Osteoarthritis: The Good, The Bad, and The Ugly

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Learning Objectives

• Describe the effectiveness of available treatment options for management of osteoarthritis (OA).

• List at least two long-term toxicities associated with chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and identify management strategies.

Osteoarthritis (OA) statistics

• Most common form of arthritis
• ~27 million Americans
• 13.9% of adults ≥ 25 years
  – 33.6% of those ≥ 60 years
• Prevalence underestimated
• More common in women
• Increases with age, levels off at ~80 years
• 7.1 million office visits

Prevalence of symptomatic OA


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Pathophysiology of OA

Clinical presentation

- Pain
  - Usage related
  - Worse at end of day, relieved by rest
  - Mild morning pain/stiffness (<30 min)
  - Episodic or variable severity; slow to change
- Joint instability and misalignment
- Crepitus and restricted movement
- Bony enlargements
- Absent or moderate effusion
- Lack of inflammation

Available guidelines

- American College of Rheumatology (ACR), 2000
- National Institute of Health and Clinical Excellence (NICE), 2008
- American Academy of Orthopaedic Surgeons (AAOS), 2008
- Agency for Healthcare Research and Quality (ARRQ), 2009
- Osteoarthritis Research Society International (OARSI), 2010

The Good

Nonpharmacological treatments

- Patient education
- Exercise
  - Strengthening
  - Aerobic (low impact)
  - Water-based
- Weight reduction
- Transcutaneous electrical nerve stimulation
- Assistive devices
- Acupuncture

Effect Sizes (ES) for OA knee pain with nonpharmacological therapies*

* ES for both hip and knee

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Pharmacological treatments

- Acetaminophen
- NSAIDs
  - Oral +/- gastroprotective agent
  - Topical
- Opioids
- Topical capsaicin
- Intra-articular (IA) corticosteroids
- IA hyaluronic acid

Effect Sizes (ES) for OA knee pain with pharmacological therapies*

<table>
<thead>
<tr>
<th>ES for Pain</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>1.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Both hip and knee OA
† Any OA


Topical NSAIDs

- Act locally at application site
- Minimal systemic absorption
- Mild to moderate pain
- Superficial joints (e.g., knees and hands)
- Few joints affected
- Used before oral NSAIDs in EULAR and NICE guidelines
- Diclofenac 1% gel and 1.5% in 45.5% dimethylsulfoxide (DMSO) solution

Topical vs. oral NSAID studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Results</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zacher et al., 2001</td>
<td>321 hand OA pts received diclofenac gel 4 times daily vs. PO ibuprofen 400 mg 3 times daily</td>
<td>Equally effective for pain at rest and on movement, stiffness, quality of life</td>
<td>Topical diclofenac fewer D/C due to treatment-related AE (1.25% vs. 8.3%) and GI AE (0.6% vs. 5.1%).</td>
</tr>
<tr>
<td>Tugwell et al., 2004</td>
<td>622 knee OA pts received diclofenac solution 3 times daily or PO diclofenac 50 mg 3 times daily</td>
<td>Improvement of 30-44% in WOMAC pain, function, stiffness and global assessment vs. 45-49% with PO</td>
<td>No serious AE with topical diclofenac. GI AE more frequent with PO (48% vs. 35%) Application site AE 27% vs. 1%.</td>
</tr>
</tbody>
</table>

Efficacy and safety of topical diclofenac containing DMSO compared to placebo, DMSO vehicle and PO diclofenac for knee OA

- Randomized, placebo controlled trial
- 755 patients with knee OA
- Treatments:
  - Topical diclofenac 1.5% (TDiclo)
  - Placebo
  - DMSO
  - Oral Diclofenac 50 mg 3 times daily (ODiclo)
  - Topical + oral diclofenac (TDiclo+ODiclo)


Topical diclofenac dosing and cost

- Dosing: 4 times daily
  - 1% gel (Voltaren® gel)
    - Lower extremities: Apply 4 g to affected area
    - Cost: $40.99 (1, 100 g tubes)
  - 1.5% solution (Pennsaid®)
    - Apply 20 drops on each painful knee
    - Cost: $180.00 (150 mL)

Costs from: www.drugstore.com

The Bad

Acetaminophen (APAP) safety concerns

- APAP-induced liver injury due to toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI)
- Leading cause of acute liver failure 1998-2003
  - 48% of APAP-related acute liver failure cases associated with accidental overdose
- From 1990-1998 estimated:
  - 56,000 ER visits
  - 26,000 hospitalizations
  - 458 deaths


TIME Health

FDA Advises Lower Dosage for Popular Painkiller

- June 30, 2009 FDA advisory panel recommended lowering maximum OTC APAP dose
- January 11, 2011 FDA limited Rx APAP dosing
  - Combination products ≥ 325 mg APAP
  - Maximum daily dose 4 g/day
  - Do not use ≥ 3 days for fever or 10 days for pain unless prescribed
  - Boxed Warning highlighting potential for severe liver injury and a warning highlighting potential for allergic reactions

http://www.time.com/time/health/article/0,8599,1908042,00.html
http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm

Overview: glucosamine/chondroitin

Glucosamine and Chondroitin

- Glucosamine
  - Hexosamine sugar
  - Precursor in synthesis of connective tissue macromolecules
  - Sulfate or hydrochloride (HCl) salt
  - May stimulate chondrocytes

- Chondroitin
  - Glycosaminoglycan (GAG) found in articular cartilage
  - Hydrophilic properties
  - Allows articular cartilage to absorb water
  - Convey and absorb compressive forces

Expenditures on glucosamine supplements

- Global sales $2 billion in 2008
- US sales $872 million
- Increased 62% since 2003
- Forecasted growth to 2013 of $2.3 billion
- US sales lag behind global sales

Studies of glucosamine and chondroitin

- Conflicting results
- Trials with positive results hampered
  - Poor study design
  - Small sample size
- Larger, methodologically sound trials often found no effect
- Publication bias?

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee OA (GAIT)

- Multicenter, double-blind, placebo- and celecoxib-controlled trial
- 1583 patients randomized to:
  - 1500 mg glucosamine daily
  - 1200 mg chondroitin daily
  - Combination
  - 200 mg celecoxib daily
  - Placebo
- 1 outcome: 20% ↓ pain baseline to week 24


GAIT results: all patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glucosamine</th>
<th>Chondroitin</th>
<th>Glucosamine + Chondroitin</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC*</td>
<td>60.1</td>
<td>64.0</td>
<td>65.4</td>
<td>66.6</td>
<td>70.1†</td>
</tr>
</tbody>
</table>

* Western Ontario and McMaster Universities Osteoarthritis Index
† p<0.008, Number needed to treat (NNT) = 10


GAIT results: patients with moderate-to-severe pain (n=354)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glucosamine</th>
<th>Chondroitin</th>
<th>Glucosamine + Chondroitin</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC*</td>
<td>54.3</td>
<td>65.7</td>
<td>61.4</td>
<td>79.2†</td>
<td>69.4‡</td>
</tr>
</tbody>
</table>

* WOMAC score 301-500
† p<0.002, NNT= 4
‡ p=0.06


Effects of glucosamine, chondroitin, or placebo in patients with OA of hip or knee

- Network meta-analysis of large RCTs
- Trials with ≥ 200 patients with OA of hip or knee
- Received glucosamine, chondroitin, or both
- 10 trials with 3,803 patients included
- Primary outcome: pain intensity on 10 cm visual analogue scale (VAS)
  - Clinically significant difference -0.9 cm
- Secondary outcomes: joint space narrowing

Change in pain intensity compared to placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Pain Intensity (10 cm VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosamine</td>
<td>0.4</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>0.3</td>
</tr>
<tr>
<td>Combination</td>
<td>0.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Additional results

- No difference in joint space narrowing
  - Glucosamine: -0.2 mm (-0.3 to 0.0 mm)
  - Chondroitin: -0.1 mm (-0.3 mm to 0.1 mm)
  - Combination: 0.0 mm (-0.2 to 0.2 mm)

- Glucosamine/chondroitin safe
  - Adverse effects similar to placebo
  - No differences in drop outs

Glucosamine and/or Chondroitin

Bottom Line

- Not recommended
- Data lacking demonstrating benefit
- Costly
- Products are safe
- If patients choose to start:
  - Use glucosamine sulfate rather than HCl
  - Choose reputable manufacturer
  - Discontinue after 3 months if no benefit

The Ugly

NSAID adverse effects and safety considerations

- Worsening hypertension
- Heart failure exacerbations
- Avoid in cirrhosis
- Renal dysfunction
- Concomitant ACE inhibitor or ARB
- Concomitant anticoagulant or ASA use
- Upper gastrointestinal (GI) events
- Cardiovascular disease (CVD)

Medication Guide for NSAIDs

- "May increase the chance of a heart attack or stroke that can lead to death. This chance increases:"
  - with longer use of NSAID medicines
  - in people who have heart disease
- "Should never be used right before or after a heart surgery called a 'coronary artery bypass graft (CABG)."
- "Can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:"
  - can happen without warning symptoms
  - may cause death
Upper GI events (UGIE) and NSAIDs

- 1:20 NSAID users develop UGIE (symptomatic or complicated ulcers)
  - 1:7 for elderly
- 30% may result in hospitalizations and/or death
- Among patients with arthritis:
  - 107,000 hospitalizations
  - 16,500 deaths

Risk factors for upper GI bleeding associated with NSAIDs

Age and NSAID induced GI toxicity

NSAIDs and Cyclo-oxygenase (COX) inhibition

Mechanism of NSAID-induced GI mucosal damage

ACCF/ACG/AHA 2008 Expert Consensus on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

- PPIs preferred for therapy and prophylaxis of NSAID- and ASA-associated GI injury
- Test for and eradicate H. pylori in patients with history of ulcer before starting chronic antiplatelet therapy
NSAIDs and risk of CVD

- Increase BP and edema
- COX-2 inhibition ↓ prostacyclin (PGI₂)
  - ↓ smooth muscle cell relaxation and vasodilation
  - ↓ inhibition of platelet aggregation
- Meta-analyses indicate:
  - COX-2 selective NSAIDs ↑ risk of CV events
  - Non selective NSAIDs also ↑ risk
  - Exception naproxen (?)


NSAIDs and CVD versus placebo

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>Meta-analysis of RCTs*</td>
<td>Vascular events</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of OlIs¹</td>
<td>CV events, mostly MI</td>
<td>0.97</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Meta-analysis of RCTS</td>
<td>Vascular events</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of OlIs</td>
<td>CV events, mostly MI</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>Registry</td>
<td>Recurrent MI</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>Registry</td>
<td>Mortality</td>
<td>1.50</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Meta-analysis of RCTS</td>
<td>Vascular events</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of OlIs</td>
<td>CV events, mostly MI</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>Registry</td>
<td>Recurrent MI</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>Registry</td>
<td>Mortality</td>
<td>2.40</td>
</tr>
</tbody>
</table>

* Randomized controlled trials
¹ Observational studies


NSAIDs and CVD versus selective COX-2 inhibitor

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>Meta-analysis of RCTs</td>
<td>Vascular events</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>Any non-naproxen NSAID*</td>
<td>Vascular events</td>
<td>1.14</td>
</tr>
</tbody>
</table>

* Primarily diclofenac or ibuprofen


2007 AHA Stepped Care Approach with Known CV Risk factors for IHD

- APAP, ASA, tramadol, opioid (short-term)
- Nonacetylated salicylates
- Select patients at low risk of thrombotic event
- Use lowest dose possible
- Add ASA 81 mg and PPI for those at increased risk of thrombotic event
- NSAID with some COX-2 activity
- COX-2 selective NSAID


Duration of treatment with NSAIDs and impact on risk of death and recurrent myocardial infarction (MI)

- Population-based Danish registry study
- 83,677 patients >30 years admitted for first MI between 1997-2006
- NSAID use evaluated at various time frames from pharmacy database
- Primary outcome: risk of death and recurrent MI according to:
  - NSAID
  - Time frame


Risk of death/RE-MI associated with NSAIDs

**Risk of death associated with all NSAIDs**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 days</td>
<td>1.34 (1.20-1.53)</td>
</tr>
<tr>
<td>7-14 days</td>
<td>1.82 (1.61-2.05)</td>
</tr>
<tr>
<td>14-30 days</td>
<td>1.58 (1.44-1.74)</td>
</tr>
<tr>
<td>30-90 days</td>
<td>1.86 (1.74-1.99)</td>
</tr>
<tr>
<td>All NSAIDs &gt;90 days</td>
<td>1.56 (1.47-1.65)</td>
</tr>
</tbody>
</table>


**Recommendations for prevention of NSAID-related ulcer complications**

<table>
<thead>
<tr>
<th>Gastrointestinal Risk*</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV risk</td>
<td>NSAID alone (least ulcerogenic)</td>
<td>NSAID + PPI/misoprostol</td>
<td>Alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol</td>
</tr>
<tr>
<td>High CV risk</td>
<td>Naproxen + PPI/misoprostol</td>
<td>Naproxen + PPI/misoprostol</td>
<td>Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy</td>
</tr>
</tbody>
</table>

* Stratification by low risk (no risk factors), moderate risk (1-2 risk factors include age (>65), high dose NSAID, previous history of uncomplicated ulcer, concurrent ASA, corticosteroids, or anticoagulants, or high risk (previous complicated ulcer or >2 risk factors).


**Summary of treatment of OA**

- Nonpharmacological therapy
  - Acetaminophen

- If high GI or CV Risk Factors:
  - NSAIDs‡
  - Topical NSAID† + gastroprotective†
  - Opioids

- If high CV disease*:
  - Nonselective NSAID‡ + COX-2 inhibitor†
  - Topical NSAID† + gastroprotective

* If high CV risk, avoid NSAIDs.
† Add additional therapies (e.g., capsacian, intraarticular injections) as appropriate
‡ Naproxen preferred initial NSAID

**Conclusions**

- Effective drug treatments for OA
- Always use with nonpharmacological modalities
- Data support use of topical NSAIDs
- Glucosamine/chondroitin appear ineffective
- Carefully weigh GI and CV risks/benefits before using oral NSAIDs

**Questions?**

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