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

What is an NSAID?

- Non steroidal Anti-inflammatory Drugs
- Weak organic acid
- Binds to serum proteins (albumin)
- Generally have low ionization constant (pKₐ)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
Effects of NSAIDs

- Analgesia
- Antiinflammatory
- Antipyresis
- Antiplatelet
  - inhibit COX-1 thus preventing thromboxane A₂ (TXA₂) production to decrease platelet aggregation


Mechanism of Action

COX isoforms

<table>
<thead>
<tr>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found in most tissues</td>
<td>Brain, kidney, sites of inflammation</td>
</tr>
<tr>
<td>Present in Platelets</td>
<td>Not in platelets</td>
</tr>
</tbody>
</table>

Theoretical GI safety for COX-2

Theoretical no bleeding risk for COX-2

NSAID Classes

<table>
<thead>
<tr>
<th>Salicylate acetylated</th>
<th>Salicylate non-acetylated</th>
<th>Propionic Acids</th>
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<td>Aspirin</td>
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</tr>
<tr>
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<td></td>
<td>Ibuprofen</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Trisalicylate</td>
<td></td>
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<td>Salsalate</td>
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### NSAID Classes

<table>
<thead>
<tr>
<th>Acetic Acids</th>
<th>Anthranilic Acids</th>
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<th>Selective Cox 2 inhibitors</th>
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<tr>
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</table>

### 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

### COX selectivity

<table>
<thead>
<tr>
<th>Low Dose</th>
<th>Aspirin</th>
<th>Ibuprofen</th>
<th>Meloxicam</th>
<th>Celecoxib</th>
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<tr>
<td></td>
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<td>Diclofenac</td>
<td>Nabumatone</td>
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**PGE₂ Inibition by NSAIDs**

- PGE₂ is the most abundant Prostaglandin (PG) at sites of inflammation¹
- Microsomal PGE synthase-1 (mPGES-1) acts in concert with COX-2 to produce high levels of PGE₂ during inflammation²
- NSAIDs block mPGES-1


**More NSAID actions**

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


**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


**NSAID metabolism**

- Hepatically biotransformed
- Renally eliminated
- NSAIDs not dialyzable due to plasma binding
  - Except for salicylic acid¹
- Genetic variation in metabolizing enzymes and variability in intestinal microbiota effect metabolism and excretion¹
- Cross Blood brain barrier²

NSAID Absorption

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

Basic Principles of NSAID Use

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

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

Perioperative Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half life (hours)</th>
<th>Withdrawal Preoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.6-1.9</td>
<td>10 hours</td>
</tr>
<tr>
<td>Naproxen</td>
<td>12-15</td>
<td>3 days</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.5</td>
<td>1 day</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2</td>
<td>10 hours</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>11</td>
<td>Continue dose</td>
</tr>
</tbody>
</table>


Perioperative Management

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

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


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

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

Topical NSAIDs


Topical NSAIDs

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

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 cm²)
  - (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 cm²)
  - (C) 150 mg oral diclofenac applied as 50-mg tablets 3 times daily.

Systemic exposure

<table>
<thead>
<tr>
<th></th>
<th>16 g</th>
<th>48 g</th>
<th>oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₂₄</td>
<td>233 ± 128 ng·h/mL</td>
<td>807 ± 478 ng·h/mL</td>
<td>3890 ± 1710 ng·h/mL</td>
</tr>
</tbody>
</table>

- 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).

NSAID Complications
Big 3 complications

- Gastrointestinal
- Renal
- Cardiovascular

Injuries to Gastric mucosa

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

Dyspepsia

- 10-20% of NSAID users
- Present even amongst COX-2 selective NSAIDs
- Improved with Proton pump inhibitors (PPI)
- Improved with histamine-2-receptor antagonists (H2RAs)

**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\(^2\)

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**Outliers in GI risks**

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>1.42</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2.69</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>9.94</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>14.54</td>
</tr>
</tbody>
</table>


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**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

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**Adjusted RR (OR)**

Adapted from Bolware, DW and Heduebert GR. Lippincott’s Primary Care Rheumatology. Lippincott Williams and Wilkens. 2013. Page282

Combination Drugs

<table>
<thead>
<tr>
<th>Combination Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrotec</td>
</tr>
<tr>
<td>Vimovo</td>
</tr>
<tr>
<td>Duexis</td>
</tr>
</tbody>
</table>

- Arthrotec more effective at reducing hospitalization for PUD or GI hemorrhage compared to coprescription\(^1\)

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\(^6\)


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\(^2\)


GI risk: Large intestine

- NSAIDs can cause colonic erosions, ulcers, hemorrhage, perforations, strictures.\(^1\)
- Consider NSAID colonopathy in the differential for inflammatory bowel disease

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


Renal Complications

Renal effects

- PGs important to solute and renovascular homeostasis
- 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
- COX-2 inhibition may result in apoptosis of medullary interstitial cells and result in papillary necrosis


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
- 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

Hypertension

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


Acute Renal Failure

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


Chronic Kidney Disease

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


Cardiovascular Risks
Cardiovascular Effects

- COX-1 isoform generates platelet TXA₂ which effects platelet aggregation and thrombus formation¹
- PGI₂ is antithrombotic and blocked by COX-2 inhibition²

Additional CV Effects

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

CV Risks

- All traditional and COX-2 selective NSAIDs associated with at least a 30% increase CV risk
  - Exception:
    - Naproxen¹
    - Once daily dosing of Celecoxib²
  - Dose and slow release formulation effect risk directly¹,³

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 2004¹
- 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 trial²
- 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.

References:

**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


**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**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (8072)</th>
<th>Naproxen (7969)</th>
<th>Ibuprofen (8046)</th>
<th>Celecoxib vs Naproxen HR</th>
<th>Celecoxib vs Ibuprofen HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTC endpoints</td>
<td>188 (2.3%)</td>
<td>201 (2.5%)</td>
<td>218 (2.7%)</td>
<td>0.93 (0.75-1.13) p=0.45</td>
<td>0.85 (0.7-1.04) p=0.12</td>
</tr>
<tr>
<td>Major CV** events</td>
<td>337 (4.2%)</td>
<td>346 (4.3%)</td>
<td>384 (4.8%)</td>
<td>0.97 (0.83-1.12) p=0.84</td>
<td>0.87 (0.75-1.01) p=0.06</td>
</tr>
<tr>
<td>Major GI events</td>
<td>55 (0.7%)</td>
<td>96 (0.7%)</td>
<td>72 (0.9%)</td>
<td>0.97 (0.67-1.40) p=0.86</td>
<td>0.76 (0.53-1.08) p=0.12</td>
</tr>
<tr>
<td>Renal events</td>
<td>57 (0.7%)</td>
<td>71 (0.9%)</td>
<td>92 (1.1%)</td>
<td>0.79 (0.56-1.12) p=0.19</td>
<td>0.61 (0.44-0.81) p=0.04</td>
</tr>
<tr>
<td>Deaths</td>
<td>132 (1.6%)</td>
<td>163 (2%)</td>
<td>142 (1.8%)</td>
<td>0.80 (0.63-1.00) p=0.052</td>
<td>0.92 (0.73-1.17) p=0.49</td>
</tr>
</tbody>
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*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

### Less Common Complications

- Cox-1 inhibition may cause:
  - Bronchospasm
  - Flushing
  - Conjunctival Injection
  - Nasal congestion

- More likely in those with chronic rhinosinusitis and nasal polyposis
- Samter’s triad= asthma, nasal polyps, aspirin sensitivity

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### Hematologic Risks

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

### Dermatologic Risks

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

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

## Additional Rare Adverse reactions
- Febrile reaction—ibuprofen
- Mediastinal lymphadenopathy—sulindac
- Stomatitis
- Small bowel webs—piroxicam
- Sulfur allergy—celecoxib
- Kidney stones—sulindac
- Reversible infertility due to interference with ovulation and implantation

## 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


**Drug Interactions**

<table>
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<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Increases plasma levels of methotrexate</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Lowers effects</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Both block COX-1 but Aspirin is irreversible, so offers cardioprotective</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Increase GI risks</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Inhibit platelet function and increase bleeding</td>
</tr>
<tr>
<td>SSRI</td>
<td>Increase GI risks</td>
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</table>

*Take Aspirin 2 hours before other NSAIDs*

**Anti-hypertensive interactions**

- ACE inhibitors
- Thiazides
- Beta Blockers

**Aspirin/salicylate intoxication**

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

*Sources:*
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

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

Treatment

- Evacuation of the stomach
- Observation
- Administration of fluids

Practical Applications

NSAIDs are not dialyzable


### 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*

### 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

### 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

*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 H₂RA*

### 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

### 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)


### 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