSAID Pharmacology

# What is an NSAID?

- Non steroidal Anti-inflammatory Drugs
- Weak organic acid
- Binds to serum proteins (albumin)
- Generally have low ionization constant ($pK_a$)[1]
  - Causing binding to sites of inflammation
    - e.g. inflamed joints have lower pH than normal joints
- Main anti-inflammatory properties due to inhibition of prostaglandin synthesis by blocking the enzyme prostaglandin G/H synthase (PGHS) also called cyclooxygenase (COX)[2]

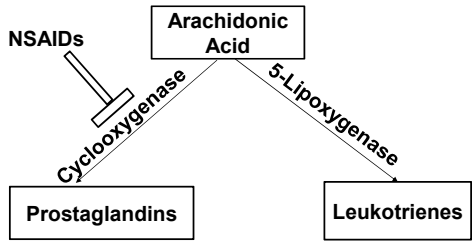
1.West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015
2.Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

# Effects of NSAIDs

- **Analgesia**
- **Antiinflammatory**
- **Antipyresis**
- **Antiplatelet**
  - **inhibit COX-1 thus preventing thromboxane $A_2$ ($TXA_2$) production to decrease platelet aggregation**

West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

# Mechanism of Action




Adapted from: . "Nonnarcotic Analgesics and Anti-inflammatory Drugs." *Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5e* Stringer JL. Stringer J.L. Ed. Janet L. Stringer. New York, NY: McGraw-Hill, , http://accessmedicine.mhmedical.com/content.aspx?bookid=2147&sectionid=161352578.

# COX isoforms

| COX-1 | COX-2 |
|---|---|
| Found in most tissues | Brain, kidney, sites of inflammation |
| Present in Platelets | Not in platelets |

**Theoretical GI safety for COX-2**

**Theoretical no bleeding risk for COX-2**

"Nonnarcotic Analgesics and Anti-inflammatory Drugs." *Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5e* Stringer JL. Stringer J.L. Ed. Janet L. Stringer. New York, NY: McGraw-Hill, , http://accessmedicine.mhmedical.com/content.aspx?bookid=2147&sectionid=161352578.

# NSAID Classes

| Salicylate acetylated | Salicylate non-acetylated | Propionic Acids | Enolic Acids |
|---|---|---|---|
| Aspirin | Diflunisal | Naproxen | Meloxicam |
| | Choline Magensium Trisalicylate | Ibuprofen | Piroxicam |
| | Salsalate | Ketoprofen | |
| | | Flubiprofen | |
| | | Oxaprozin | |

# NSAID Classes

| Acetic Acids | Anthranilic Acids | Nonacidic | Selective Cox 2 inhibitors |
|---|---|---|---|
| Diclofenac | meclofenamate | nabumatone | Celecoxib |
| Etodolac | Mefanamic acid | | Etorcoxib (not available in USA) |
| Indomethacin | | | |
| Sulindac | | | |
| Tolmetin | | | |

# Class Chemistry

- **All NSAIDs inhibit the COX active site.**
- **Variances in how the NSAIDs interact and bind with the active site result in pharmacologic differences**

# Aspirin in its' own class

**Aspirin**

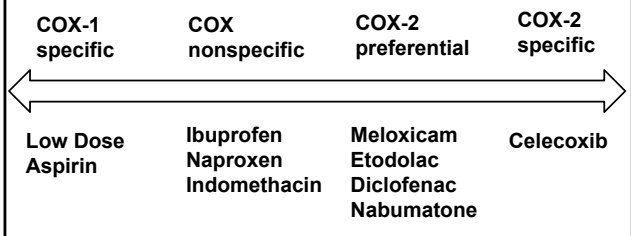
- **Covalent, irreversible binding of COX-1 and COX-2**
- **10 to 100 fold less affinity for COX-2 due to larger active site on COX-2**

**Other NSAIDS**

- **Competitive inhibitors, competing for arachidonic acid for binding in the active site**

1.Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.
2. Spite M et al. Novel Lipd mediators promote resolution of acute inflammation: impact of aspirin and statins. Circ Res. 107:1170-1184. 2010

# COX selectivity




West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

## $PGE_2$ Inibition by NSAIDs

- $PGE_2$ is the most abundant Prostaglandin (PG) at sites of inflammation[1]
- Microsomal PGE synthase-1 (mPGES-1) acts in concert with COX-2 to produce high levels of $PGE_2$ during inflammation[2]
- NSAIDs block mPGES-1

1. Hara S, et al. Prostgalndin E synthases: understanding their pathophysiological rolees thorugh mouse generic models. Biochemi 92:651-659, 2010
2. 2.Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

## cAMP Decreased by NSAIDs

- Can inhibit phosphodiesterases which lead to increased cAMP levels resulting in inhibition of:
  - peripheral blood lymphocyte response to mitogen stimulation
  - Monocyte and neutrophil migration
  - Neutrophil aggregation

Tegeder, I, et al. Cyclooxygenase-independent action of cyclooxygenast inhibitors, FASEB J 15:2057-2072, 2001

## More NSAID actions

- Scavenge free radicals
- Inhibit superoxide production by PMNs
- Reduce mononuclear cell phospholipase C activity
- Inhibit inducible nitic oxide synthase activity
- Aspirin and salicylate inhibit NFκB activation
- Bind to and activate members of the peroxisome proliferator-activated receptor (PPAR) family

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

## NSAID metabolism

- Hepatically biotransformed
- Renally eliminated
  - NSAIDs not dialyzable due to plasma binding
    - Except for salicylic acid[1]
- Genetic variation in metabolizing enzymes and variability in intestinal microbiota effect metabolism and excretion[1]
- Cross Blood brain barrier[2]

1. Grosser, Tilo, et al.. "Pharmacotherapy of Inflammation, Fever, Pain, and Gout." Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e Brunton LL, Hilal-Dandan R, Knollmann BC. Brunton L.L., Hilal-Dandan R, Knollmann B.C. Eds. Laurence L. Brunton, et al. New York, NY: McGraw-Hill, . http://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=170271972.
2. Rella, Joseph G., and Wallace A. Carter.. "Nonsteroidal Anti-Inflammatory Drugs." Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8e Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Cline DM. Tintinalli J.E., Stapczynski J, Ma O, Yealy D.M., Meckler G.D., Cline D.M. Eds. Judith E. Tintinalli, et al. New York, NY: McGraw-Hill, 2016, http://accessmedicine.mhmedical.com/content.aspx?bookid=1658&sectionid=109414780.

# NSAID Absorption

- **2-3 hours to reach Peak Plasma Concentrations**
- **Antacids may delay absorption**

**Grosser, Tilo, et al.. "Pharmacotherapy of Inflammation, Fever, Pain, and Gout." *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e* Brunton LL, Hilal-Dandan R, Knollmann BC. Brunton L.L., Hilal-Dandan R, Knollmann B.C. Eds. Laurence L. Brunton, et al. New York, NY: McGraw-Hill, , http://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=170271972.**

# Basic Principles of NSAID Use

# NSAID Classes

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# NSAID Classes

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| Indomethacin | | | |
| Sulindac | | | |
| Tolmetin | | | |

- **Generally start at low doses, then titrate up**
- **2 week drug trials[1]**
- **If drug failure switch to alternate class**

**1. Smuggr SS, et al. Early response to COX-2 inhibitors as a predictor of overall response in osteoarthritis: pooled results from two identical trials comparing etoricoxib, celecoxib and placeboRheumatology (Oxford). 2009;48(9):1122.**

# Monitoring

- When starting chronic NSAIDs
  - Recommend checking kidney and liver function within first few months
- For chronic uses at least once yearly:
  - BUN/Creatinine
  - Liver Function Tests
  - CBC

# Comorbidities which Restrict NSAID use

- Cardiovascular disease
  - Coronary artery disease
  - Myocardial infarction
  - Stroke
- Chronic Kidney Disease Stage IV-V
- Aspirin Exacerbated Respiratory disease (AERD)
- Peptic Ulcer Disease

Solomon, Daniel. NSAIDs: Therapeutic use and variability of response in adults https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults?search=nsaid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed Jan 1, 2018.

# Perioperative Management

| | Half life (hours) | Withdrawal Preoperatively |
|---|---|---|
| Ibuprofen | 1.6-1.9 | 10 hours |
| Naproxen | 12-15 | 3 days |
| Indomethacin | 4.5 | 1 day |
| Diclofenac | 2 | 10 hours |
| Celecoxib | 11 | Continue dose |

Adapted from: Connelly CS, Panush RS. Should nonsteroidal anti-inflammatory drugs be stopped before elective surgery. Arch Intern Med. 1991;151((10)):1963–6.

# Perioperative Management

- Continue Aspirin if being used for Cardiovascular prevention[1]
- No changes in bleeding in Carotid Endarterectomy[2]
- Postoperative hematomas were not significantly increased in cholecystectomy, appendectomy, open or laparoscopic inguinal hernia repair, liver surgery and hip and knee arthroscopy[3-5]


1. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141((2 Suppl)):e326S–50S.
2. Tytgat SHAJ, Laman DM, Rijken AM, Klicks R, Voorwinde A, Ultee JM, et al. Emboli rate during and early after carotid endarterectomy after a single preoperative dose of 120 mg acetylsalicylic acid–a prospective double-blind placebo controlled randomised trial. Eur J Vasc Endovasc Surg. 2005 Feb;29((2)):156–61
3. Oscarsson A, Gupta A, Fredrikson M, Järhult J, Nyström M, Pettersson E, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth. 2010;104((3)):305–12.
4. 4Ong W, Shen T, Tan WB, Lomanto D. Is preoperative withdrawal of aspirin necessary in patients undergoing elective inguinal hernia repair. Surg Endosc. 2016;30((12)):5542–9.
5. Ferraris VA, Swanson E. Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. Surg Gynecol Obstet. 1983;156((4)):439–42.

# Perioperative Management

- NSAIDs may prevent heterotopic ossification (HO) post arthroplasty
- HO more common in Ankylosing spondylitis and psoriatic arthritis
- Indomethacin 75-100 mg/d or celecoxib 400 mg/d recommended ideally 24-48 hours post op and continued for 20 days


1. Slappendel R, Weber EW, Benraad B, Dirksen R, Bugter ML. Does ibuprofen increase perioperative blood loss during hip arthroplasty. Eur J Anaesthesiol. 2002;19((11)):829–31.
2. Kienapfel H, Koller M, Wüst A, Sprey C, Merte H, Engenhart-Cabillic R, et al. Prevention of heterotopic bone formation after total hip arthroplasty: a prospective randomised study comparing postoperative radiation therapy with indomethacin medication. Arch Orthop Trauma Surg. 1999;119((5–6)):296–302.
3. 3. Iorio R, Healy WL. Heterotopic ossification after hip and knee arthroplasty: risk factors, prevention, and treatment. J Am Acad Orthop Surg. 2002;10((6)):409–16.
4. Franco As et al. Perioperative management of drugs commonly used in patients with rheumatic diseases: a review. Clinics (sao Paulo) 2017 Jun; 72(6): 386–390.


# Obstetric Management

- May interfere with ovulation and implantation
- May result in premature closure of the patent ductus arteriosus.
- Recommendations:
  - Avoid NSAIDs after 30 weeks of gestation
  - Limited Data with lactation
    - Ibuprofen is only secreted in small amounts in breast milk


Bermas, Bonnie, Safety of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation. https://www-uptodate-com.proxy.lib.ohio-state.edu/contents/safety-of-antiinflammatory-and-immunosuppressive-drugs-in-rheumatic-diseases-during-pregnancy-and-lactation?sectionName=NSAIDs&anchor=H7&source=see_link#H7 Accessed January 1, 2018


# Management in Elderly

- More likely to experience CV and GI effects
- More likely to have drug-drug interactions given higher likelihood of polypharmacy
- More likely to make dosing errors


Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.


# Topical NSAIDs

## Topical NSAIDs

- Recommended for knee osteoarthritis (OA)
  - American Association of Orthopaedic Surgeons (AAOS) 2013[1]
  - American College of Rheumatology (ACR) 2012[2]
  - European League Against Rheumatism (EULAR) 2003, 2007[3,4]
  - National Institute for Health and Clinical Excellence (NICE, United Kingdom) 2008 [5]
  - Osteoarthritis Research Society International (OARSI) 2008[5]
- Recommended for hand OA
  - ACR[2]
  - EULAR[3,4]
  - NICE[4]
- Recommended for localized pain
  - American Geriatric Society (AGS) 2009[6]
  - American Pain Society (APS) 2002[7]
  - NICE[4]

## Systemic bioavailability of topical NSAIDs

- 3 way cross over study 39 healthy volunteers received three 7-day diclofenac regimens:
  - (A) 16 g gel applied as 4 g to 1 knee 4 times daily (4 g on surface area 400 $cm^2$)
  - (B) 48 g gel applied as 4 g per knee 4 times daily to 2 knees plus 2 g gel per hand applied 4 times daily to 2 hands (12 g on 1200 $cm^2$)
  - (C) 150 mg oral diclofenac applied as 50-mg tablets 3 times daily.

Kienzler JK, Gold M, Nollaveaux. Systemic Bioavailability of Topical Diclofenac Sodium Gel 1% Versus Oral Diclofenac Sodium in Healthy Volunteers. The Journal of Clinical Pharmacology. Volume 50, Issue 1January 2010 Pages 50–61

## Systemic bioavailability of topical NSAIDs

| | 16 g | 48 g | oral |
|---|---|---|---|
| Systemic exposure | $AUC_{0-24}$, 233 ± 128 ng·h/mL | $AUC_{0-24}$, 807 ± 478 ng·h/mL | $AUC_{0-24}$, 3890 ± 1710 ng·h/mL |

- Topical diclofenac did not inhibit platelet aggregation and inhibited COX-1 and COX-2 less than oral diclofenac.
- Treatment-related adverse events were mild and limited to application site reactions with diclofenac sodium gel 1% (n = 4) and gastrointestinal reactions with oral diclofenac (n = 3).

Kienzler JK, Gold M, Nollaveaux. Systemic Bioavailability of Topical Diclofenac Sodium Gel 1% Versus Oral Diclofenac Sodium in Healthy Volunteers. The Journal of Clinical Pharmacology. Volume 50, Issue 1January 2010 Pages 50–61

## NSAID Complications

# Big 3 complications

- Gastrointestinal
- Renal
- Cardiovascular

# GI Complications

# Injuries to Gastric mucosa

- NSAIDs may disrupt the gastric epithelial cell barrier causing mucosal erosions
- PG depletion perpetuates the development of clinically significant ulcerations[1]
- pKa important in determining risk of topical injury
  - Aspirin prone to mucosal injury
  - Nonacidic NSAIDs (nabumatone, etodolac, celexcoxib) not prone to acute mucosal lesions

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

# Dyspepsia

- 10-20% of NSAID users[1]
- Present even amongst COX-2 selective NSAIDs[1]
- Improved with Proton pump inhibitors (PPI)[2]
- Improved with histamine-2-receptor antagonists ($H_2$RAs)[3]

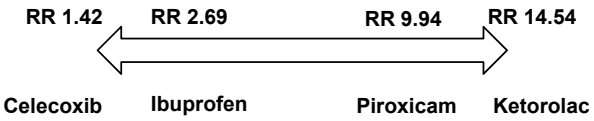

1. Strauss WI etl al. Do NSAIDs cause dyspepsia? A meta-analysis evaluating alternative dyspepsia dfefinitions. Am J Gastroeneterol 97:1951-1958.2002
2. Hawkey CJ et al. Maintenance treatment with esomeprazole following initial relief of non-steroidal anti-inflammatory drug-associated upper gastrointestinal lsymptoms: the NASA@ and SPACE2 studies, Arthritis Res Ther 7:R17, 2007
3. Velduyzen van Zanten SJ et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in Helicobacter pylori negative, pirimary care patients with dyspepsia: the CADET-HN study, Am J Gastroenterol 100:1477-1488,2005

# Gastritis and Gastroduodenal Ulcer

- Risk highest in first 3 months[1]
- Risk is dose dependant[2]
- RR 4.5 (95% CI, 3.82 to 5.31) for traditional NSAIDs
- RR 1.88 (95% CI, 0.96 to 3.71) for selective COX-2 inhibitors[2]


1. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.
2. 2. Masso Gonzalaez EL et al. Variability among nonsteroidal anti-inflammatory drugs in risk of upper gastrointestinal bleeding, arthritis rheum 62:1592-1601, 2010


# Outliers in GI risks





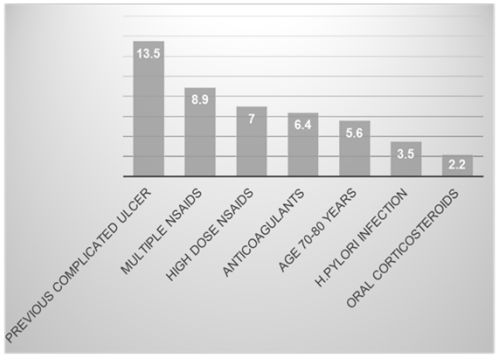
. Masso Gonzalaez EL et al. Variability among nonsteroidal anti-inflammatory drugs in risk of upper gastrointestinal bleeding, arthritis rheum 62:1592-1601, 2010


# Risk Factors for NSAID-Induced GI Bleeding and perforation

- Previous peptic ulcer disease
- Previous GI bleed
- Previous hospitalization for GI disease
- History of NSAID-induced gastritis or dyspepsia
- Use of H2 blocker or antacid for dyspepsia
- Concurrent steroid use
- Older age
- History of CV disease
- Smoking
- Alcoholism

Adapted from Bolware, DW and Heduebert GR. Lippinocott's Primary Care rheumatology. Lipincott Williams and Wilkens. 2013. Page282

# Adjusted RR (OR)





Adapted from
1. Gutthann Sp et al. Individiual non-steroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation, Epidemiology 8:19-24, 1997.
2. 2. huang JQ, Sridhar S, et al Role of Helicobacter pylori infeciout and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta analysis, Lancet 359:14-22, 2002.
3. 3. Lanas A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclooxygenase-2 inhibitors, tradictional no-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations, Gut 55:1731-1738, 2006
4. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

# Combination Drugs

| | |
|---|---|
| Arthrotec | Diclfoenac and misoprostol |
| Vimovo | Naproxen and Esomeprazole |
| Duexis | Ibuprofen and Famotadine |

- **Arthrotec more effective at reducing hospitalization for PUD or GI hemorrhage compared to coprescription[1]**

1. Ashworth NL et al. Risk of hospitalization with peptic ulcer disease or gastrointestinal hemorrhage associated with nabumatone, arthrotec, diclofenac, and naparoxen in a population based cohort study, J rheumatol 32:2212-2217, 2005.

# GI Risks: Small Intestine

- **Short-term NSAIDs medication associated with small intestinal injuries in 50% to 70% of subjects[1-3]**
- **NSAID Suppression of prostaglandin synthesis renders the intestinal mucosa more susceptible to injury and less efficient in undergoing repair[4-5]**
- **Gram negative bacteria suppression with a PPI could exacerbate NSAID-induced small intestinal damage[6]**

1. Graham DY, Opekun AR, Willingham FF, et al. Visible smallintestinal mucosal injury in chronic NSAID users. Clin Gastroenterol Hepatol. 2005;3:55–59
2. Goldstein JL, Eisen GM, Lewis B, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol. 2005;3:133–141
3. Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Ther. 2007;25:1211–1222
4. B.K. Reuter, N.M. Davies, J.L. WallaceNonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation Gastroenterology, 112 (1997), pp. 109-117
5. A. Tanaka, S. Hase, T. Miyazawa, *et al*.Up-regulation of cyclooxygenase-2 by inhibition of cyclooxygenase-1: a key to nonsteroidal anti-inflammatory drug-induced intestinal damage J Pharmacol Exp Ther, 300 (2002), pp. 754-761
6. Wallace JL, Syer S, Denou E, et al. Proton Pump Inhibitors Exacerbate NSAID-Induced Small Intestinal Injury by Inducing Dysbiosis. Gastroenterology, 141 (2011), Pages 1314-1322.e5

# GI Risks: Small Intestine

- **Video Capsule endoscopy (VCE) studies:**
- **After 2 week treatment in healthy volunteers mucosal break rates:**
  - **16% (18/115) celecoxib 200 mg BID**
  - **55% (61/111) naproxen 500 mg BID + omeprazole 20 mg daily**
  - **7% (8/113) of placebo[1]**
- **After 2 week treatment in healthy volunteers mucosal break rates:**
  - **6% (7/109) of celecoxib group 200 mg BID**
  - **26%(30/112) of ibuprofen 800 mg TID + omeprazole 20 mg**
  - **7%(8/113) of placebo group[2]**

1. Goldstein JL, Eisen GM, Lewis B, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol. 2005;3:133–141.
2. Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Ther. 2007;25: 1211–1222.

# GI risk: Large intestine

- **NSAIDs can cause colonic erosions, ulcers, hemorrhage, perforations, strictures.[1]**
- **Consider NSAID colonopathy in the differential for inflammatory bowel disease**

1. Hawkey CJ: NSAIDs, coxibs, and the intesting, J Cardiovasc Pharmacol 47:S72-S74, 2006

# Hepatotoxicity risks

- Up to 15% have reversible elevations in AST and ALT
- More likely with diclofenac
- Usually occurs in first 6 months of use
- Severe hepatitis has been reported with:
  - Indomethacin
  - Diclofenac
  - Sulindac

West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

# Renal Complications

# Renal effects

- PGs important to solute and renovascular homeostasis[1]
- COX-1 expressed in renal vasculature, glomerular mesangial cells, and collecting duct
- COX-2 expressed in vasculature, cortical thick ascending limb (cells in macula densa), medullary interstitial cells[2]
- COX-2 inhibition may result in apoptosis of medullary interstitial cells and result in papillary necrosis[3]

1. Rater DC: Anti-inflammatory agents and renal function, Semin Arthrtis Rheum 32:33-42, 200
2. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013
3. Brater DC et al. Renal effects of COX-2 selective inhibitors, Am J Nephrol 21:1-15, 2001

# Sodium Excretion

- PGs inhibit active transport of sodium in the thick ascending limb and the collecting ducts and increase renal water excretion by blunting the actions of vasopressin[1]
- Sodium retention reported in up to 25% of NSAID treated patients
  - More likely in those with heart failure or liver disease
- Consider if weight gain or peripheral edema

1. Brater DC et al. Renal effects of COX-2 seledtive inhibitors, Am J Nephrol 21:1-15:2001.

## Hypertension

- Average increase of mean arterial blood pressure 5 to 10 mm Hg
- NSAIDs may attenuate antihypertensives[1]
  - Diuretics
  - ACE inhibitors
  - Beta blockers
- NSAID treated patients may develop hyporeninemic hypoaldosteronism manifesting as type IV renal tubular acidosis[2]

1. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013
2. Brater DC et al. Renal effects of COX-2 selective inhibitors, Am J Nephrol 21:1-15, 2001.

## Acute Renal Failure

- Due to vasoconstrictive effects of NSAIDs
- Can be reversible
- More common in those with:
  - CHF
  - Cirrhosis
  - Renal insufficiency

Brater DC et al. Renal effects of COX-2 selective inhibitors, Am J Nephrol 21:1-15, 2001

## Chronic Kidney Disease

- Chronic aspirin or acetaminophe users have 2.5 times greater risk of developing CKD[1]
- No association between the use of non-aspirin NSAIDs and chronic renal failure detected after adjusting for aspirin and acetaminophe[1]

1. Fored CM eg atl. Acetaminophen, aspirin, and chronic renal failures. A nationwide case-control studyin sweden., N Engl j med 345:1801-1808, 2001.

## Cardiovascular Risks

# Cardiovascular Effects

- COX-1 isoform generates platelet $TXA_2$ which effects platelet aggregation and thrombus formation[1]
- $PGI_2$ is antithrombotic and blocked by COX-2 inhibition[2]

1. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013
2. Garcia Rodriguez LA, eet al. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-ontoinflammatory drugs in the general populations, J Am Coll Cardiol 52:1628-1636, 2008.

# Additional CV Effects

- NSAIDs effect:
  - Blood pressure
  - Endothelial function
  - Nitric oxide production
  - May interfere with Aspirin (particularly ibuprofen and naproxen)

1. Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis, BMJ 342:c7086, 2011.
2. FitzGerald GA: Coxibs and cardiovascular disease, N Engl j Med 351:1709-1711, 2004.
3. Harirforoosh S, et al. Extent of renal effect of cyclo-oxygenase-2-selective inhibitors is pharmacokinetic dependent, Clin Exp Pharmaocol Physiol 33:917-924, 2006
4. Garcia Rodriguez LA, eet al. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-ontoinflammatory drugs in the general populations, J Am Coll Cardiol 52:1628-1636, 2008.

# CV Risks

- All traditional and COX-2 selective NSAIDs associated with at least a 30% increase CV risk
  - Exception:
    - Naproxen[1]
    - Once daily dosing of Celecoxib[2]
- Dose and slow release formulation effect risk directly[1,3]

1. Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs network meta-analysis, BMJ 342:c7086, 2011.
2. Solomon SD et al. Cardiovascular risks of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis, Circulation 117:2105-2113, 2008
3. Garcia, Rodrigueze LA, et al: Role of dose potencty in the predictin of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general populations, J Am Coll Cardiol 52:1628-1636, 2008

# Withdrawal of COX-2 Drugs

- VIGOR trial showed adverse cardiovascular (CV) outcomes in a placebo-controlled trial resulted in the withdrawal of the selective COX-2 inhibitor rofecoxib in 2004[1]
- Celecoxib suggested to result in CV harm from use of higher doses, therefore the Food and Drug Administration (FDA) allowed continued marketing of celecoxib, but mandated a cardiovascular safety trial[2]
- Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) assessed CV, gastrointestinal (GI), renal, and other outcomes with celecoxib as compared with two nonselective NSAIDs.

1. Food and Drug Administration. FDA public health advisory: safety of Vioxx.September 30, 2004 (http://www .fda .gov/Drugs/ DrugSafety/ postmarketDrugSafetyInformationforPatientsandProviders/ucm106274 .htm).
2. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352: 1071-80.

# PRECISION trial

- **Inclusion: established cardiovascular disease (CVD) or an increased risk of the development of CVD**
- **24,081 patients Randomly assigned, in a 1:1:1 ratio, to receive celecoxib (100 mg twice a day), ibuprofen (600 mg three times a day), or naproxen (375 mg twice a day)**
- **For RA could increase the dose of celecoxib to 200 mg twice a day, the dose of ibuprofen to 800 mg three times a day, or the dose of naproxen to 500 mg twice a day**
- **Esomeprazole (20 to 40 mg) was provided to all patients for gastric protection**
- **low-dose aspirin (≤325 mg daily) was permitted**
- **Average duration of treatment about 20 months**
- **Average duration of follow up about 34 months**

Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, Wang Q, Menon V, Ruschitzka F, Gaffney M, Beckerman B, Berger MF, Bao W, Lincoff AM; PRECISION Trial Investigators.
N Engl J Med. 2016 Dec 29;375(26):2519-29

# PRECISION Trial

- **Adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria:**
  - **Death from cardiovascular causes**
  - **Hemorrhagic death**
  - **Nonfatal myocardial infarction**
  - **Nonfatal stroke**
- **Major CV events**
  - **Coronary Revascularization**
  - **Hospitalization for Unstable Angina**
  - **Hospitalization for Transient Ischemic Attack (TIA)**

# PRECISION Outcomes

| | Celecoxib (8072) | Naproxen (7969) | Ibuprofen (8040) | Celecoxib vs Naproxen HR | Celecoxib vs Ibuprofen HR |
|---|---|---|---|---|---|
| APTC* endpoints | 188 (2.3%) | 201 (2.5%) | 218 (2.7%) | 0.93(0.76-1.13) p=0.45 | 0.85(0.7-1.04) P=0.12 |
| Major CV** events | 337 (4.2%) | 346 (4.3%) | 384 (4.8%) | 0.97(0.83-1.12) p=0.64 | 0.87(0.75-1.01) p=0.06 |
| Major GI events | 55 (0.7%) | 56 (0.7%) | 72 (0.9%) | 0.97(0.67-1.40) p=0.86 | 0.76(0.53-1.08) p=0.12 |
| Renal events | 57 (0.7%) | 71 (0.9%) | 92 (1.1%) | 0.79(0.56-1.12) p=0.19 | 0.61(0.44-0.81)p=0.004 |
| Deaths | 132 (1.6%) | 163 (2%) | 142 (1.8%) | 0.80(0.63-1.00) p=0.052 | 0.92(0.73-1.17) p=0.49 |

*APTC=Antiplatelet Trialist Collaboration Criteria (i.e., death from CV causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke.
**APTC and coronary revascularization or hospitalization for unstable angina or transient ischemic attack (TIA)

# Heart Failure Complications

- **NSAIDs effect:**
  - **Sodium excretion**
  - **Volume Expansion**
  - **Increased Preload**
  - **Hypertension**
- **Pre-existing heart failure patients at risk of decompensation**
  - **RR 3.8 (95% CI, 1.1 to 12.7)**
  - **RR 9.9 (95% CI, 1.7 to 57) when adjusted for age, sex, and concomitant medication**

Feenstra J, et al. Association of nonsteroidal anti-inflammatory drugs with first occurance of heart failure and with relapsing heart failure: the Rodderdam Study, Arch Intern med 162:265-270, 2002

# Less Common Complications

## Aspirin Exacerbated Respiratory Disease (AERD)

- Cox-1 inhibition may cause:
  - Bronchospasm
  - Flushing
  - Conjunctival Injection
  - Nasal congestion[1]
- More likely in those with chronic rhinosinusitis and nasal polyposis[1]
- Samter's triad= asthma, nasal polyps, aspirin sensitivity[2]


1. Solomon, Daniel. Nonselective NSAIDs: Overview of adverse effects https://www.uptodate.com/contents/nonselective-nsaids-overview-of-adverse-effects?search=nsaid&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 Accessed January 1, 2018.
2. West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015


## Hematologic Risks

- Aplastic anemia
- Pure red cell aplasia
- Thrombocytopenia
- Neutropenia


West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015


## Dermatologic Risks

- Photosensitivity
- Urticaria
- Angioedema
- Erythema multiforme
- Toxic epidermal necrolysis


West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

## Neurologic Risks

- Aseptic meningitis (especially in systemic lupus erythematosus patients)—ibuprofen
- Headaches
- Dizziness
- Loss of concentration
- Depersonalization
- Tremor
- Psychosis—indomethacin

West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

## Additional Rare Adverse reactions

- Febrile reaction—ibuprofen
- Mediastinal lymphadenopathy—sulindac
- Stomatitis
- Small bowel webs—piroxicam
- Sulfa allergy—celecoxib
- Kidney stones—sulindac
- Reversible infertility due to interference with ovulation and implantation

West, Sterling. Rheumatology secrets. Elsiever Mosby. 2015

# Drug Interactions

## Plasma binding interactions

- NSAIDs may displace other drugs from binding to plasma binding sites thereby increasing drug toxicity:
  - Sulfonylurea
  - Hypoglycemic agents
  - Oral anticoagulant
  - Phenytoin
  - Sulfonamides
  - Methotrexate

Brater DC, Drug-drug and drug-disease interactions with nonsteroidal anti-inflammatory drugs, Am J Med 80:62-77, 1986.

# Drug Interactions

| | |
|---|---|
| Methotrexate | Increases plasma levels of methotrexate |
| ACE inhibitors | Lowers effects |
| Aspirin | Both block COX-1 but Aspirin is irreversible, so offers cardioprotective effects |
| Glucocorticoids | Increase GI risks |
| Anticoagulants | Inhibit platelet function and increase bleeding |
| SSRI | Increase GI risks |

**Take Aspirin 2 hours before other NSAIDs**

Solomon, Daniel. NSAIDs: Therapeutic use and variability of response in adults https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults?search=nsaid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed Jan 1, 2018.

# Anti-hypertensive interactions

- **ACE inhibitors**
- **Thiazides**
- **Beta Blockers**

# NSAID Overdose

# Aspirin/salicylate intoxication

- **Signs/symptoms**
  - **Tachypnea**
  - **Confusion**
  - **Ataxia**
  - **Oliguria**
  - **Increased BUN/Cr**

1. Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

## Aspirin/salicylate intoxication

- Metabolic acidosis may be masked by hyperventilation due to stimulation of respiratory centers
- Therapy:
  - Evacuation of the stomach
  - Forced diuresis while maintaining urinary pH in alkaline range
  - Potassium replacement
  - Hemodialysis
  - Consider Vitamin K as salicylates may interfere with synthesis of vitamin K depended clotting factors

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

## Non-Aspirin/salicylate NSAID overdose

- Signs/symptoms
  - CNS depression
  - Seizures
  - Apnea
  - Nystagmus
  - Blurred vision
  - Diplopia
  - Headache
  - Tinnitus
  - Bradycardia
  - Hypotension
  - Abnormal renal function
  - Coma
  - Cardiac arrest

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.

## Non-Aspirin/salicylate NSAID overdose

- Treatment
  - Evacuation of the stomach
  - Observation
  - Administration of fluids[1]

**NSAIDs are not dialyzable[2]**

1.Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013.
2. Grosser, Tilo, et al.. "Pharmacotherapy of Inflammation, Fever, Pain, and Gout." *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e* Brunton LL, Hilal-Dandan R, Knollmann BC. Brunton L.L., Hilal-Dandan R, Knollmann B.C. Eds. Laurence L. Brunton, et al. New York, NY: McGraw-Hill, , http://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=170271972.

## Practical Applications

# Low Risk

- <65 years old
- No CV risks
- No requirement for high dose or chronic therapy
- No concomitant aspirin, corticosteroids, or anticoagulants

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**Traditional NSAID**
**Shortest duration**
**Lowest Dose possible**

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013

# Intermediate Risk

- ≥65 Years old
- No history of previous complicated GI ulceration
- Low cardiovascular risk (may be using aspirin for primary prevention)
- Requirement for chronic therapy and/or high-dose therapy

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- ≥65 Years old
- No history of previous complicated GI ulceration
- Low cardiovascular risk (may be using aspirin for primary prevention)
- Requirement for chronic therapy and/or high-dose therapy

**Traditional NSAID + GI protective agent***
**Once daily celecoxib + GI Protective agent***

**If using Aspirin:**
**Take low dose (75-81 mg)**
**Traditional NSAID ≥ 2 hours after aspirin dose**

***PPI, misoprostol, or high dose $H_2RA$**

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013

# High Risk

- Elderly, especially if frail, hypertension, renal disease or liver disease
- History of previous complicated ulcer of multiple GI factors
- History of cardiovascular disease and on aspirin or other antiplatelet agent for secondary hypertension
- History of heart failure

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- Elderly, especially if frail, hypertension, renal disease or liver disease
- History of previous complicated ulcer of multiple GI factors
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- History of heart failure

Use acetaminophen
Avoid chronic NSAIDs if possible
Use intermittent NSAID dosing,
Use low-dose, short half life NSAIDs
Avoid extended release formulations

If GI risk > CV:
Once-daily celecoxib + PPI/misoprostol
If CV risk > GI: Naproxen + PPI/misoprostol

Avoid PPI if using antiplatelet agent (e.g. clopidogrel)

Firestein GS, et al. Kelley's Textbook of Rheumatoogy. Elsiever Saunders. voll. 2013

# Final Thoughts

- NSAIDs analgesic, antipyretic, anti-inflammatory properties permit many applications
- NSAIDs have a variety of complications including GI, Renal, and CV
- Comorbidities and risks with different NSAIDs can help in better selecting specific NSAID regimens

## References for Topical NSAIDs


1. Rosemont IL. Treatment of Osteoarthritis of the Knee Evidence-Based Guideline 2nd Edition. American Academy of Orthopaedic Surgeons; 2013.
2. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P. American college of rheumatology 2012 recommendations for the use of Nonpharmacologic and pharmacologic therapies for osteoarthritis of the hand, hip and knee. Arthritis Care Res (Hoboken) 2012;64:465–474.
3. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M. on behalf of the Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT) Ann Rheum Dis. 2003;62:1145–1155
4. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, Dinçer F, Dziedzic K, Häuselmann HJ, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Maheu E, Martin-Mola E, Pavelka K, Punzi L, Reiter S, Sautner J, Smolen J, Verbruggen G, Zimmermann-Górska I. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT) Ann Rheum Dis. 2007;66:377–388
5. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008;16:137–162
6. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–1346
7. 7. Simon LS, Lipman AG, Jacox AK, Caudill-Slosberg M, Gill LH, Keefe FJ, Kerr KL, Minor MA, Sherry DD, Vallerand AH, Vasudevan S. Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis. 2. American Pain Society: Glenview, IL; 2002. (Clinical Practice Guidelines no. 2).