Osteoarthritis

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Disclosure

• Consultant/Independent Contractor: Analgesic Solutions, AstraZeneca, MyMatrixx, Pfizer, Purdue
Learning Objectives

• Describe the pathophysiology of osteoarthritis
• Review pharmacologic treatment options for osteoarthritis
• Identify non-pharmacologic treatment options for osteoarthritis
Overview

1. Pathophysiology, the old, the new...
   • Peripheral and central changes
   • Is OA central pain?

2. Pharmacologic evidence
   • NSAID Review
   • Recent warnings on NSAIDs
   • NGF antiboide

3. Nonpharmacologic Interventions
   • Obesity
   • Exercise. Why bother?
   • Regenerative therapies

4. Assessment of Hip Pain
Pain Processing: From Transduction to Perception

The Role of Plasticity in OA

- Injury
  - Acute Pain

- Normal Healing
  - Pain Relief

- Healing With Plasticity
  - Hyperalgesia
  - Allodynia
    - Chronic Pain

Osteoarthritis Classification

- Localized Osteoarthritis
  - Usually 1 to 2 joints only
- Generalized Osteoarthritis
  - Spine or hand and at least 2 other joint regions
- Knee, hip, and hands are the most commonly affected joints
- Other classification considerations include
  - Age of onset
  - Presumed etiology or associated condition
  - Radiographic evidence
  - Rate of progression
Osteoarthritis
Cartilage to the Whole Joint

Normal

Osteoarthritis

Cartilage
• Fibrillated/Destroyed

Synovium
• Episodically inflamed

Bone
• Bony outgrowths

INJURY

Tissue Damage

PERIPHERAL ACTIVITY

Nerve Damage

SYMPTOMS

Hyperalgesia

Spontaneous Pain

Allodynia

CENTRAL SENSITIZATION

Increased Spontaneous activity

Expansion of Receptive field

Decreased threshold to peripheral stimuli
Terminology

- Central Sensitivity Syndrome (CSS)
- Central sensitization (CS)
- Temporal summation (TS)
- CS as secondary hyperalgesia
- Diffuse Noxious Inhibitory Control (DNIC)

Yunus, M. *Current Rheumatology Reviews* 2015;11:70-85.
Classification of CS (proposed)

A. Acute: physical trauma; nerve injury, post-surgical

B. Chronic
   1. Primary without underlying disease
      Central sensitivity syndromes (CSS): fibromyalgia, IBS, RLS
      Neurovasomotor diseases (CRPS)
   2. Secondary to well-defined pathology
      Well defined: OA, RA, SLE, MS, malignancy
      Infection: Viral, bacteria, fungi
      Drugs: morphine
      Neonatal and childhood stress
      Trauma: surgical, physical trauma
   3. Neuropathies irrespective of 1° or 2° cause
   4. Poor sleep irrespective of 1° or 2° cause

Pain Outcomes after TKA

Study\textsubscript{1}: 1217 patients
- Up to 20\% of patients dissatisfied with outcomes

Study\textsubscript{2}:
- Preoperative low threshold to electric stimulation predicted persistent post-operative pain

Measured:
1. Pressure Pain Thresholds (PPTs)
2. Temporal summation
3. Pain after IM hypertonic saline
4. Pressure pain modulation by DNIC

N=24 patients (knee pain on VAS ≥6) and 24 control subjects. Sequential pressure stimulation (10 stimuli, 1-s duration, 1-s interval) was applied to affected knee and remote site (tibialis anterior). VAS= visual analog scale.


*P<.05.
CS after joint replacement

• Normalization of widespread pressure pain hypersensitivity after THA associated with clinical and functional improvements\textsuperscript{1}

• Widespread sensitization in patients with pain after re-TKA reported, highlighting importance of ongoing nociceptive input for the chronification process\textsuperscript{2}

2. Pharmacotherapy

Acetaminophen

NSAIDs

OPIOIDS

TOPICALS

COX-2 (-)
Acetaminophen

- 325, 500, 650 mg
- Relative bioavailability 85-98%
- Liver metabolized
  - Conjugation with glucuronide (phase II)
  - Conjugation with sulfate
  - Oxidation via cytochrome P-450 (phase I): NAPQ1
- Low molecular weight and protein binding: passes blood brain barrier
Acetaminophen: Mechanism

- Peripheral and central effect
- Central COX-3 effect controversial
- Possible 5-HT3 receptor effect
- Granisetron (Kytril) blocks analgesic effects of acetaminophen

Cox-2 Inhibitors

First generation
Nimesulide

Etodolac
Meloxicam

Marketed compounds
Celecoxib
Rofecoxib

Clinical candidates
Valdecoxib
Etoricoxib
Classic NSAIDs

- Acetylsalicylic acid
- Indomethacin
- Diclofenac
- Naproxen
- Ibuprofen
Traditional NSAIDs

• **Salicylates**
  – Aspirin
  – Diflunisal

• **Acetic acid derivatives**
  – Indomethacin
  – Sulindac
  – Edodolac
  – Mefenamic acid
  – Meclofenamate
  – Tolmetin
  – Ketorolac
  – Diclofenac

• **Proprionic acid derivatives**
  – Ibuprofen
  – Naproxen
  – Ketoprofen
  – Oxaprozin

• **Enolic acid derivatives**
  – Piroxicam
  – Meloxicam
  – Nabumetone
Acetic acid derivatives

- Indomethacin (INDOCIN)
- Sulindac (CLINORIL)
- Edodolac (LODINE)
- Tolmetin (TOLECTIN)
- Ketorolac (TORADOL)
- Diclofenac (VOLTAREN, ARTHROTEC)
Proprionic acid derivatives

- Ibuprofen (ADVIL, MOTRIN, NUPRIN)
- Naproxen (ALLEVE, NAPROSYN)
- Ketoprofen (ORUDIS, ORUVAL)
- Oxaprozin (DAYPRO)
Celecoxib: pharmacokinetics

• Absorbed slowly and incompletely
• Significant first past metabolism (20-60% oral bioavailability)
• Variable elimination ½ life: 6-12 hours
The rise and fall of the COX-2 inhibitors

January 1994
FDA approves over-the-counter sale of naproxen (Aleve).

May 1999
FDA approves rofecoxib (Vioxx).

December 1999
Celebrex generates $1.4 billion in annual sales, a record for a drug in its first year on the market.

August 2001
Review of CLASS and VIGOR studies written by Dr. Eric Topol and his colleagues at the Cleveland Clinic published in JAMA. They call for a study of cardiovascular risks of the COX-2 inhibitors.

November 2001
FDA approves valdecoxib (Bextra).

April 2002
FDA changes label on Vioxx, advising doctors to use caution when prescribing for patients with heart disease.

December 2003
Combined annual sales for the COX-2 drugs reach $5.3 billion.

June 2000
Study published in the New England Journal of Medicine (NEJM) reports that Celebrex reduces polyp growth in people with familial adenomatous polyposis, a condition that leads to colorectal cancer.

September 2000
CLASS study of Celebrex published in the Journal of the American Medical Association (JAMA). Study focuses on gastrointestinal effects. No difference reported in cardiovascular events between Celebrex and placebo group.

November 2000
VIGOR study comparing Vioxx with naproxen published in the NEJM. Like CLASS study, it focuses on gastrointestinal effects. Heart attacks are rare, but they occur more often (0.4% vs. 0.1%) in those taking Vioxx.

September 2004
Merck pulls Vioxx off the market after 25-mg dose increases heart disease risk in a colon cancer trial.

Dec. 9, 2004
FDA puts strongest “black box” label on Bextra to warn about rare but life-threatening skin reaction and against prescribing the drug for people who have had coronary bypass.

Dec. 17, 2004
NIH halts colon cancer prevention study after researchers find Celebrex increases cardiovascular event risk by 2.5 times. Pfizer keeps Celebrex on the market, but stops advertising the drug to the public.

Dec. 20, 2004
NIH stops Alzheimer’s disease prevention trial after naproxen seems to cause increased risk of cardiovascular events. Drug stays on the market. FDA emphasizes recommended dosage (220 mg twice a day) and duration (no longer than 10 days) limits.

Sources: IMS Health, FDA, news sources.

Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With NSAIDs and COX-2s

**NSAIDs**

<table>
<thead>
<tr>
<th></th>
<th>Naproxen</th>
<th>Diclofenac</th>
<th>Ibuprofen</th>
<th>Indomethacin</th>
<th>Any/Other NSAIDs</th>
<th>Piroxicam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary Relative Risk</strong></td>
<td>0.97</td>
<td>1.40</td>
<td>1.07</td>
<td>1.30</td>
<td>1.10</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>0.87-1.07</td>
<td>1.16-1.70</td>
<td>0.97-1.18</td>
<td>1.07-1.60</td>
<td>1.00-1.21</td>
<td>0.70-1.59</td>
</tr>
</tbody>
</table>

**COX-2s**

<table>
<thead>
<tr>
<th></th>
<th>All Celecoxib</th>
<th>All Rofecoxib</th>
<th>Rofecoxib ≤25mg/d</th>
<th>Rofecoxib ≥25mg/d</th>
<th>Meloxicam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary Relative Risk</strong></td>
<td>1.06</td>
<td>1.35</td>
<td>1.33</td>
<td>2.19</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>0.91-1.23</td>
<td>1.15-1.59</td>
<td>1.00-1.79</td>
<td>1.64-2.91</td>
<td>1.00-1.55</td>
</tr>
</tbody>
</table>

FDA hearing: actions taken

- Class effect
- Black Box Warning
- Direct to Consumer Advertising (DTCA)
- Medication Guide
- Need for comparative trials

The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk appears greater at higher doses. It was previously thought that all NSAIDs may have a similar risk. NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors. 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 who were not treated with NSAIDs. There is an increased risk of heart failure with NSAID use.

FDA, July 9, 2015.
Antibodies to Nerve Growth Factor (NGF)?

• Tanezumab\textsubscript{1}
• Fulranumab\textsubscript{2}, Fasinumab\textsubscript{3}
• Report of serious joint-related adverse events\textsubscript{4}
• FDA hold (2010)\textsubscript{5}

5. http:\/\slash\slash www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307880
Knee OA: Changing scope of guidelines

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Topical NSAIDs</th>
<th>Oral NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>Conditionally recommended for initial therapy at a</td>
<td>Conditionally recommended for initial therapy;</td>
</tr>
<tr>
<td></td>
<td>maximal dose of 3000 mg/day</td>
<td>strongly recommended in patients unresponsive to</td>
</tr>
<tr>
<td>EULAR</td>
<td>Recommended as initial therapy; no dose</td>
<td>paracetamol</td>
</tr>
<tr>
<td>OARSI</td>
<td>recommendation</td>
<td>Consider in patients unresponsive to paracetamol</td>
</tr>
<tr>
<td>NICE</td>
<td>Appropriate for individuals without relevant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>co-morbidities, with conservative dosing and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>treatment duration</td>
<td></td>
</tr>
<tr>
<td>ESCEO</td>
<td>Offer paracetamol in regular doses for pain relief</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conditionally recommended for initial therapy either</td>
<td></td>
</tr>
<tr>
<td></td>
<td>alone or with paracetamol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical NSAIDs have efficacy and are safe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appropriate for individuals with knee OA only (with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or without co-morbidities)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider ahead of oral NSAIDs or opioids; can be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>used with paracetamol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommended with paracetamol or SySADOAs when</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients have insufficient pain relief</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appropriate for individuals without relevant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>co-morbidities; uncertain for those with moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>co-morbidity risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use when paracetamol and/or topical NSAIDs are</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ineffective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommended when paracetamol or SySADOAs and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>topical NSAIDs are not adequately effective</td>
<td></td>
</tr>
</tbody>
</table>

Treatments for OA: NICE Guidelines

NSAIDs=nonsteroidal anti-inflammatory drugs; COX-2=cyclooxygenase-2
# Topicals for OA Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association of Orthopedic Surgeons&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Symptomatic OA of knee and increased GI risk may receive one of the following analgesics for pain: paracetamol (&lt;4g/day), topical NSAIDs, nonselective oral NSAIDs plus gastroprotective agent, or COX-2 inhibitor</td>
</tr>
<tr>
<td>American Geriatric Society&lt;sub&gt;2&lt;/sub&gt;</td>
<td>All patients with localized non-neuropathic persistent pain may be candidates for topical NSAIDs</td>
</tr>
<tr>
<td>European League Against Rheumatism&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe treatments for hand OA</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Topical NSAIDs for pain relief in addition to core treatment for people with knee or hand OA. Topical NSAIDs or paracetamol should be considered ahead of oral NSAIDs, COX-2 inhibitors or opioids</td>
</tr>
</tbody>
</table>

1. Amer Academy Orthopaedic Surgeons, 2008.;
Topical Diclofenac: FDA Approved

3 approved products

- Diclofenac epolamine patch (FLECTOR® Patch)
  - Indication: acute pain due to minor sprains, strains, & contusions
  - BID
- Diclofenac sodium gel (Voltaren® Gel)
  - Indication: relief of pain of OA of joints amenable to topical treatment, such as the knees & those of the hands
  - QID
- Diclofenac 1.5% (Pennsaid®)
  - Treatment of signs and symptoms of osteoarthritis of the knee
  - 40 drops to each painful knee 4 times per day
Regenerative Medicine
PRP: Platelet Rich Plasma

Platelet-Rich Plasma (PRP)

- Provides milieu of bioactive growth factors
- Growth factors: stimulate cartilage matrix synthesis and mitigate catabolic cytokines (IL-1) and tumor necrosis factor-alpha (TNF-alpha)
- Platelets also store proteins with antibacterial and fungicidal effects, coag factors, membrane glycoproteins
PRP: clinical utility

- PRP enhanced proliferation and proteoglycan synthesis
- Clinical application:
  - Cartilage avulsion
  - Mesenchymal stromal cells mixed with PRP in cartilage defect
  - Pilot studies comparing PRP to hyaluronic acid in knee OA

3. Nonpharmacologic Treatments

**Psychological Support**
- CBT
- Biofeedback
- Relaxation training
- Supportive psychotherapy

**Lifestyle Change**
- Exercise
- Weight loss

**CAM**
- Massage
- Spinal manipulation
- Supplements
- Acupuncture

**Physical Medicine and Rehabilitation**
- Hot/cold presses
- Physiotherapy
- TENS
- Hydrotherapy

CAM = complementary and alternative medicine; TENS = transcutaneous electrical nerve stimulation.
Effect Size of Exercise: Pain

Guidelines for Exercise

- World health organization recommendation of 30 minutes of regular, moderate-intensity physical activity, 5 days/wk

- EULAR for HOA and KOA
  Regular exercise optimal exercise regimen not yet determined

- NHS for HOA and KOA
  Activity and exercise recommended irrespective of age, comorbidity, pain, or disability. Local strengthening, general aerobic fitness. Manipulation and stretching as adjunct Rx for hip OA

- SRS for OA
  6-8 wks exercise. Exercise goal determines type of exercise. Do daily activities exercise with <50° knee flexion. Individual exercise as effective as group exercise. Supervised exercise greater pain relief and compliance than home exercises

- OARSI HOA and KOA
  Referral to physical therapist for evaluation and instruction in appropriate exercises. Patients encouraged to undertake & maintain regular exercise- aerobic, strengthening and range of motion. For patients with symptomatic hip OA water exercises can be helpful

- ACR for HOA and KOA
  Aerobic, Range-of-motion and muscle strengthening exercises
  Physical and occupational therapy
How about weight loss?
Leptin in OA

• Central pathologic feature beyond cartilage
• "global joint disorder"
• Age-dependent deterioration of chondrocytes or "chondrosenescence"
• Leptin: adipocyte-derived hormone
• Synovial fluid leptin correlated with radiographic severity
• Leptin and cartilage homeostasis

Scotece M, Mobasher A. Life Sciences 2015, in press.
4. Assessment: Hip Pain

“Oh, it’s probably just arthritis . . . .”
Hip Pain: Differential Diagnosis

- Osteoarthritis
- Rheumatoid Arthritis
- FemoroAcetabular Impingement (FAI)
- Labral Tears
- Coxa Saltans ("Snapping Hip")
- Iliopsoas Bursitis
- Piriformis Syndrome
- Greater Trochanteric Bursitis
- Myofascial Pain
- Sacroiliac Joint Pain

Hip Exam

• Active/Passive ROM: FABER
• Motor Strength
• Provocative Testing
• Myofascial Assessment
  – Gluteus muscles, Adductors
  – Tensor Fascia Lata
• Bursa
• Iliotibial Band (ITB)
Hip Pain Physical Exam

- Hip loading
- Hip internal and external rotation
- Ober Test
- Trochanteric bursa testing
- Thomas Test: hip flexor tightness
- FABER
  (FlexionABductionExternal Rotation)
## Causes of pain around Hip joint

<table>
<thead>
<tr>
<th>Intra-Articular</th>
<th>Extra-Articular</th>
<th>Hip Mimickers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labral tears</td>
<td>Iliopsoas tendonitis</td>
<td>Athletic pubalgia</td>
</tr>
<tr>
<td>Loose bodies</td>
<td>Iliotibial band</td>
<td>Sports Hernia</td>
</tr>
<tr>
<td>Femoroacetabular impingement</td>
<td>Gluteus medius or minimus</td>
<td>Osteitis pubis</td>
</tr>
<tr>
<td>Capsular laxity</td>
<td>Greater trochanteric bursitis</td>
<td></td>
</tr>
<tr>
<td>Ligamentum teres rupture</td>
<td>Stress fracture</td>
<td></td>
</tr>
<tr>
<td>Chondral damage</td>
<td>Adductor strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piriformis syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sacroiliac joint</td>
<td></td>
</tr>
</tbody>
</table>

Labral Tears of Hip

- Common in females
- Groin and anterior hip pain
- Stabilizes the hip joint by deepening and increasing surface area of acetabulum
- Acts as a seal
- Tears commonly anteriorly
- Causes: trauma, femoroacetabular impingement, capsular laxity, dysplasia, degeneration

Hip Pain: Differential Diagnosis

NERVE ENTRAPMENT SYNDROMES

Iliohypogastric: pain in inguinal and suprapubic region

Ilioinguinal: pain in iliac fossa, groin, scrotum or labia majora, proximal medial thigh and back

Genitofemoral: pain and burning in groin, inner thigh

Lateral Cutaneous: anterolateral thigh

Obturator: hypoaesthesia, paresthesia or pain in medial thigh, groin or pubic bone

Thank you

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