NSAID Use in Older Adults: Balancing Risks and Benefits

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Conflict of Interest

I, Kristen Helms, have no actual or potential conflict of interest in relation to this program.

Objectives

- Describe cardiovascular, renal, and gastrointestinal risks associated with use of non-steroidal anti-inflammatory drugs (NSAIDs)
- Compare and contrast risk of adverse effects amongst various NSAIDs
- Identify patient characteristics in older adults that may increase the risk of adverse effects from NSAID use
- Explain strategies for minimizing risks associated with NSAID use in older adults
Use of NSAIDs

- One of the most commonly used classes of drugs
- Ibuprofen and naproxen most common in US
- In 2010, ~13% of adults estimated to be using NSAIDs at least 3 times weekly for at least 3 months
- 43% increase from 2005
- In 2012, 98 million prescriptions were written for NSAIDs in the US
- In 2007, up to 40% of people over 65 reported used prescription or OTC NSAIDs

Conaghan P. Rheumatol Int 2012

Why NSAIDs?

- More than 30% of people use NSAIDs for arthritis or common aches and pains
- American College of Rheumatology (ACR) Osteoarthritis Guidelines
  - Hand, Knee, Hip
- American Academy of Neurology Migraine Guidelines

http://www.nature.com/scitable/topicpage/fatty-acid-molecules-a-role-in-cell-14231940
NSAID Characteristics

- No differences in efficacy amongst NSAIDs
- Good oral bioavailability and gastrointestinal absorption
- Variable rates of absorption
- Low hepatic clearance
- Half-lives vary
  - Short (<6 hours)
  - Long
- Selectivity for COX 1 vs COX 2 varies

<table>
<thead>
<tr>
<th>NSAID</th>
<th>COX 2 selectivity</th>
<th>Half-life</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Non-selective (1.05)</td>
<td>2</td>
<td>1-2</td>
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<tr>
<td>Diclofenac</td>
<td>Non-selective (1.97)</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Naproxen</td>
<td>Non-selective (0.33)</td>
<td>12-17</td>
<td>2-4</td>
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<tr>
<td>Meloxicam</td>
<td>Selective (2.04)</td>
<td>15-20</td>
<td>4-6</td>
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<tr>
<td>Celecoxib</td>
<td>Selective (7.70)</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Non-selective (0.02)</td>
<td>2.1</td>
<td>&lt;2</td>
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Adapted from Conaghan P. Rheumatol Int 2012

What are the risks?

- Gastrointestinal
- Renal
- Cardiovascular
- Others: hepatic, hematologic

- However, more than half of patients using NSAID are unaware of risks

Adapted from Wilcox CM and Cryer B. Rheumatol J Rheumatol 2010
Case 1

- JT is a 72 year old male with long-standing osteoarthritis in both hips. He has failed scheduled acetaminophen at maximum doses and is inquiring about the use of NSAIDs. Celecoxib is cost-prohibitive, so his physician is asking for a recommendation on other NSAIDs.

- Which of the following NSAIDs would be most appropriate for use in this patient?
  - A. Naproxen
  - B. Ibuprofen
  - C. Diclofenac
  - D. The only appropriate NSAID is celecoxib
Characterizing the Risk

- 10-30% of people receiving NSAIDs develop ulcers in the upper GI tract
- 1-2% experience serious complications
- Potential risk to lower GI tract
- Hospitalization rates due to GI ADRs increase with age
  - GI mucosal senescence
  - Increased fragility of blood vessels in GI tract
  - Decrease in mucosal defense strategies

- Dose dependent relationship
- Synergistic effect on GI risk with H. pylori infection and NSAID use
- Increased GI ADRs with non-selective NSAIDs
  - Risk still evident with selective agents

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<table>
<thead>
<tr>
<th>NSAID</th>
<th>Upper GI Bleed</th>
<th>All upper GI complications (obstruction, perforation, bleed)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rate Ratio (95% CI)</td>
<td>P value</td>
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<tr>
<td>Celcoxib</td>
<td>2.22 (1.64-4.33)</td>
<td>0.0014</td>
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<tr>
<td>Diclofenac</td>
<td>2.20 (1.06-4.54)</td>
<td>0.0051</td>
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<tr>
<td>Ibuprofen</td>
<td>3.63 (1.09-12.12)</td>
<td>0.0059</td>
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<tr>
<td>Naproxen</td>
<td>5.49 (2.74-10.99)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
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Adapted from Coxiib and Traditional NSAID Trialists' Collaboration. Lancet 2013.
Characterizing the Risk

- Relative risk of upper GI bleeding increased with increased COX 1 inhibition
- Risk not affected by amount of COX 2 inhibition
- Highest relative risk in agents with strong COX 1 and COX 2 inhibition: indomethacin, ketorolac, naproxen, piroxicam
- NSAIDs with short half lives (e.g., ibuprofen) had decreased risk compared to those with longer half lives (e.g., piroxicam)

Adapted from Conaghan P. Rheumatol Int 2012
Mitigating Gastrointestinal Risk

- Choose COX 2 selective agents (e.g., celecoxib), when possible
- Use the lowest effective dose
- Choose medications with shorter half lives (e.g., ibuprofen)
- Use gastric protective agents such as proton pump inhibitors
  - Can be combined with selective or non-selective NSAIDs for benefit

Case 1

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Renal Risk
Normal GFR maintained through vasodilatory prostaglandins at the afferent arteriole and angiotensin II (vasoconstriction) at the efferent arteriole.

Effects of NSAIDs on the Glomerulus

Addition of an NSAID results in:
1. Blocking of prostaglandins at afferent arteriole
   - BLOCKS vasodilation, causes vasoconstriction
2. Unopposed angiotensin II at efferent arteriole
   - Continued vasoconstriction
3. Decreased glomerular perfusion

NSAIDs and Renal Risk

- Both nonselective and selective NSAIDs have been linked to renal toxicity
- Risk is greatest in older adults and those with diabetic nephropathy, hypertension, and/or heart failure
- COX1 has been associated with sodium excretion in the collecting duct
- Potential link with hypertensive effects of NSAIDs
- Risk of nephrotoxicity greatest with higher doses and NSAIDs with longer half lives (e.g., naproxen, piroxicam)
Mitigating Risk

- Avoid use of NSAIDs in patients with heart failure, uncontrolled hypertension, and/or heart failure
- Use the lowest effective dose
- Choose an NSAID with a short half-life (e.g., ibuprofen)

CARDIOVASCULAR RISK

In the News....

- 2005: Addition of Black Box Warnings to non-Aspirin NSAIDs
- February 10-11, 2014: Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee
- July 9, 2015: Update to Boxed warning issued by FDA
General CV Risk Concerns

- Thrombotic Risks:
  - Myocardial Infarction (MI)
  - Stroke
  - Heart Failure (secondary to MI)

Theoretical Perspective

- Impact of COX inhibition:
  - Imbalance between COX 2 mediated production of thromboxane in platelets and prostaglandins blocking aggregation in endothelial cells
  - May lead to vasoconstriction, platelet aggregation, and thrombosis

- Initial school of thought
  - Increases in COX2 selectivity associated with increase CV risk
  - HOWEVER, non-selective NSAIDs carry the same COX2 inhibition as non-selective NSAIDs
Case 2

- LL is an 80 year old female with RA and history of MI 10 years prior. NKDA.
- Medications: Methotrexate 7.5 mg PO weekly, folic acid 1 mg daily, aspirin immediate release 81 mg daily, metoprolol 25 mg twice daily, lisinopril 5 mg daily
- Which of the following is the most appropriate NSAID in this patient?
  - A. Ibuprofen
  - B. Naproxen
  - C. Celecoxib
  - D. Diclofenac

Historical Perspective

- Vioxx Gastrointestinal Outcomes Research (VIGOR) study
  - Rofecoxib 50 mg daily increased incidence of MI by 4 fold compared to naproxen 100 mg daily in patients with RA
- Adenomatous Poly Prevention On Vioxx (APPROVe) study
  - Patients with h/o colorectal adenomas
  - Rofecoxib 25 mg daily increased RR (vs placebo) of thrombotic events after 18 months
  - Rofecoxib 25 mg daily increased RR of MI after 18 months
  - Early study discontinuation due to CV findings
  - Resulted in removal of rofecoxib (2004) and valdecoxib (2005) from market

Major CV Risk Trials

In 2006:
- Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT)
- Adenoma Prevention with Celecoxib (APC) study
- Prevention of colorectal Sporadic Adenomatous Polyps (PreSAP) study
  - Celecoxib 200-400 mg daily associated with increase in death from CV causes in APC study
  - Results not confirmed in ADAPT or PreSAP but all three discontinued
Other CV Risk Findings

- Systematic review by Chen YF, et al. found a greater risk of MI with use of celecoxib in patients with RA or OA compared to patients receiving non-selective NSAIDs.
- However, a similar study and meta-analysis found no difference in CV risk between non-selective and COX 2 selective NSAIDs.
- Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Meta-analysis of three trials
- Etoricoxib 60 or 90 mg daily vs diclofenac 150 mg daily
- Risk for thrombotic CV events similar between NSAIDs (hazard ration 0.95, 95% CI 0.81-1.11)

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Other CV Risk Findings

- McGetlin, et al. meta-analysis
  -Diclofenac associated with greater risk of CV events (RR 1.40) than ibuprofen (1.07) and naproxen (0.97)
- Kearney, et al. meta-analysis
  -High dose ibuprofen and high dose diclofenac associated with a moderately increased risk of all vascular events (ibuprofen rate ratio 1.51, diclofenac rate ratio 1.63)
  -Risk similar to that with COX2 selective agents
  -Risk with naproxen significantly lower (rate ratio 0.92)

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Other CV Risk Findings

Danish Cohort Study:
- Evaluated CV events in healthy NSAID users vs nonusers
  -NSAIDs used for 1 week to 1 month at low doses
  -Diclofenac >100 mg daily increased risk of CV death (OR 2.04), coronary death or nonfatal MI (OR 2.01), fatal or nonfatal stroke (OR 1.70)
- Same study: rofecoxib OR 1.66 for CV death
  -Celecoxib doubled odds of coronary death or nonfatal MI
  -Only at ≥200 mg daily (contradicts dose-relationship in early trials)
- Naproxen increased the risk of fatal and nonfatal stroke (OR 1.91)
Coxib and traditional NSAID Trialists’ (CNT) Collaboration

- **Meta-analyses**
  - 280 trials of NSAIDs versus placebo
  - 474 trials of one NSAID versus another NSAID

- **Outcomes**
  - Major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death)
  - Major coronary events (non-fatal myocardial infarction or coronary death)
  - Stroke
  - Mortality
  - Heart failure
  - Upper gastrointestinal complications (perforation, obstruction, or bleed)

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Coxib and traditional NSAID Trialists’ (CNT) Collaboration

- **Major vascular events**
  - Increased by ~33% with COX 2 selective agents (rate ratio 1.37, 95% CI 1.14-1.66; p=0.0009) or diclofenac (rate ratio 1.41, 1.12-1.78; p=0.0036)
  - Increase independent of patient baseline characteristics (e.g., vascular risk)
  - No significant increase in major vascular events with ibuprofen or naproxen

- **Major coronary events**
  - Increased with coxibs (1.76, 1.31-2.37; p=0.001) and diclofenac (1.70, 1.10-2.41; p=0.002)
  - Increased with ibuprofen (2.22, 1.10-4.48; p=0.025)

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Coxib and traditional NSAID Trialists’ (CNT) Collaboration

- **Vascular death**
  - Increased significantly by COX2 selective agents (1.58, 95% CI 1.00-2.49; p=0.0193) and diclofenac (1.85, 0.95-3.68; p=0.0187)
  - No significant increase with naproxen or ibuprofen

- **Heart Failure**
  - Risk of heart failure doubled with all NSAIDs
FDA Conclusions

1. The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
2. The risk appears greater at higher doses.
3. It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; • Newer information is not sufficient to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

4. NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease.
5. In general, patients with heart disease or risk factors have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors
6. Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients not treated with NSAIDs
7. There is an increased risk of heart failure with NSAID use.

Mitigating CV Risk

• Consider use of naproxen preferentially over ibuprofen for all patients on chronic therapy, regardless of cardiovascular risk
• Avoid NSAIDs in patients less than 1 year out from a cardiovascular event or stroke
• Consider alternatives to NSAIDs when possible
• Use all NSAIDs at lowest effective dose
• Avoid systemic diclofenac in all patients
Case 2

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Which of the following is the most appropriate NSAID in this patient?
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Case 3

After recommending naproxen for this patient, the physician inquires about the combination of aspirin and NSAIDs. How should LL be directed to take the NSAID you recommended?
A. Take the recommended NSAID 1 hour prior to aspirin
B. Take the recommended NSAID 4 hours prior to aspirin
C. Take the aspirin 2 hours prior to the recommended NSAID
D. Aspirin and NSAIDs may be taken at the same time

Aspirin and NSAIDs

Aspirin irreversibly acetylates COX1 in platelets preventing formation of thromboxane for the life of the platelet
NSAID antiplatelet effects are variable and reversible and can block aspirin access to the site of action
Ability to block aspirin depends on COX1 affinity
Aspirin and NSAIDs

Mitigating Risk

- Non-enteric coated aspirin takes approximately 60 minutes to reach site of action and irreversibly inhibit platelet aggregation
- Catella-Lawson et al. found that ibuprofen taken 2 hours after ingestion of non-enteric coated aspirin prevents interference with aspirin's antiplatelet effects
- Similar findings in research with naproxen and non-enteric coated aspirin
- Another study found that ibuprofen taken 2, 7 and 12 hours after enteric coated aspirin still interfered with anti-platelet effects

Mitigating Risk

- For patients taking both NSAIDs and aspirin, recommend the following:
  - Use of non-enteric coated aspirin
  - Consider immediate-release NSAIDs
  - Naproxen or ibuprofen as NSAIDs of choice
  - Take NSAID at least 2 hours after aspirin dose
  - Considering PK, take aspirin dose early in morning with last NSAID dose night prior
  - Naproxen at least 6 hours prior to aspirin dose
  - Use NSAIDs as infrequently as possible
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BALANCING THE RISKS

Additional Risk Mitigation Strategies

- EDUCATE
- Acetaminophen
- Topical products
  - Non-NSAIDs (e.g., capsaicin)
  - NSAIDs (e.g., diclofenac)
- Non-pharmacologic management of pain
  - Physical therapy
  - Weight loss
  - Assistive devices
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