Speaker Disclosure

• Research funding from Pfizer
• NIH K12HD051958
• NIH P50 AR060752
• NIH P50 AR063043
Learning Objectives

• Recognize that the course of pain in osteoarthritis is episodic and fluctuating.
• Become familiar with research that supports new medication aimed at ameliorating central pain mechanisms.
• Become acquainted with potential medications for treating osteoarthritis and pain under study.
Historical Perspective

• “Ulcerated cartilage is a troublesome thing, once destroyed it is not repaired”.
• W. Hunter 1743.
Definition

• 1994 NIAMs, NIA, Arthritis Foundation and American Academy of Orthopedic Surgeons at workshop entitled “New Horizons in Osteoarthritis” developed a new definition:
  – “…..Disease process that involves the entire joint-subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles. Ultimately, the articular cartilage degenerates…”
Osteoarthritis (OA)

- The most common joint disorder (arthritis)
- A disease of ‘aging’?
  - Uncommon before age 40
  - O.A. Pathology nearly universal (≥85%) in at least one joint after age 75
Manifestations of OA

• Joint pain, loss of motion

• Physical disability (walking, stairs, squatting)

• Reduced quality of life (unable to participate in family and society)
Global Social and Economic Impact

- Musculoskeletal conditions:
  - 2nd most prevalent cause of disability worldwide
  - 4th greatest impact on worldwide health, considering both death and disability

- OA occurs much more frequently in women
- OA is the fastest growing major health condition
- Knee OA affects 250 million people worldwide

Global Burden of Disease
2010, Lancet 2012
Burden of OA in the U.S.

- Painful knee or hip OA affects
  - 8% of U.S. adults (13 million)
  - 15-20% of people age ≥ 60 (6-9 million)
- #1 cause of mobility impairment
- #1 cause of disability in the elderly
- Total joint replacements
  - knee: 150,000/year
  - hip: 100,000/year
- Annual cost > $15-20 billion
  - treatment (<50%) and disability (>50%)
OA Joint Pathology by X-ray, Pain and Disability

Joint Pathology* (e.g. joint space narrowing)

Joint Pain

Disability

* assessed by x-ray
What is Osteoarthritis Pathologically?

• A group of overlapping disorders with similar morphologic and clinical outcomes: joint failure.

• Whole joint is affected
  • Bone
  • Cartilage
  • Joint capsule
  • Synovium
  • Periarticular muscles
OA Pathology on X-ray

Most commonly used method to assess OA

- Joint space narrowing
- Osteophytes
Systemic Factors:
- Age*
- Gender
- Racial Characteristics*
- Genetics*
- Bone density*
- Estrogen replacement therapy (in post-menopausal women)
- Nutritional factors (?)*
- Other systematic Factors

Local Biomechanical Factors:
- Joint injury*
- Obesity*
- Joint deformity
- Muscle weakness*

Susceptibility to Osteoarthritis

OSTEOARTHRITIS

A schema of the pathogenesis of osteoarthritis with putative risk factors.
Oliveria, Arthritis Rheum 1995
## OBESITY AND KNEE OA IN CAUCASIAN FEMALES*

Percent with Radiographic Knee Osteoarthritis (≥ Grade 2)

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34</td>
<td>0</td>
<td>.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>35-44</td>
<td>0</td>
<td>.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>45-54</td>
<td>.5%</td>
<td>1.9%</td>
<td>13.2%</td>
</tr>
<tr>
<td>55-64</td>
<td>2.6%</td>
<td>5.2%</td>
<td>17.5%</td>
</tr>
<tr>
<td>65-74</td>
<td>5.8%</td>
<td>17.7%</td>
<td>49.0%</td>
</tr>
</tbody>
</table>

*from Anderson and National Center for Health Statistics*
BMD and Prevalence of OA at Baseline: Framingham Study

Prevalence (%)

BMD Quartiles

1 (low)  2  3  4 (high)
## Relationship of Physical Activity to Incident X-Ray Knee OA in Framingham Study Elders

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity level, 1st Quartile vs. 4th Quartile**</td>
<td>3.8 (0.9-17.3)</td>
<td>3.1 (1.1-8.6)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, weight change

**Quartiles range from high (1st) to low (4th) activity levels
Association of knee OA with combinations of occupational lifting, kneeling, and squatting in two studies†

<table>
<thead>
<tr>
<th>Occupational activities</th>
<th>Framingham Men</th>
<th>Men</th>
<th>Both Sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No kneeling/squatting or heavy lifting</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kneeling/squatting but no heavy lifting</td>
<td>1.1</td>
<td>2.0</td>
<td>1.7*</td>
</tr>
<tr>
<td>Heavy lifting but no kneeling/squatting</td>
<td>1.0</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Both kneeling/squatting and heavy lifting</td>
<td>2.2**</td>
<td>2.9*</td>
<td>3.0**</td>
</tr>
</tbody>
</table>

† Framingham OA Study & Study by Coggon et al, 2000, * p<.05, ** p<.001
Vitamin D and Osteoarthritis

• The nature of the bony response may influence whether OA stabilizes or progresses
• Since bone remodeling is dependent on Vitamin D, low levels may impair bone response and predispose to OA progression
• Vitamin D receptors are present on the surface of hypertrophic chondrocytes, not normal chondrocytes
Association of 25-OH Vitamin D Level &
The Development or Progression of
Radiographic OA over 8 years

<table>
<thead>
<tr>
<th>25-OH Vitamin D level</th>
<th>Risk of Knee OA Progression*</th>
<th>Risk of severe hip joint space narrowing**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Third</td>
<td>2.9 (1.0, 8.3)</td>
<td>3.3 (1.1, 9.9)</td>
</tr>
<tr>
<td>Middle Third</td>
<td>2.8 (1.0, 7.9)</td>
<td>3.2 (1.1, 9.7)</td>
</tr>
<tr>
<td>Highest Third</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
</tbody>
</table>

* From the Framingham OA Study (McAlindon, et al) for progressive x-ray knee OA. No assoc’n found for incident disease.

** From S.O.F. (Lane et al) Weaker assoc’n found for other definitions of hip osteoarthritis.

• Recent supplementation trials showed no effect
### History of Major Knee Injury and the Prevalence of Radiographic Knee OA - Framingham

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of knee injury</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>History of major knee injury</td>
<td>5.5 (2.8, 10.9)</td>
<td>3.4 (2.0, 6.0)</td>
</tr>
</tbody>
</table>
Malalignment and Knee OA Progression in Medial Compartment

Sharma, JAMA 2001
What is Symptomatic OA?

• Presence of joint symptoms (pain, stiffness) in a joint affected by OA pathologically
• Symptoms are usually activity-related
  --- e.g. worse with walking, climbing
• Operationalized in studies as symptoms on most days of a month + x-ray OA
Pain in OA

• Pain from OA is generally thought of as chronic
• However, many patients experience OA pain as a series of episodes of pain interspersed with periods of mild or no pain
Pain in OA

- Boston Osteoarthritis of the Knee Study
  - 39% of patients with symptomatic knee OA had change from *no or little pain* to *severe pain* at different assessments over 3 years

- Internet-based trial of Glucosamine in knee OA
  - 49% had change from *no or little* to *severe pain* on a monthly basis
Why does it hurt some people?
Psychological Factors and Osteoarthritis Pain

Barton Wise¹,⁴, Jingbo Niu¹, Na Wang¹, Yuqing Zhang¹, Joanne M Jordan², Ernest Choy³, David J Hunter¹

¹Boston University School of Medicine and School of Public Health, Boston, MA. ²University of North Carolina, Chapel Hill, NC. ³Kings College, London. ⁴University of California, Davis School of Medicine.
Background

• Depression is common\(^1\)
• Worse psychological well-being has been associated with disability in patients with OA\(^2\)
• Anxiety associated with knee pain in women\(^3\)

Cross-sectional Association between MHI-5 and WOMAC Pain

MHI-5

1st Quart (28-30)
2nd Quart (26-27)
3rd Quart (23-25)
4th Quart (13-22)

WOMAC PAIN

Adjusted for age, sex, BMI, medication usage
Challenges in Studying Risk Factors for Pain

- Pain is a subjective experience that is unique to the individual
- Natural variability in pain sensitivity, perception and tolerance to pain stimuli
- Variability based on:
  - genetic predisposition
  - prior experience
  - idiosyncratic appraisals
  - expectations
  - socio-cultural environment
## Relation of MHI-5 to pain flares

<table>
<thead>
<tr>
<th>MHI-5</th>
<th>N Case Periods</th>
<th>N Control Periods</th>
<th>Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-30 (ref)</td>
<td>24</td>
<td>37</td>
<td>1.00</td>
</tr>
<tr>
<td>26-27</td>
<td>4</td>
<td>11</td>
<td>0.49</td>
</tr>
<tr>
<td>23-25</td>
<td>24</td>
<td>16</td>
<td>3.08</td>
</tr>
<tr>
<td>13-22</td>
<td>20</td>
<td>10</td>
<td>17.12</td>
</tr>
</tbody>
</table>

**P for trend**: 0.002
Knee Replacement: Multicenter OA Study (MOST)

• Frequent Knee Pain question
• Telephone and clinic interviews 1 month apart
• Exposure variable: No pain vs. Inconsistent pain vs. Consistent pain
• Outcome: KR
• Logistic regression analysis
Covariates: age, race, site, education, employment, baseline WOMAC pain severity, K/L grade at baseline

The graph shows the relationship between consistency and severity with risk ratios (RR) for different levels of consistency and severity.
Management of Knee OA

• “If there is an illness for which people offer many remedies, you may be sure that particular illness is incurable, …”

– Leonid Andreevich Gayev, The Cherry Orchard, Anton Checkov
OSTEOARTHRITIS TREATMENT

- Inflammation/Pain
  - NSAID/Cox2 Inhibitors
  - Glucosamine/chondroitin

- Laxity/Malalignment
  - Bracing, orthotics

- Muscle weakness
  - Strengthening, retraining
SUMMARY OF O.A. TREATMENT

- NSAID’s better than acetaminophen
- Glucosamine/chondroitin: likely ineffective
- Hyaluronic Acid: best evidence suggests no effect
- Opiates, steroid injections all options

- Bracing effective if deformity exists
- Exercise may work—which is optimal and compliance?
- Effects of nonsurgical Rx small; combination Rx indicated
- Knee Replacement: a great solution for severe disease
Osteoarthritis Treatment - 2012

- Combination therapy
  - COX2 inhibitors, NSAIDS
  - The refinement of exercise and strengthening programs
  - Individualization of biomechanical treatments

- New Treatments
  - Metalloprotease inhibitors (including tetracyclines)
  - Treatments targeted at bone (bisphosphonates?)
  - Bioengineering (cartilage transplant, etc.)
  - Cytokine inhibitors
  - Genomics
Treatment of Pain from Knee OA with a Central Pain inhibitor
A double blind randomized Placebo Controlled Trial of the Efficacy and Safety of Duloxetine for the treatment of chronic pain due to knee OA

Chappell et al, Pain Practice 2011 (1):33-41
A double blind randomized Placebo Controlled Trial of the Efficacy and Safety of Duloxetine for the treatment of chronic pain due to knee OA

Chappell et al Pain Practice 2011 (1):33-41
Treatment of Pain by Inhibiting Peripheral Sensory Nerves
Nerve Growth Factor (NGF)

- Discovered 50 years ago
- Involved in development of the fetal nervous system, particularly crest cell migration
- Recently it has attracted new interest
- Expressed in adults
- Large variety of different tissues
- Probably very complicated actions in nervous system, immune system, joints and other organs
NGF Mechanisms for Inducing Pain and Hyperalgesia

• NGF is released during injury, inflammation

• NGF released during injury enhances pain and hypersensitivity
  – Induction of NGF occurs early in pain cascade

• NGF is upregulated in post-injury pain, stimulating sensory neurons

NGF modulates pain signalling pathways, so there has been growing interest in the analgesic potential of NGF inhibition.
Tanezumab, a humanized anti-NGF antibody

- Tanezumab is a humanized IgG₂ monoclonal antibody against NGF
- It reduced pain as effectively as indomethacin in a rat model of chronic arthritic pain
- Tanezumab was also shown to reduce pain in patients with OA of the knee in a Phase 1 trial

Lane et al A&R, Supplement 1, 2008
Tanezumab Study 1008: Walking Pain in Index Knee Mean Change from Baseline

- Tanezumab treatment of subjects with moderate to severe knee OA resulted in a significant, more than 50% reduction in walking knee pain and subject global assessment of pain.
- Side effects included some peripheral sensory changes and most were transient with increasing doses of tanezumab

Current Status of Anti-NGF development Program for Pain

- FDA put nearly all programs on clinical hold
- Some study subjects required total joint replacement.
- A few of the subjects that required total joint replacement had reports of osteonecrosis.
- This issue is currently being studied by all pharmaceutical companies developing these agents
- FDA in discussion
Strontium Ranelate

• Stimulates human cartilage matrix formation in vitro

• Decreases excretion of CTX-II, a marker of cartilage destruction in post-menopausal women

• Dissociates bone remodeling by:
  – Increasing bone formation
  – Decreasing bone resorption

Henrotin, J Bone Mineral Res 2001
Meunier, NEJM 2000
Alexandersen, Bone 2007
Strontium Ranelate

• TROPOS and SOTI trials combined:
  – 1105 subjects with lumbar radiographs over 3 years
  – Treatment with strontium ranelate associated with:
    • 42% lower overall progression of OA score ("Lane Score")
    • 34% increase in subjects free of back pain

Bruyere, ARD 2008
Strontium Ranelate – SEKOIA Study

- Knee OA phase 3 double-blind, randomized placebo-controlled trial
  - Three parallel groups
    - Strontium 1g/day, 2g/day, vs. placebo
  - 98 centers in 18 countries – 1683 participants
  - Men and women 50 or older with symptomatic medial compartment knee OA
  - Annual visits and radiographs for 3 years
  - Outcomes: Joint Space Width and pain
  - Funded by Servier, France

Cooper, CMSO 2012
Strontium Ranelate – ACR 2012

• Structural progression:
  – JSW decrease in mm:
    • 2g/day: -0.23±0.56
    • 1g/day: -0.27±0.63
    • Placebo: -0.37±0.59

• Symptom improvement:
  – 2g/day had greater improvement in WOMAC pain than placebo group (p=0.028)

Reginster, ACR abstract # 1596
2012
Acknowledgements

- UC Davis Building Interdisciplinary Research Careers in Women’s Health Program – NIH K12HD051958
- NIH/NIAMS SCOR P50-AR063043
- NIH CORT P50-AR060752
- CIRM
- UC Davis Internal Medicine Department
- Mentors: Nancy Lane, Yuqing Zhang (both contributed some slides), Ellen Gold
- LEAP dataset
- MOST Study Participants