NSAIDs: Friend or Foe in the Battle against Pain?

Presented by
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NO Conflicts of Interest to Declare
Old & Natural!

- 1763 fever Rx- bark/leaves of willow/myrtle (salicylic acid)
- 1859-chemical structure discovered & synthesized in Germany
- 1914- Bayer Co. started manufacturing ASA
  - Current sales 11 billion (2014)
- Early 20th Century- NSAIDs discovered
- 1971- discovered mechanism of action of NSAIDs by John R. Vane
- 1990s-COX-2 isoenzyme successfully identified & cloned
- Current- script & OTC use -> 30 billion doses/yr of NSAIDs In US
  - Numbers increase every year
Prostaglandin (PG) Mechanism of Action

- Prostaglandins (PG) - lipids derived from acids: i.e. arachidonic (AA), lineolic, others
- PGs have Variety of functions
  - Constitutive
    - GI mucosal protection
    - Kidney function
  - Trauma response
    - Cell membrane trauma releases AA & COX enzyme converts to PGs → inflammation
    - Peripheral & central sensitization of nociceptors to mechanical & chemical stimuli
  - Pyretic response
    - PGs rise in CSF w/ pyrogen introduction
    - Although not an NSAID, acetaminophen blocks brain PG synthetase (COX3 inhibition)
Cyclo-oxygenase (COX): “The Convertors”

- Cyclo-oxygenase 1&2 = isoenzymes that convert AA to PGs (i.e. prostacyclin, & thromboxanes)

- **COX-1**
  - Expressed regularly- provides gastric & duodenal mucosal protection
  - Stimulates production mucin/bicarbonate/phospholipid that covers surface of stomach
  - Enhances GI mucosal blood flow w/ local vasodilation
  - Enhanced epithelial cell reproduction & migration towards lumen
  - Can be induced under stress
**More Cyclo-oxygenase (COX) Specifics**

- **COX2**
  - Regular expression in CNS (regulates brain injury/inflammation) & kidney
  - Also induced by trauma, endotoxins, neurotransmitters, cytokines, growth factors, hormones, etc
  - Promotes inflammation
    - Both peripheral inflammation & central actions
    - Increases electrical nerve activity (blunted w/ neural blockade & COX-2 inhibitors)
    - Humoral (biochemical) signal raises COX2 in CNS when inflammation occurs (blunted only by COX2 inhibition in CNS)
  - May help heal gastric ulcers
NSAID Class Characteristics

- Highly protein bound-
  - Hemodialysis does not remove them
  - Hypoalbuminemia will increase circulating level

- Effective analgesics- many studies
  - Opiate sparing (25-55% less opioid when NSAID used)
  - Multimodal use postop- less nausea, vomiting, sedation
    - Improved postop outcomes/recovery

- Different chemical subgroupings
  - If one ineffective at max dosing, try a different category

- COX-1 & COX-2
  - All NSAIDs inhibit BOTH to varying degrees
  - COX-2 selectivity in NSAIDs is a continuum- not an absolute
Relative COX Selectivity

<table>
<thead>
<tr>
<th>5-50 fold COX-2 preference</th>
<th>&lt; 5 fold COX-2 preference</th>
<th>COX-1 Preference</th>
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<tbody>
<tr>
<td>Etodolac</td>
<td>Diclofenac</td>
<td>Fenoprofen</td>
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<tr>
<td>Meloxicam</td>
<td>Sulindac</td>
<td>Ibuprofen</td>
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<tr>
<td>Celecoxib</td>
<td>Meclofenamate</td>
<td>Tolmetin</td>
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<td>Piroxicam</td>
<td>Naproxen</td>
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<td></td>
<td>Diflunisal</td>
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<td>Indomethacin</td>
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<td>Ketoprofen</td>
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<td>Flurbiprofen</td>
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<td>Ketorolac</td>
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## Chemical Grouping of NSAIDs

<table>
<thead>
<tr>
<th>Acetylated Salicylate</th>
<th>Non-acetylated Salicylates</th>
<th>Propionic Acids</th>
<th>Acetic Acids</th>
<th>Oxicams (Enolic acids)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Diflunisal</td>
<td>Naproxen</td>
<td>Diclofenac</td>
<td>Meloxicam</td>
<td>Nabumetone</td>
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<tr>
<td>Choline Mg Trisalicylate</td>
<td>Ibuprofen</td>
<td>Etodolac</td>
<td>Piroxicam</td>
<td></td>
<td>Selective COX-2 inhibitors:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Celecoxib</td>
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<tr>
<td>Salsalate</td>
<td>Ketoprofen</td>
<td>Indomethacin</td>
<td>Meclofenamate</td>
<td></td>
<td>• Etoricoxib (Unavailable in US)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Tolmetin</td>
<td></td>
<td>Mefenamic acid</td>
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<tr>
<td>Oxaprozin</td>
<td>Sulindac</td>
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<td>Ketorolac</td>
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</table>
NSAID TOXICITIES

- NSAIDs implicated in nearly 25% of all ADRs (mild to serious)
  - Most common GI irritation/dyspepsia
- More Serious; 5-7% of hospital admission r/t adverse effects of drugs
  - 11-12% of those admission r/t NSAIDs
  - 10% elder admissions r/t ADR; 2.3 - 33% of those admissions r/t NSAIDs
- Often cited > 100,000 hospitalizations and > 16,000 deaths/yr in US
- Based on 1999 obs study (ARAMIS) -found 19 NSAID bleeding deaths
  - Inaccurate extrapolations to general population
- 2004 study = 3,200 deaths/yr NSAID GI bleeding (Tarone et al., Am J Ther)
- 2010 study (Solomon et al, Arch Intern Med)
  - Nonselective NSAID mortality 48/1000 person yrs
  - Opioid mortality 75/1000 person yrs
NSAID OVERDOSE & TOXICITY

- Toxic incidence likely to increase per CDC
  - Aging population w/ increases in degenerative & inflammatory conditions
  - Potential increase as opioid alternatives

- Acute overdose (accidental or intentional) of single large dose
  - Typically well tolerated
  - May cause n/v, drowsiness, blurred vision, dizziness- rarely serious

- Chronic use → most toxicities
Toxicity #1 - Hematologic

- COX-1 converts AA to PGs
  - PG in platelets = Thromboxane A2 (TXA2) - activates platelets & vasoconstricts
  - PGI₂ in vascular endothelium - inhibits platelets & vasodilates

- ASA irreversibly inhibits COX-1 action ---- inhibits platelet aggregation
  - Platelets vulnerable to COX-1 inhibition as cannot regenerate PGs like other cells
  - Effects last for life of platelet (7-10+ days)

- Non-selective NSAIDs reversibly inhibit COX-1 = transient effect
  - Single dose Ibuprofen 300-900mg inhibits platelet aggregation x 2 hr
    - Effect completely gone in 24hr
  - Piroxicam - can last several days after discontinuation
Toxicity #1 - Hematologic

- Possible bleeding risk with platelet inhibition
  - NSAIDs with lower platelet effect
    - Non-acetylated (diflunisal, choline Mg trisalicylate, salsalate)
    - COX-2 (celexocib)
  - No COX-2 activity found in platelets

- Neutropenia and aplastic anemia - rare (<1% of NSAID users)
  - Indomethacin associated with higher risk
NSAIDs & Peri-Op Bleeding Risks

- Studies showing **higher postop bleeding** risk
  - w/ nonsutured tissues – i.e. tonsillectomy, joint replacement
  - NSAIDs w/ ½ life > 6hr
  - NSAIDs given before surgical control of bleeding
- Many studies **historically w/ low risk** peri-operative bleeding
  - 1985-87 = no difference in THA/TURP w/ diclofenac vs placebo (Lindgren, Acta Aneas Scan ;Bricker et al, Eur J Anesth)
  - 2000-toradol 60mg w/ anorectal surgery- no increase in bleeding (Coloma et al.,Anesth, Analg)
  - 2009 meta-analysis variety surgeries show **slight increased risk** w NSAIDs (Meylan et al., J Anesth)
    - Severe bleeding (1.7% vs 0%) and Any bleeding (1.7% vs 0.2%)
- Pre-Op Stoppage of NSAID
  - Gen rule--Hold NSAID 3 days to normalize Platelet function
  - Ibuprofen effect gone in 24 hr
  - ASA- stop at least 1 week
Most NSAIDs potentiate warfarin activity
- Displace its protein binding & inhibit hepatic metabolism---- increased circulating levels of warfarin
- Elders w/ increased bleeding risk w/ combo NSAID and warfarin

Rx Combination Risks
- Post MI study 2 groups ; clopidogrel, ASA or warfarin with and without added NSAID
- Bleeding risk doubled w/ NSAID addition
- Bleeding risk seen as early as 1st three days of NSAID use
- CAUTION w/ NSAID Rx w/ other anticoagulants (avoid, limit dose/duration)
Toxicity #2 -- GI Effects

- ADRs- range of dyspepsia, gastric/duodenal ulcers and GI bleeding

Pathophysiology of Gastric damage
- NSAID w/ systemic effect decreasing COX (post-absorptive effect)
- COX-1 enzymes produce mucosal protective PGs (cytoprotection)
  - Stimulates GI secretion – bicarbonate, mucin, phospholipids
  - Produces alkaline, unstirred water layer on gastric mucosa
  - Protects against acid & pepsin erosion
- Enhances epithelial cell blood flow, migration to surface(repair), cell proliferation
- COX block --Increases risk of mucosal injury and decreased repair response
  - Gastric repair (restitution) associated w/ COX-2 activity

- Enteric coating
  - Clinically no difference in preventing ulcers/bleeding
  - Ulcers & bleeding due to systemic effect, small topical effect on mucosa
Gastro-duodenal Toxicity

- ASA- irreversible COX inhibition
  - Doses 10mg/day inhibit gastric PG and can damage stomach
  - Damage increases as dose increases
  - After d/c of low dose ASA -- 5-8 days for stomach to recover full COX-1 synthesis/activity

- Other NSAIDS- even transient COX inhibition damages gastric mucosa
  - < 1 week Rx unlikely to cause major GI damage
  - Damage most common in first three months of Rx

- Duodenal damage r/t gastric acid (not due to COX inhibition)
  - H2 blockers may help (but not w/ gastric damage)
  - H. Pylori infection– independent AND synergistic risk of ulcers w/ NSAIDs
## Risk Factors & NSAID Gastro/duodenal Toxicity

### Risk Stratification

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk Stratification</th>
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</thead>
<tbody>
<tr>
<td>Hx of Uncomplicated Ulcer</td>
<td>HIGH= hx of complicated ulcer OR ≥ 3 risk factors</td>
</tr>
<tr>
<td>( No bleeding, perforation, obstruction)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>MOD= 1-2 risk factors</td>
</tr>
<tr>
<td>High dose NSAID (2-3x risk)</td>
<td>LOW= zero risk factors</td>
</tr>
<tr>
<td>Meds: Concurrent use ASA (any dose), glucocorticoids, anticoagulants.</td>
<td></td>
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<tr>
<td>( Includes anti-platelet, warfarin, heparin, direct thrombin &amp; factor Xa inhibitors)</td>
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</tbody>
</table>

### OTHER RISK FACTORS (beyond ACG table)

- Untreated H. Pylori infection
- Chronic use (2004 meta-analysis = avg 84 days before s/s toxicity)
- Concurrent use SSRI (platelet serotonin effect inhibits activation)
- Ketorolac- 5.5x more likely than other NSAIDs to cause GI toxicity
  (limit 5 day use)
Risk Reduction with Medications

**PPI**

- Once daily dosing, well tolerated; probably all with equal effect
- COX-2 plus PPI outcomes better than other NSAIDs plus PPI
- PRECISION Study (2016)- with ASA use -- less upper GI events with PPI & COX-2 vs PPI & Non-selective NSAIDs
- CONCERN Study (2017)- on ASA– Hx healed ulcers after GI bleeding; PPI with celecoxib or naproxen
  - Recurrent GI bleed 5.6% celecoxib and 12% naproxen
  - Risk lower but still significant for Celecoxib & PPI = 1 in 20 patients with recurrent GI bleeding

- **Misoprostol** (prostaglandin analogue) 200 mcg qid
  - Less well tolerated than PPI (dyspepsia, diarrhea, abd pain)
  - Less than qid ineffective risk reduction
GI (Gastro-duodenal) Risk Reduction Actions

Use COX-2: mod reduction GI bleeding compared to non-selective NSAIDs
- Risk still increased c/w placebo
- Low risk benefit lessened w/ concurrent low dose ASA or warfarin

Test & treat H. Pylori --BEFORE starting NSAIDs if hx of ulcers OR long-term NSAID anticipated

PPIs: Best Practice Advice expert opinion (Freedberg et al. , Gastroenterology, 2017)
- If High Risk for GI ulcer/bleeding --- PPI as long as on NSAID
- Use lowest dose PPI- review periodically
- Long-term PPI use
  - Do NOT routinely raise intake Ca, Vit B12, Mg
  - Do NOT routinely take probiotics to prevent infection
  - Do NOT routinely monitor bone density, creatinine, Mg, B12

PPI Side effects- Low quality data; i.e. Vit B12 deficiency, possible Osteoporosis
PPI Potential Side Effects (low quality data)

Potential adverse effects of PPIs and their relative risks.

Notes: Data collated from Freedberg et al. Overall quality of evidence low/very low.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817415/figure/f4-jpr-11-361/?report=objectonly
Monitoring Gastro-duodenal toxicity

- GI toxicity often asymptomatic until shortly before clinical event
  - Little correlation between dyspepsia & presence of ulcers/erosions
  - Drugs w/o COX inhibition can cause dyspepsia w/o known ulcer risk
    - i.e. Acetaminophen
  - Suspect ulceration if:
    - unexplained blood loss anemia
    - Iron deficiency
    - Significant dyspepsia
    - Any s/s GI bleeding
  - Endoscopy indicated w/ suspicion
  - CT abd if perforation suspected
Small Bowel Injury (SBI)-Beyond duodenum

Under-reported; affected area beyond reach of routine endoscopy

- Video Capsule Endoscopy (VCE) increased findings in distal small bowel
- Erosions, Ulcers, scars, strictures

High Incidence

- 53-75% in healthy short-term NSAID users: 50-71% in long-term use (>3 months)
  - While on acid suppression
  - Can occur as early as 2 weeks of use

SBI manifestations

- Iron deficiency anemia r/t occult bleeding
- Protein-losing enteropathy/malnutrition (↑permeability)
- Recurrent abdominal pain assoc w/ strictures
- Small bowel diaphragm disease
  - circular mucosal membranes divide & narrow bowel lumen– potential strictures & obstruction.

Srinivasa & DeCruz (2017). Scan J of Gastro
Small Bowel Injury

- Lit Review - **Increased risk** w/Oxicams & diclofenac
- **NSAIDs w/ ASA more damaging** than ASA alone
- **Not associated w/ duration** of NSAIDs OR lowered w/PPI use
  - Lesions can persist > 18 months after stopping NSAID
- **Prophylaxis**
  - PPIs & H$_2$ blockers shown effective w/ gastro-duodenal dz
  - **PPI may worsen** NSAID SBI- r/t GI altered bacteria (Gwee et al. *J Pain Res*. 2018)
  - **Celecoxib w/o PPI = lowered risk** in some studies
  - Rebamipide (not available in US) & misoprostol co-prescription
    - Studies show prevention & enhanced healing of SBI
  - Rx for Inflammatory Bowel Dz (IBD) reduces SBI
    - i.e. sulfaxalazine, mesalazine
  - Novel agent- nitric oxide donors (mucosal blood flow, bicarb secretion, mucous production)
### Risk Factors Gastro/duodenal

<table>
<thead>
<tr>
<th>Risk Factors Gastro/duodenal</th>
<th>Risk Factors SBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>Age &gt; 70 years</td>
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<tr>
<td>&gt; 7 days of therapy</td>
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<tr>
<td>High dose NSAID</td>
<td></td>
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<tr>
<td>Prior Peptic Ulcer Dz/Prior NSAID toxicity</td>
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</tr>
<tr>
<td>H. Pylori infection</td>
<td>Comorbid arthropathy</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td>Concurrent use anti-platelets, glucocorticoids, anticoagulants, SSRIs</td>
<td>Concurrent anti-platelet Rx</td>
</tr>
<tr>
<td>Use of diclofenac and oxicams (i.e., meloxicam)</td>
<td>Use of diclofenac and oxicams (i.e., meloxicam)</td>
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</table>

PPI Use (Gwee et al., J Pain Research 2018)
Toxicity # 3 --Cardiovascular

- CV thrombotic events, MI, stroke

- Increased risk w/ COX-2 inhibitors- (more studied: initial view)
  - Unbalanced synthesis PG1 (vessel endothelium) & thromboxane (platelets)
    - Normal platelet action is a balance between PG1 and TXA2
  - PG1= platelet inhibitor & vasodilator
  - TXA2= platelet activator & vasoconstrictor
  - COX-2 Inhibitors block PG1 only
    - Contributes to atherosclerosis & exaggerated thrombotic response to plaque rupture
    - MI/CVA risk-= 1.7 -5x risk w/ rofecoxib in VIGOR & APPROVE studies in 9-18 mo
      - VIGOR- included high risk pts w/ RA but no ASA used
      - Uncertain risk w/ ASA use in high risk pts
      - Voluntarily withdrawn from market 2004
Cardiovascular Risk-Celecoxib

- **(Adenoma Prevention w/ Celecoxib) APC study** (2004)= 200-400mg bid x 33 mo
  - 2.3- 3.4 x increase in CV events after 12 month
- **PreSAP study** (2002)= 400mg qd vs placebo x 32 months
  - Smaller increase in CV events
- **(Alzheimers Dz Anti-inflam Prev Trial) ADAPT study** (2004)= 200mg qd vs placebo
  - No increase in risk celecoxib ; but Increase risk w/ naproxen
- Valdecoxib studies -- increase risk w/ supramaximal doses x 14 days (40mg bid)- but not w/ therapeutic dosing
- **2005 FDA**
  - Affirmed risk of celecoxib similar to non-selective NSAIDs
  - Deemed risk high w/ valdecoxib and requested withdrawal from market
  - Black box warning for NSAID category- script & OTC
Figure 2. Combined analysis showing 3 separate dosing regimens in the PreSAP and APC studies.

Study, Celecoxib dose

- PreSAP, 400mg once daily
  - Hazard ratio (95% CI): 1.3 (0.6, 2.6)
- APC, 200mg twice daily
  - Hazard ratio (95% CI): 2.6 (1.1, 6.1)
- APC, 400mg twice daily
  - Hazard ratio (95% CI): 3.4 (1.5, 7.9)

Overall (95% CI)
  - Hazard ratio (95% CI): 1.9 (1.1, 3.1)

Scott D. Solomon et al. Circulation. 2006;114:1028-1035
Cardiovascular Risk Updates

- All NSAIDs can contribute to HTN
  - Celecoxib w/ possible lower effect
  - Rated CV thrombotic risk of various NSAIDs in 31 million patients
    - Rofecoxib- 45% increase
    - Diclofenac – 40% increase (increases w/ higher doses)
    - Indomethacin- 30% increase
    - Meloxicam- 20% increase
    - Ibuprofen - no increase at lower doses; increase w/ higher doses
    - Naproxen- slight increase at any dose
    - Celecoxib- similar to ibuprofen
2016 PRECISION Study: CV Safety of celecoxib, naproxen or ibuprofen

- 24,081 patients w/ RA/OA w/ increased CV risk; ASA 80mg /day allowed
- Avg /day = Celecoxib 200 mg, naproxen 875mg, ibuprofen 2045 mg
  - Rx for 20 months & follow up 34 months
- Esomeprazole 20-40mg qd for all patients
- Analysis of CV related death, nonfatal MI/CVA
  - Celecoxib 2.3% vs Naproxen 2.5% vs Ibuprofen 2.7%
- CONCLUSION;
  - CV RISK W/ CELECOXIB AT MODERATE DOSES IS NOT GREATER THAN RISK WITH NON-SELECTIVE NSAIDs.
OTHER PRECISION OUTCOMES

- Pain control similar w/ all 3 drugs w/ small benefit w/ naproxen
- Does **NOT** support naproxen as safer CV side effect profile
- **Serious GI events lower in celecoxib group**
- Serious renal events lower in celecoxib group vs ibuprofen but not naproxen
- Hospitalization for HTN lower in celecoxib group than ibuprofen but not naproxen

**Secondary Analysis Study** (Solomon et al, Rheum 2018)

- **COX2** has superior safety profile to NSAIDs—but ASA eliminates that advantage (likely r/t GI effects ?) and equalizes overall safety compared to non-selective NSAIDs
NSAID Competition w/ ASA

400mg Ibuprofen & ASA together may lower antiplatelet effect of ASA

- ASA irreversible effect on COX-1 in platelets
  - ASA has short half life of 0.25-0.5hr- so short window for irreversible action to occur
- Nonselective NSAIDs compete w/ ASA for binding sites on platelets
  - Studies show ibuprofen, naproxen interfere w/ ASA platelet effect
- Cox-2 NSAIDs – no competition w/ ASA (meloxicam, diclofenac, celecoxib)

2006 & 2016 FDA recommendations

- Ingest Ibuprofen 8 hr before or 30min after ASA dose
- Ingest Naprosyn 30 min after ASA
- COX-2 selective has NO interference (ASA acts on COX-1)
- Other non-selective NSAIDs w/ same potential- although studies lacking
- Unclear timing w/ enteric ASA as absorption/action delayed
- 2018 FDA added warning w/ naproxen and concomitant ASA
Aspirin Action Film!

Eats (receptor binding)
Shoots (inhibits platelets)
Leaves (short half-life)
Toxicity #4 - Renal

- Incidence = 1-5% of NSAID users ( > 2.5 million patients/ year)
- NSAID- induced renal disorders include:
  - Hemodynamically mediated acute injury (AKI)
  - Electrolyte and acid-base disorders
  - Acute interstitial nephritis (AIN)
  - Papillary necrosis (PN)
- 2 main mechanisms of injury
  - Functional & inflammatory
- COXs locally produced at multiple sites in kidney
  - Vasodilation pre-glomerulus and peritubular capillaries
  - Increases renin, enhances sodium excretion, lowers ADH
Functional Mechanism - hemodynamics

- COX (more COX1) = renal vasodilator -- controls hemodynamics & GFR
  - Block COX1 → decrease renal synthesis of PGs affecting autoregulation of renal blood flow
    - Decreases GFR (glomerular filtration rate)
    - Renal ischemia

- GFR **NOT** PG dependent in **normal renal function** & normal hemodynamics
  - Renal poor perfusion -- PG mechanisms necessary to maintain renal blood flow and normal GFR
    - i.e. dehydration, AKI, CHF, cirrhosis
**NSAID & Renal Electrolyte Effects**

- **COX (More COX2)** - promotes excretion salt & H2O
  - **Na+ & Fluid retention** r/t COX2 blockade = edema/HTN
    - Chronic NSAID Rx = 0.5-1Kg weight gain in healthy pts
    - Fluid retention usually resolves w/ongoing NSAID in 1-8 weeks
    - NSAIDS can alter/block diuretic binding or diuretic effect
  - **Hyperkalemia**
    - NSAIDs impair renin & aldosterone secretion
    - Mild effect in healthy pts w/o additional risk factors
      - Additive effect in AKI
    - Increased effect w/ ACE inhibitors/ARB drugs, K-sparing diuretics
  - **Hyponatremia** (Uncommon)
    - NSAIDs enhance ADH--- increased water reabsorption---dilutional low Na
    - Clinical effect if underlying ADH conditions (SIADH, volume depletion)
NSAID & Renal Toxicity

Inflammatory Mechanism
- Interstitial nephritis & glomerulopathy = Hypersensitivity reaction
- Non-dose dependent, allergic type response
- Proteinuria and leukocytes in urine (may lead to nephrotic syndrome)

Summary of Risk Factors for renal toxicities
- Chronic NSAID use
- Multiple NSAIDs used
- Dehydration
- Age > 60 yr
- Comorbid renal dz, CHF, Lupus, liver dz, hypercalcemia (affects renal perfusion)
- Concurrent Medications -- diuretics, ACE inhibitors, ARBs (inhibit vasoconstriction w/ low volume states – renal ischemia risk)
- Nephrotoxic drugs/contrast- heightened response w/ NSAID
NSAID Renal Toxicity - Clinical Monitoring

- Asymptomatic till advanced injury
- Monitor for Increased plasma creatinine
  - Can occur in first 3-7 days of therapy (time to reach max PG blockage)
  - Can occur at any time in therapy
- Monitor UA
  - AKI- UA w/ low proteinuria (< 500 mg/day), no hematuria, maybe hyaline casts
  - ATN- UA w/ epithelial cell casts, granular casts, WBCs, WBC cell casts
- Meta-analysis of 114 trials (116,00 pts) suggests heterogeneity among NSAIDs w/ renal effect
  - Celecoxib lower risk than other NSAIDs (RR 0.83)
Renal Toxicity INTERVENTIONS

- Stop NSAID
- Fluid balance - replace, treat underlying disease
- Correct electrolytes if needed
- Expect AKI recovery w/ norm creatinine in 3-7 days
  - If delayed recovery, further w/u ultrasound or biopsy
- NSAID choice
  - ALL carry risk
  - Indomethacin MAY be more toxic
  - Lower risk w/ sulindac & ASA & possibly celecoxib
    - ASA partial/temp effect on renal COX
- Restarting NSAID after AKI resolved
  - Cautiously if NO underlying dz, low risk factors & reversible/corrected cause (i.e. dehydration)
Toxicity #5 -- Liver

- Drug induced liver injury (DILI)
  - Less common than other toxicities but less studied

- U.S. Registry of drug induced liver injury 2016 report (1221 cases)
  - 30 cases assoc w/ 8 different NSAIDs (2.45% of all cases)
  - Mean onset 67 days post NSAID start
    - Hepatocellular injury most common pattern (70%) vs autoantibodies (30%)
    - Diclofenac most frequently implicated

- Caution/avoid w/ advanced liver disease
  - Increases variceal bleeding risk
  - Contributes to diuretic resistant ascites
Toxicity # 6 --BONE HEALING

- Literature in early 2000s stated risk of non-union of spinal fusion /fx
  - Animal studies often used
  - No level 1 evidence from human studies

- Study of 9995 pts w/ humeral fx (Arthritis Rheum 2005)
  - NSAID use in first 90 days significantly assoc w/ nonunion
  - BUT only days 61-90 showed relationship between NSAID & nonunion
  - Same relationship demonstrated w/ opioid use in days 61-90
  - Suggest painful non-union fx may be cause of NSAID & opioid use
NSAIDs & BONE HEALING

- Systematic review of 138 studies (Sivaganesan, Eur Spine J, 2017)
  - Studies after 2005 show use < 2 weeks postop w/o effect on non-union
  - Particularly low risk x 48 hr use postop

- Systematic review of 38 yr literature & 12,895 pts (J Clin Anesth 2018)
  - Overall study quality low w/ conflicting data; RCTs needed
  - Human trials w/ NO strong evidence of NSAIDs increasing non-union after fx or fusion
  - Animal & human tissue studies
    - Short perioperative use not deleterious
A Word on Topical NSAIDs

- **Comparable efficacy** to oral NSAIDs w/OA /musculoskeletal pain in RCTs and meta-analysis (Rannou et al, Sem Arth Rheum 2016)
  - 50% pain relief in OA w/ diclofenac over 8-12 weeks
  - Number needed to treat (NNT) 6 for solution & 11 for gel formulation
  - Ketoprofen recent studies failed to show benefit over placebo
  - Topical salicylates separated out in some studies - Slightly less effective

- **Variable topical absorption rates through skin**
  - Etofenamate(21%)– diclofenac (6%) --ibuprofen (5%) --ketoprofen (1%) – salicylic acid (1-23%).

- Evidence for accumulation in target tissues- synovium,fascia,muscle, ligament
  - Diclofenac 10-20 x higher in synovial tissue than plasma w/ topical use
TOPICAL NSAIDs

- Use may lower po NSAID use
  - Study 3500 pts w/ 40% reduction in po NSAID w/top etofenamate
- Lower toxicity profile
  - Blood level w/ topical 0.4 -2.2% of blood level w/ po diclofenac
  - No GI harm or renal failure noted
- Improved tolerability
  - Mild skin rash- most common side effect
- American College of Rheumatology
  - Strongly recommended over po NSAID for patients > 75 yrs
# NSAID vs Opioids: which is better?

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<tr>
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<th>NSAIDs</th>
<th>OPIOIDs</th>
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<tr>
<td><strong>Side Effects</strong></td>
<td>Y - increase w/ use</td>
<td>Y - decrease w/ use</td>
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<tr>
<td><strong>Major Organ toxicity</strong></td>
<td>Y (GI, kidney, liver, CV)</td>
<td>N</td>
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<tr>
<td></td>
<td>Y</td>
<td>Sex hormone decrease; May diminish immune sys</td>
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<td>** Observable early S/S of toxicity**</td>
<td>Often NO</td>
<td>Y (sedation)</td>
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<td><strong>Fluid/Electrolyte imbalance effect</strong></td>
<td>Y</td>
<td>N</td>
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<tr>
<td><strong>Life–threatening toxicities</strong></td>
<td>Y (bleeding, MI, CVA, renal failure)</td>
<td>Y (Resp depression/arrest)</td>
</tr>
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<td><strong>Substance Use Disorder Risk</strong></td>
<td>N</td>
<td>Y</td>
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NSAID AS FRENEMY!
KNOW HOW TO USE IT & WHEN NOT TO!

- Effective Analgesic
- Anti-inflammatory
- Opioid sparing
- Non-serious & serious side effects
- Helpful in acute & chronic nociceptive pain
- Unlikely to replace opioids for mod/severe pain
  - Adjunctive use helpful
  - Limited effect on neuropathic pain
- Best use- time limited, dose limited, appropriate patient selection, monitored side effects
References

- Available on request
PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.

  - 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

  - No cost.

For more information visit:

pcssnow.org/mentoring
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now ›
**PCSS** is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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