Osteoarthritis: Yesterday, Today, and Maybe Tomorrow

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Speaker Disclosure

- Research funding from Pfizer
- NIH

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 pain in osteoarthritis 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)

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

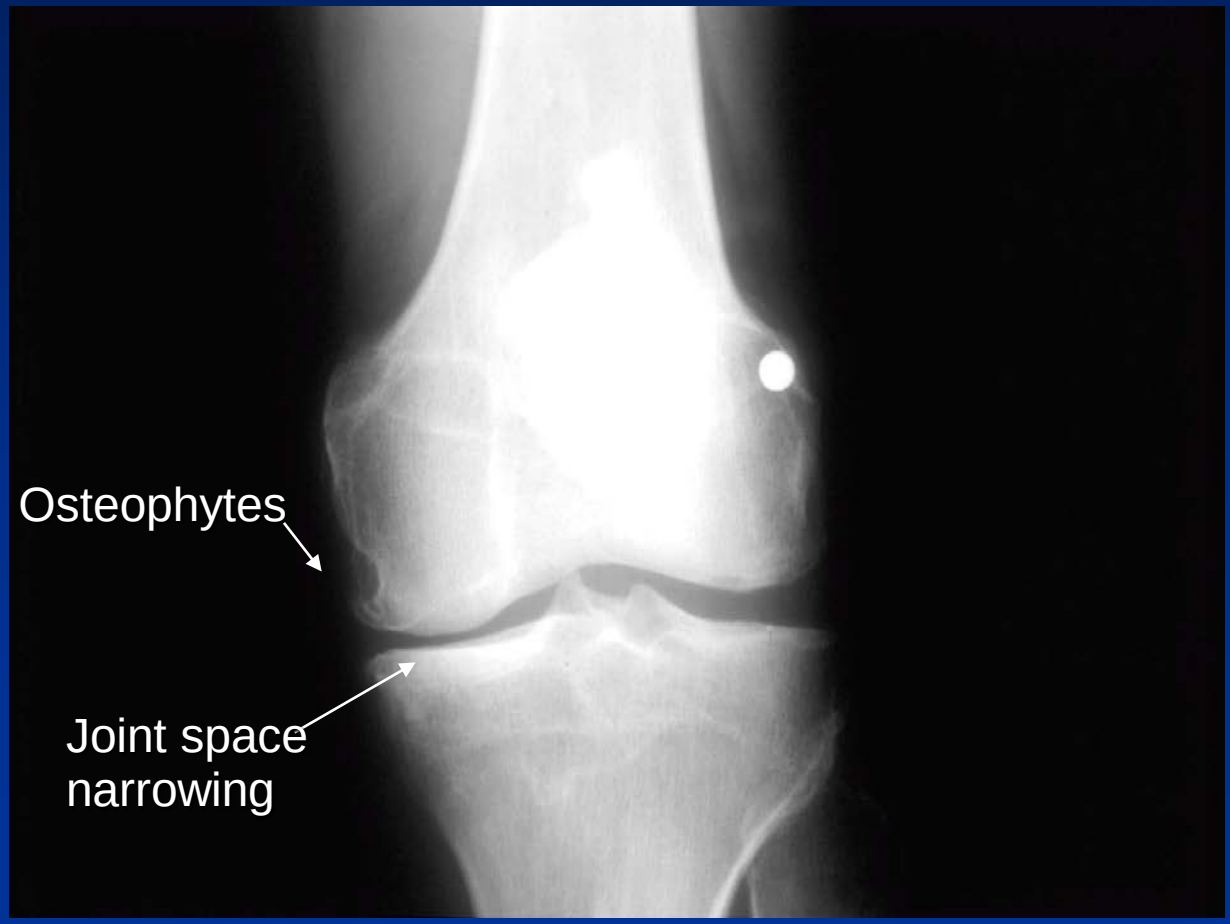
* assessed by x-ray (e.g. joint space narrowing)

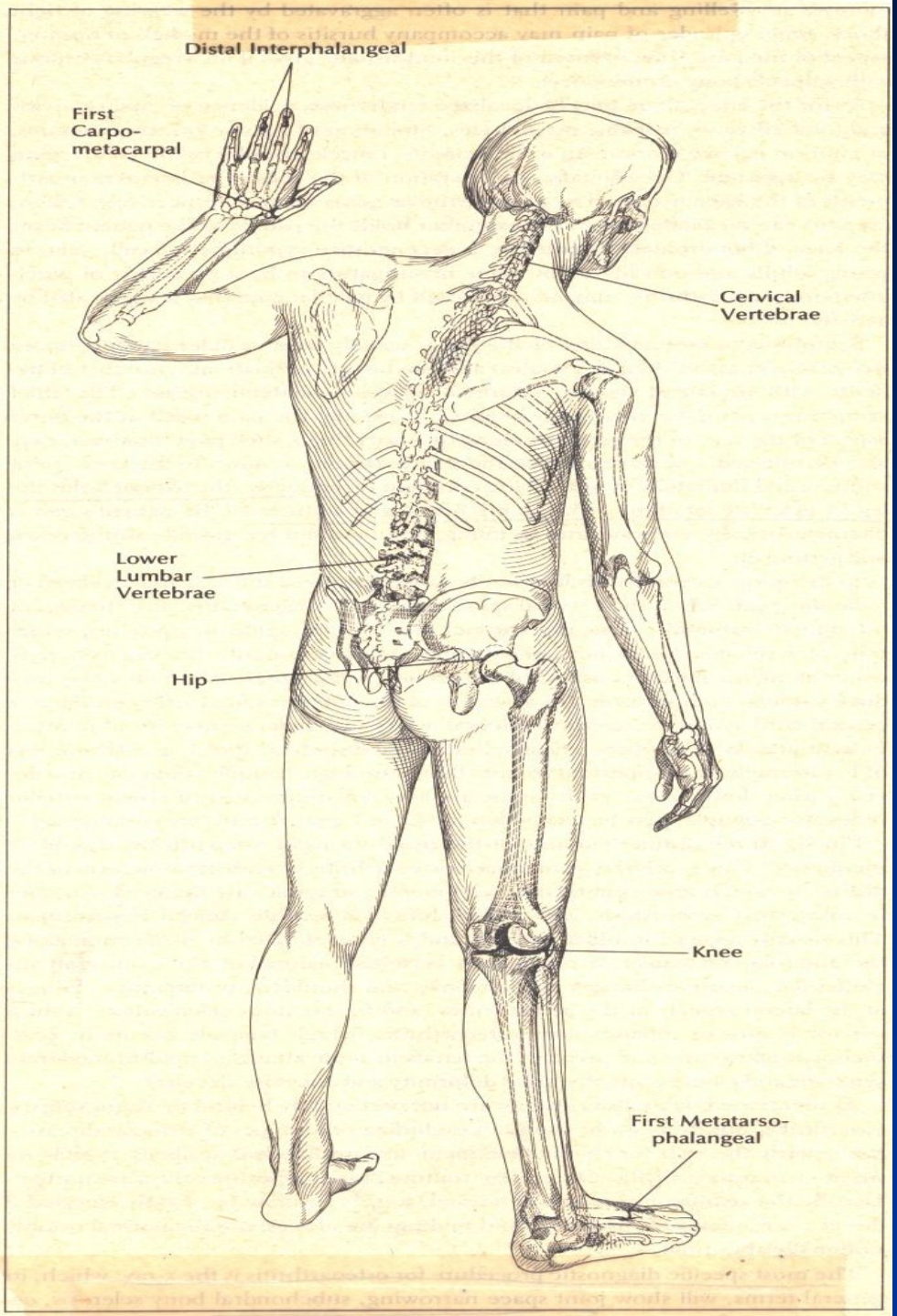
What is Osteoarthritis Pathologically?

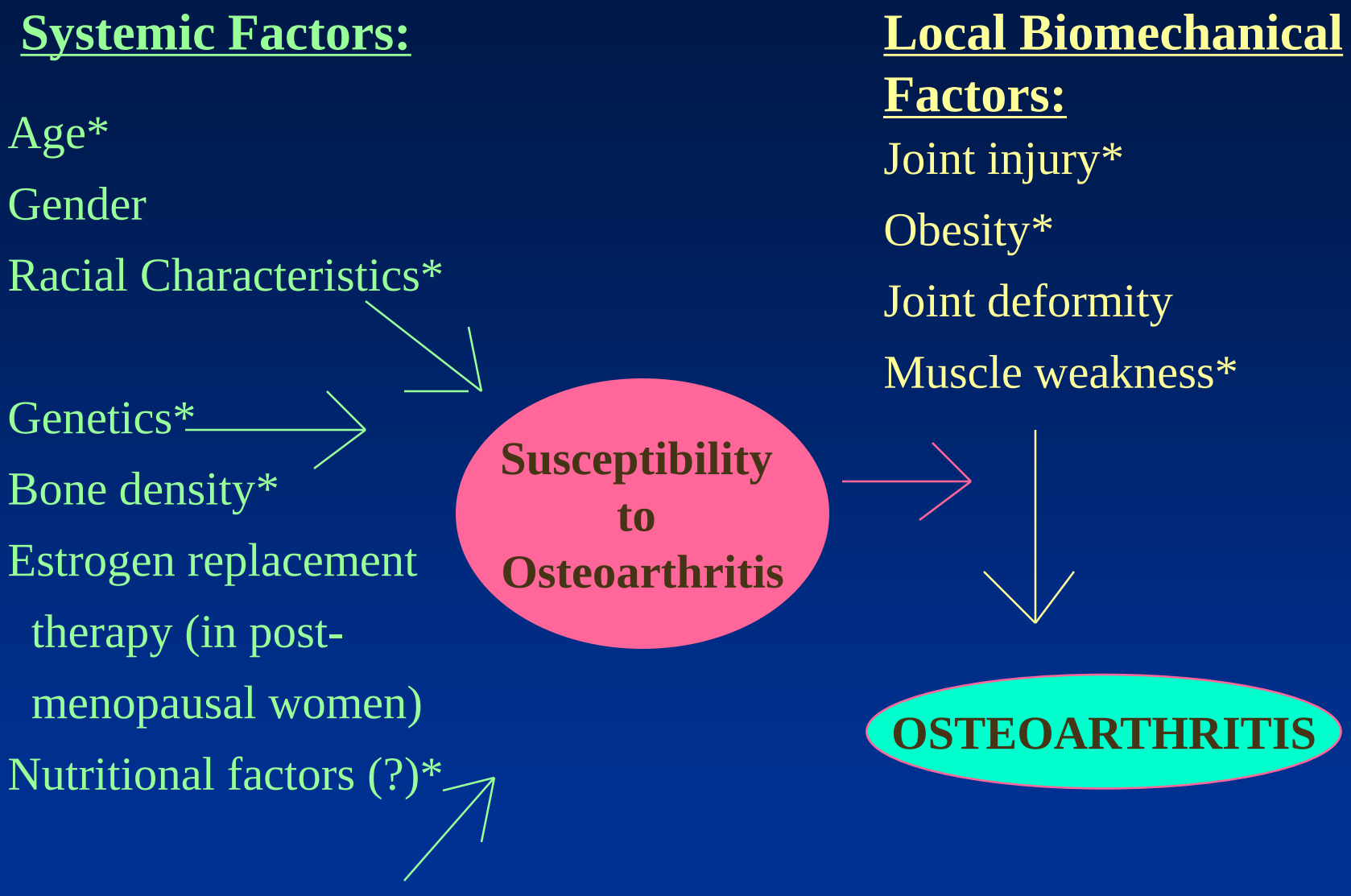
- A group of overlapping disorders with similar morphologic and clinical outcomes: joint failure.
- Whole joint is affected
  - Bone
  - Cartilage
  - Joint capsule
  - Synovium
  - Periarticular muscles

OA Pathology on X-ray

Most commonly used method to assess OA

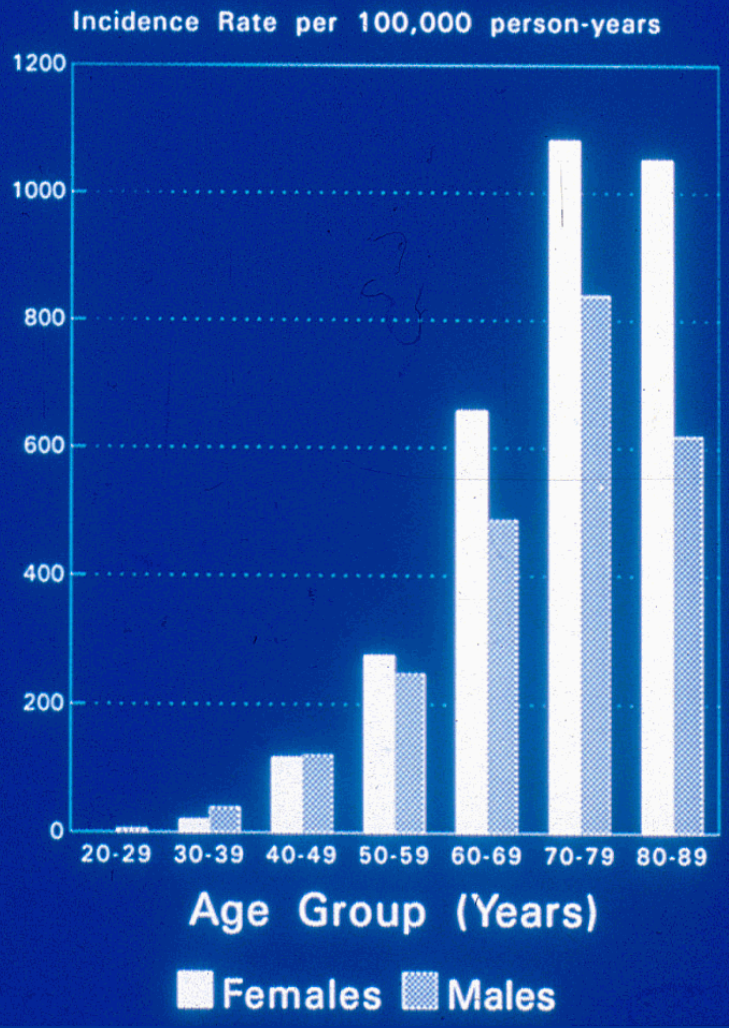



Distal Interphalangeal
First
Carpo-
metacarpal
Cervical
Vertebrae
Lower
Lumbar
Vertebrae
Hip
Knee
First Metatarso-
phalangeal



A schema of the pathogenesis of osteoarthritis with putative risk factors.

Incidence of Knee Osteoarthritis



Oliveria, Arthritis Rheum 1995

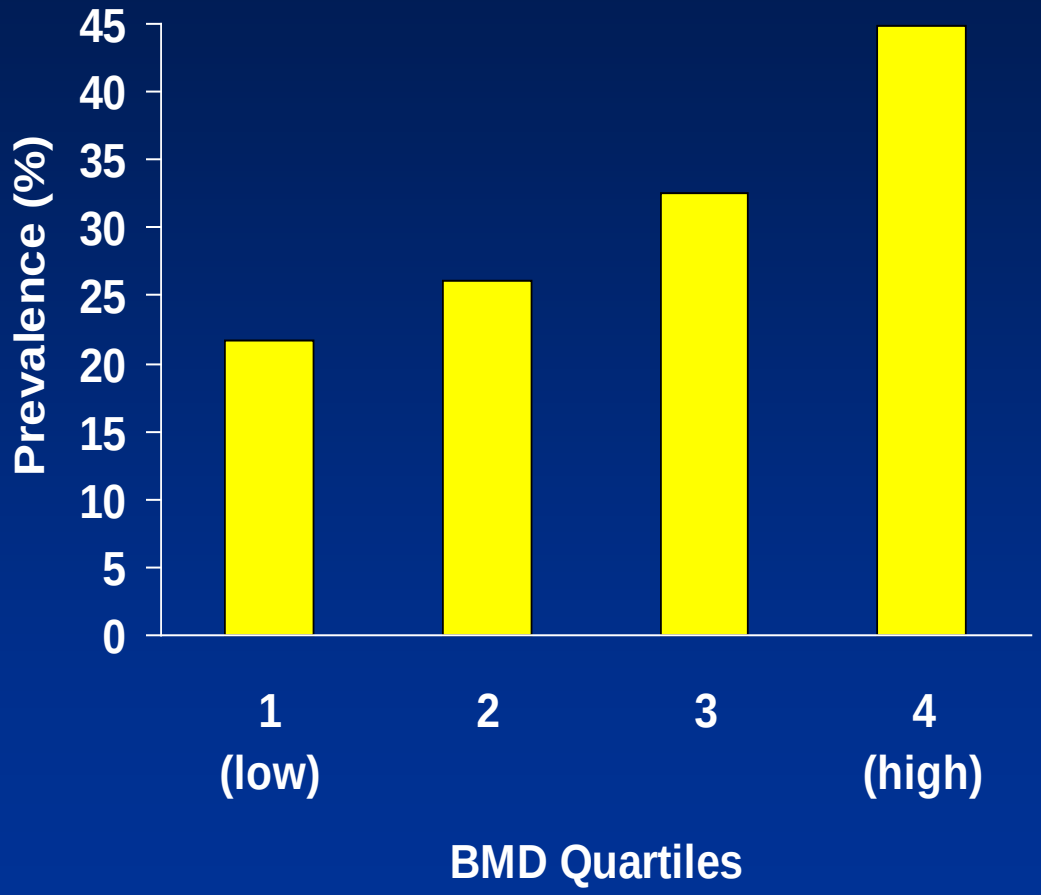
OBESITY AND KNEE OA IN CAUCASIAN FEMALES*

Percent with Radiographic Knee Osteoarthritis (≥ Grade 2)

Age	Normal	Overweight	Obese
25-34	0	.3%	2.2%
35-44	0	.3%	11.1%
45-54	.5%	1.9%	13.2%
55-64	2.6%	5.2%	17.5%
65-74	5.8%	17.7%	49.0%

*from Anderson and National Center for Health Statistics

BMD and Prevalence of OA at Baseline: Framingham Study



Relationship of Physical Activity to Incident X-Ray Knee OA in Framingham Study Elders

	Adjusted OR (95% CI)*	
Risk Factor	Male	Female
Physical activity level, 1st Quartile vs. 4th Quartile**	3.8 (0.9-17.3)	3.1 (1.1-8.6)

*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†

Occupational activities	Framingham Men	English Study Men	English Study Both Sexes
No kneeling/squatting or heavy lifting	1	1	1
Kneeling/squatting but no heavy lifting	1.1	2.0	1.7*
Heavy lifting but no kneeling/squatting	1.0	1.6	1.5
Both kneeling/squatting and heavy lifting	2.2**	2.9*	3.0**

† 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

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

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

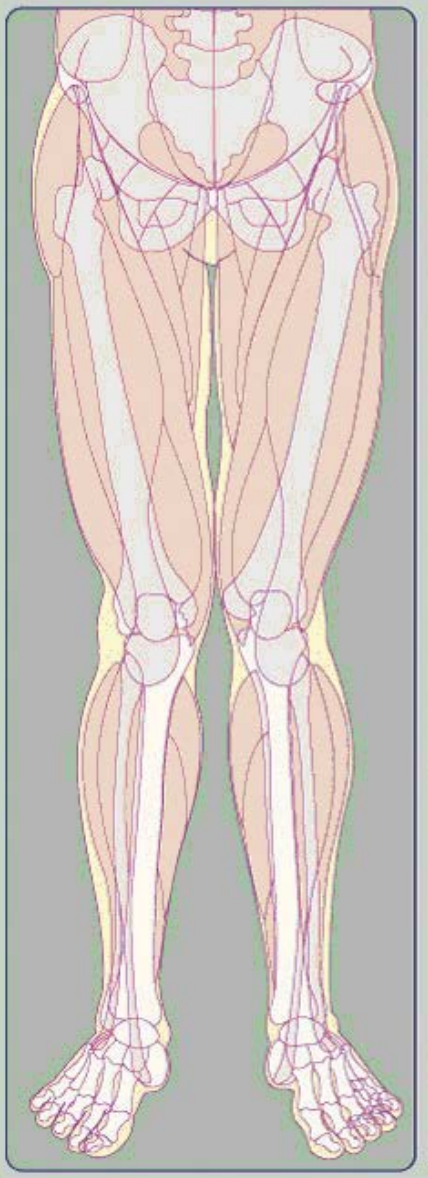
** From S.O.F. (Lane et al) Weaker assoc'n found for other definitions of hip osteoarthritis.

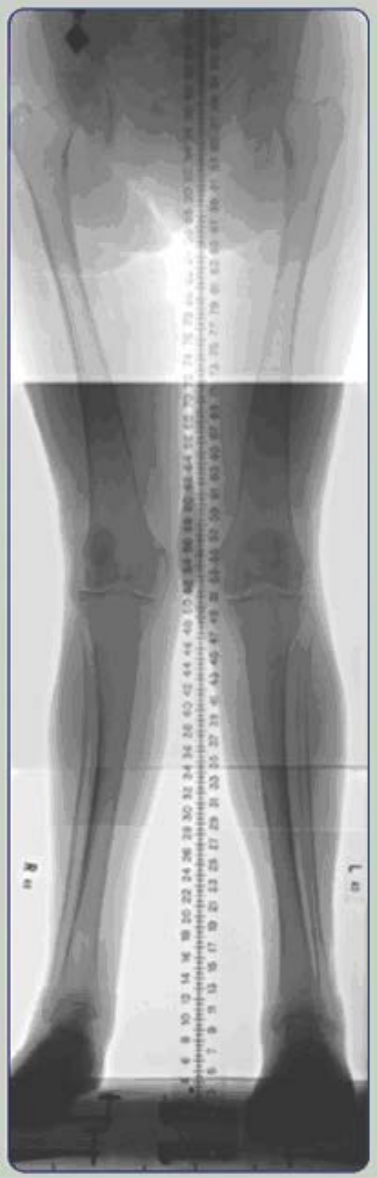
- Recent supplementation trials showed no effect

History of Major Knee Injury and the Prevalence of Radiographic Knee OA-Framingham

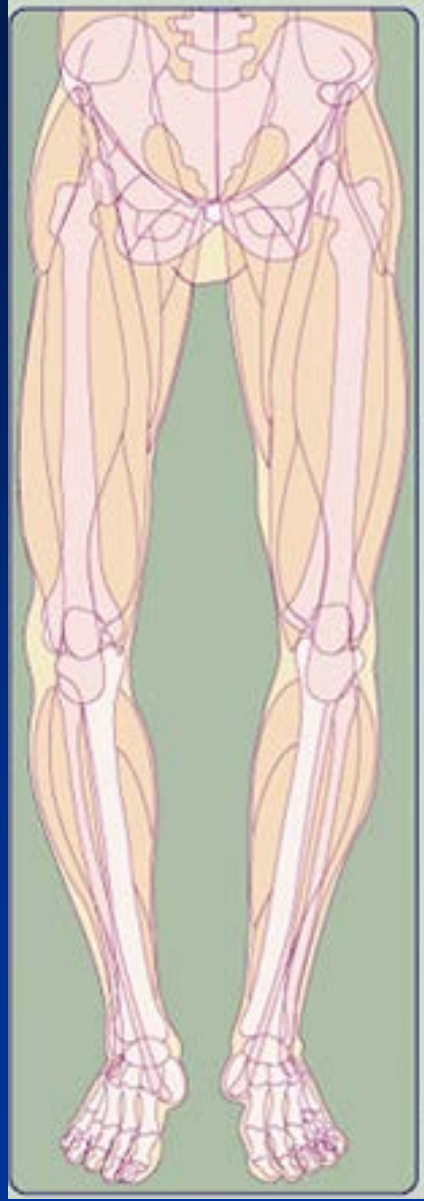
	Adjusted OR of Knee OA (95% CI)	
	Men	Women
No history of knee injury	1 (ref)	1 (ref)
History of major knee injury	5.5 (2.8, 10.9)	3.4 (2.0, 6.0)

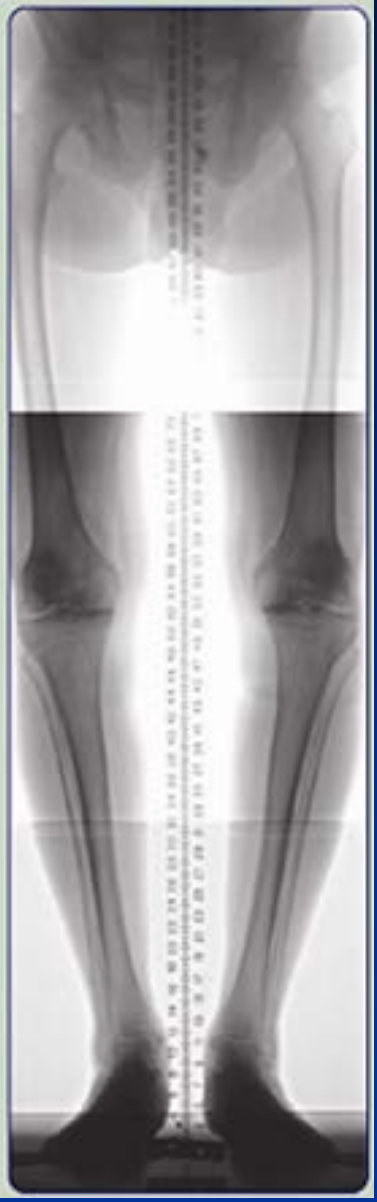
Valgus (Knock-Knee)



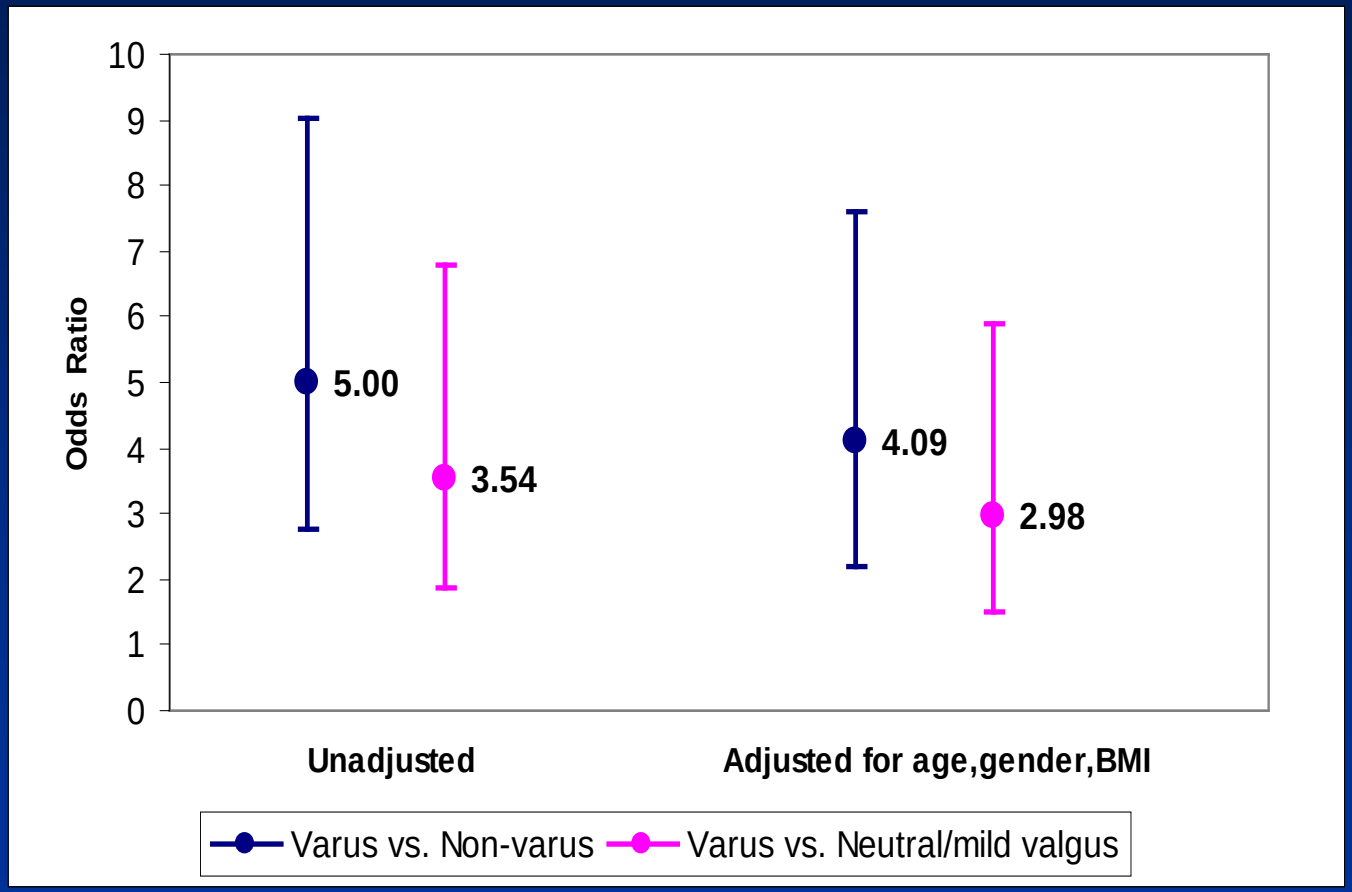


Varus (Bow-Legged)





Malalignment and Knee OA Progression in Medial Compartment



Sharma, JAMA 2001

What is Symptomatic OA?

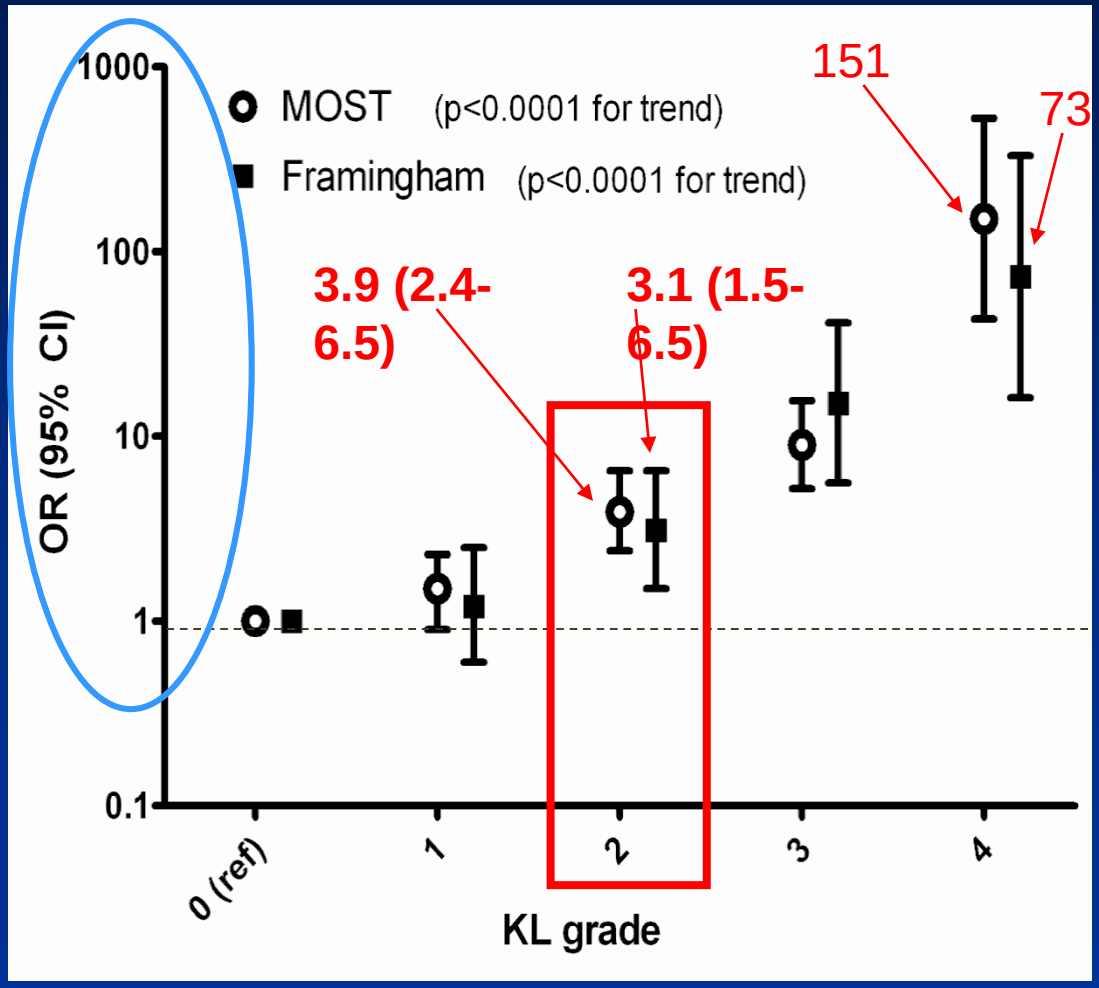
- Presence of joint symptoms (pain, stiffness) in a joint affected by OA pathologically
- Symptoms are usually activity-related

  ---e.g. worse with walking, climbing
- Operationalized in studies as symptoms on most days of a month + x-ray OA

Background

- Radiograph has been considered a “gold standard” to define structural change in knee OA (ROA)
- Most previous studies have only found a modest association between ROA and pain, especially for less severe ROA

K/L Grade with Frequent Knee Pain



Neogi 2008

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 Wise[1,4], Jingbo Niu[1], Na Wang[1], Yuqing Zhang[1], Joanne M Jordan[2], Ernest Choy[3], David J Hunter[1]

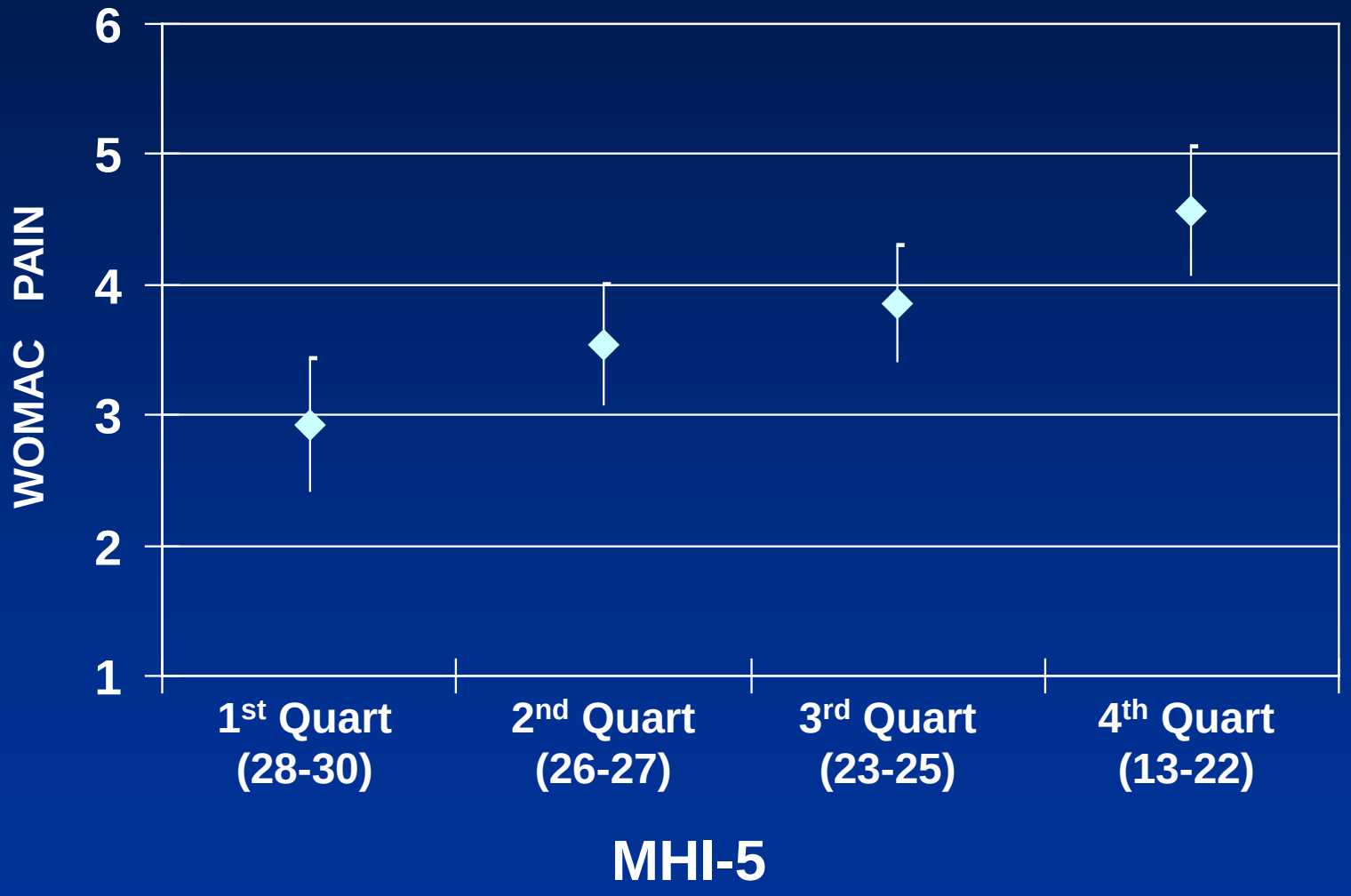
[1]Boston University School of Medicine and School of Public Health, Boston, MA. [2]University of North Carolina, Chapel Hill, NC. [3]Kings College, London. [4]University of California, Davis School of Medicine.

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]

1. Barrett, J Affect Disord 1987;12(2):167-74
2. Van Baar, J Rheumatol 1998;25(1):125-33
3. Creamer, Arthritis Care Res 1999;12(1):3-7; J Rheumatol 1999;26(8):1785-92

Cross-sectional Association between MHI-5 and WOMAC Pain



Adjusted for age, sex, BMI, medication usage

Challenges in Studying Risk Factors for Pain

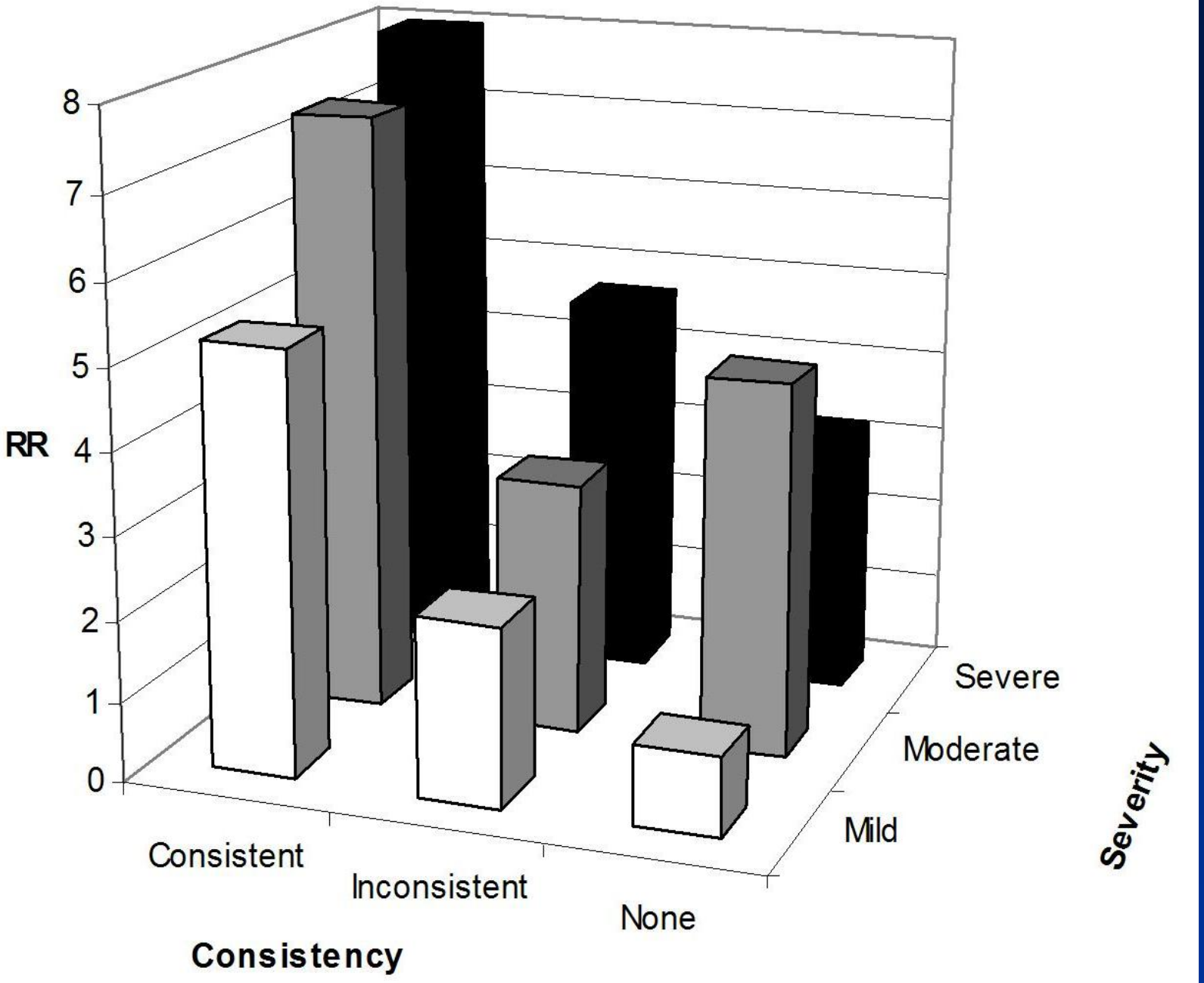
- Pain is a subjective experience that is unique to the individual
- Natural variability in pain sensitivity, perception and tolerance to pain stimuli
- Variability based on:
  - genetic predisposition
  - prior experience
  - idiosyncratic appraisals
  - expectations
  - socio-cultural environment

Relation of MHI-5 to pain flares

MHI-5	N Case Periods	N Control Periods	Odds Ratios
28-30 (ref)	24	37	1.00
26-27	4	11	0.49
23-25	24	16	3.08
13-22	20	10	17.12
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



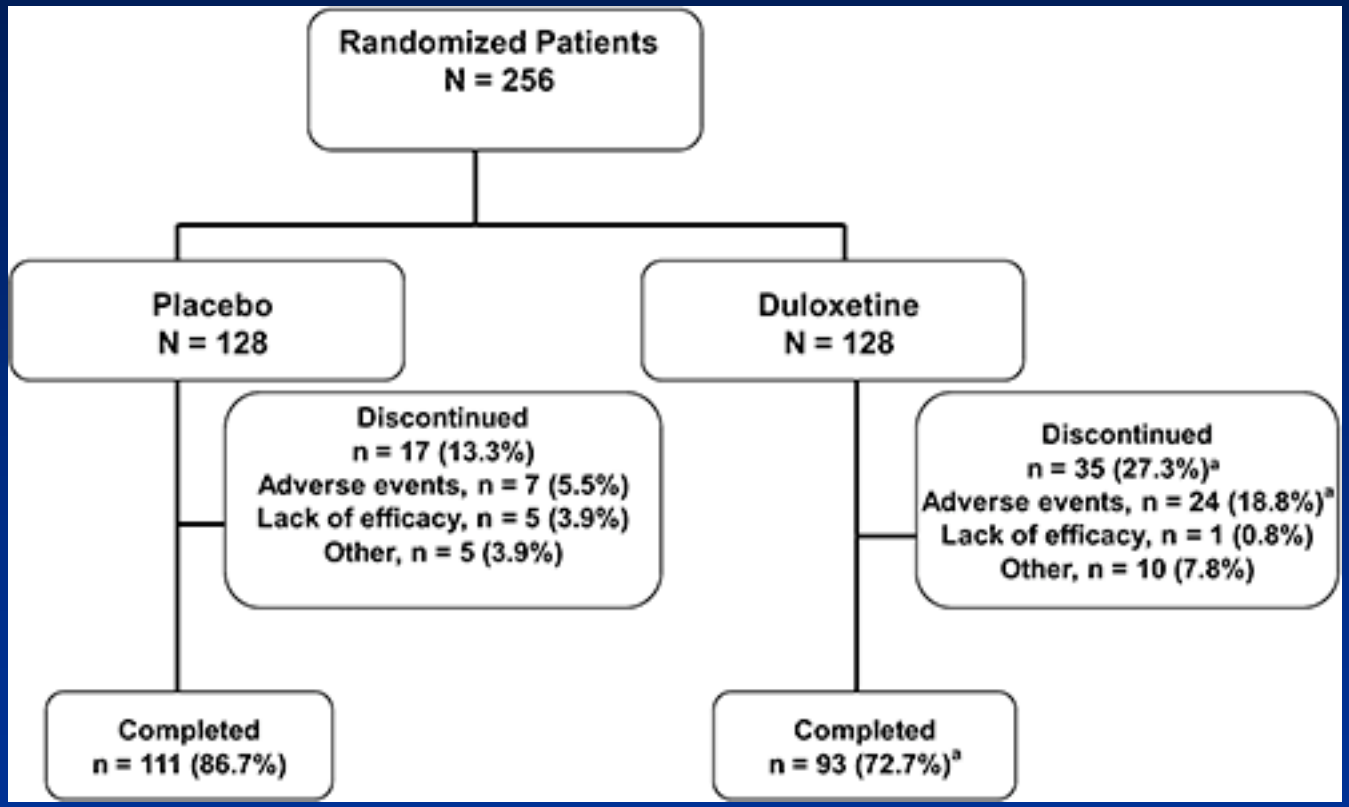
Covariates: age, race, site, education, employment, baseline WOMAC pain severity, K/L grade at baseline

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

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

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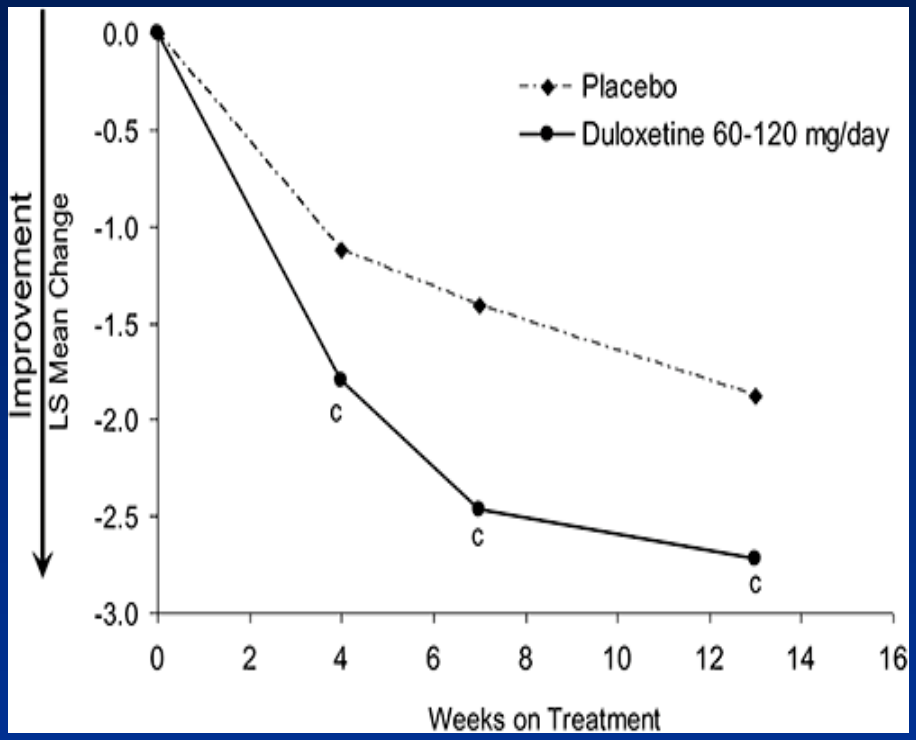
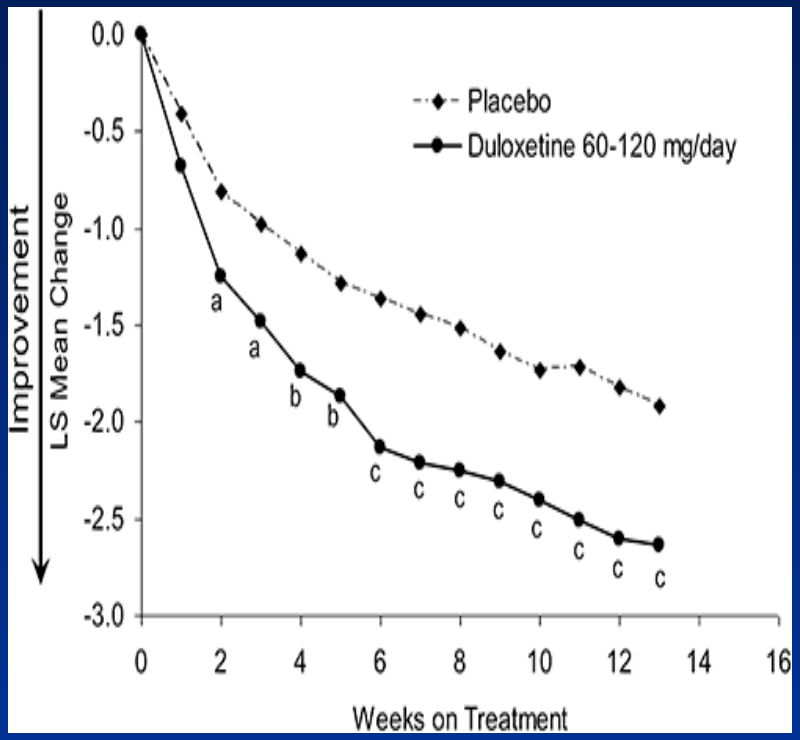




Chappell et al Pain Practice 2011 (1):33-41

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
  - Metalloproteinase inhibitors (including tetracyclines)
  - Treatments targeted at bone (bisphosphonates?)
  - Bioengineering (cartilage transplant, etc.)
  - Cytokine inhibitors
  - Genomics

Treatment of Pain by Inhibiting Peripheral Sensory Nerves

Nerve Growth Factor (NGF)

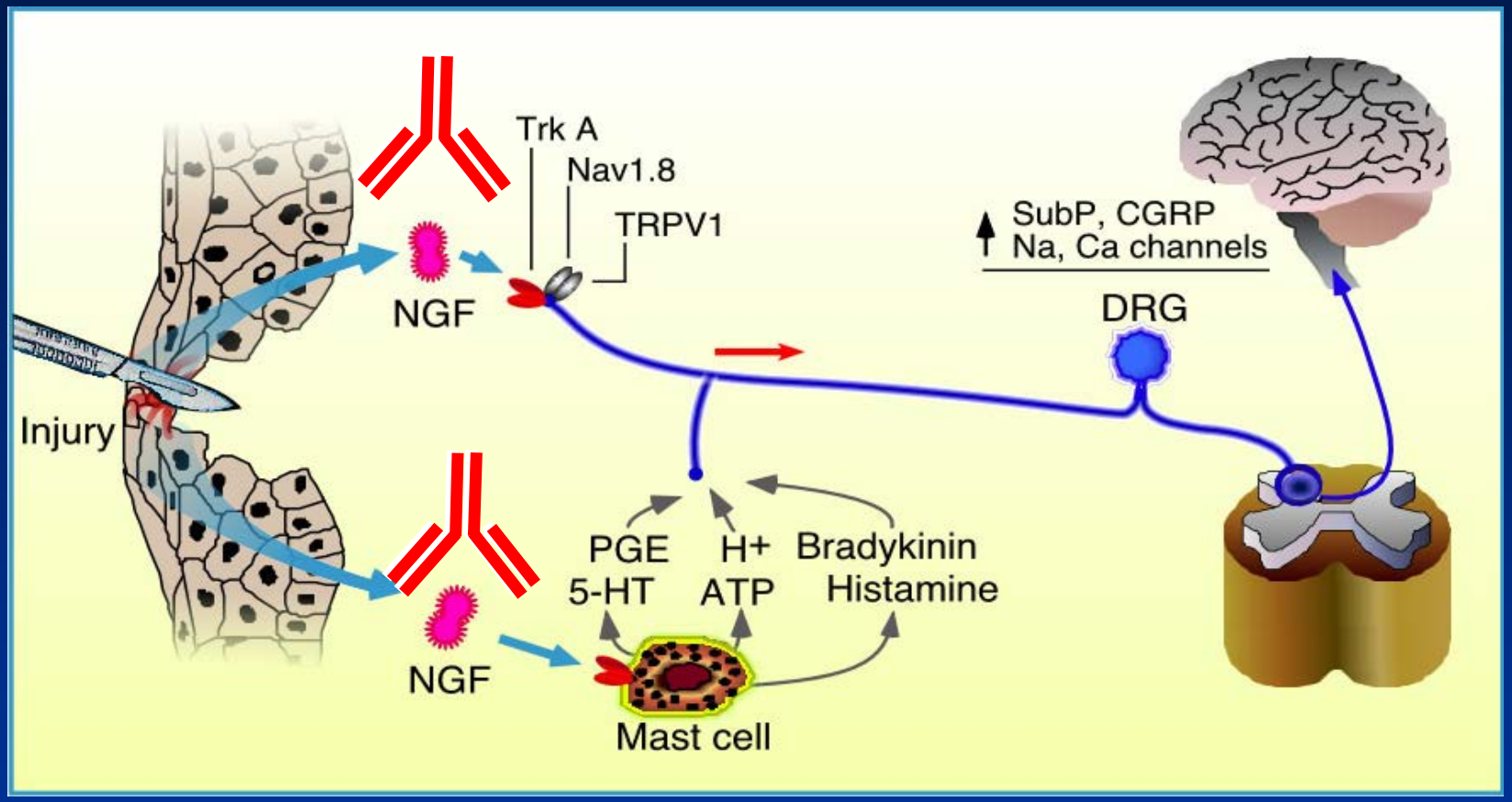
- Discovered 50 years ago
- Involved in development of the fetal nervous system, particularly crest cell migration
- Recently it has attracted new interest
- Expressed in adults
- Large variety of different tissues
- Probably very complicated actions in nervous system, immune system, joints and other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

Nicol GD, Vasko MR. *Mol Interven*. 2007;7:26-41.
Hefti FF et al. *Trends Pharmacol Sci.* 2006;27:85-91.
Xian CJ, Zhou XF. *Nat Clin Pract Rheumatol.* 2009;5:92-98.

NGF-mediated pain pathways



- NGF modulates pain signalling pathways, so there has been growing interest in the analgesic potential of NGF inhibition

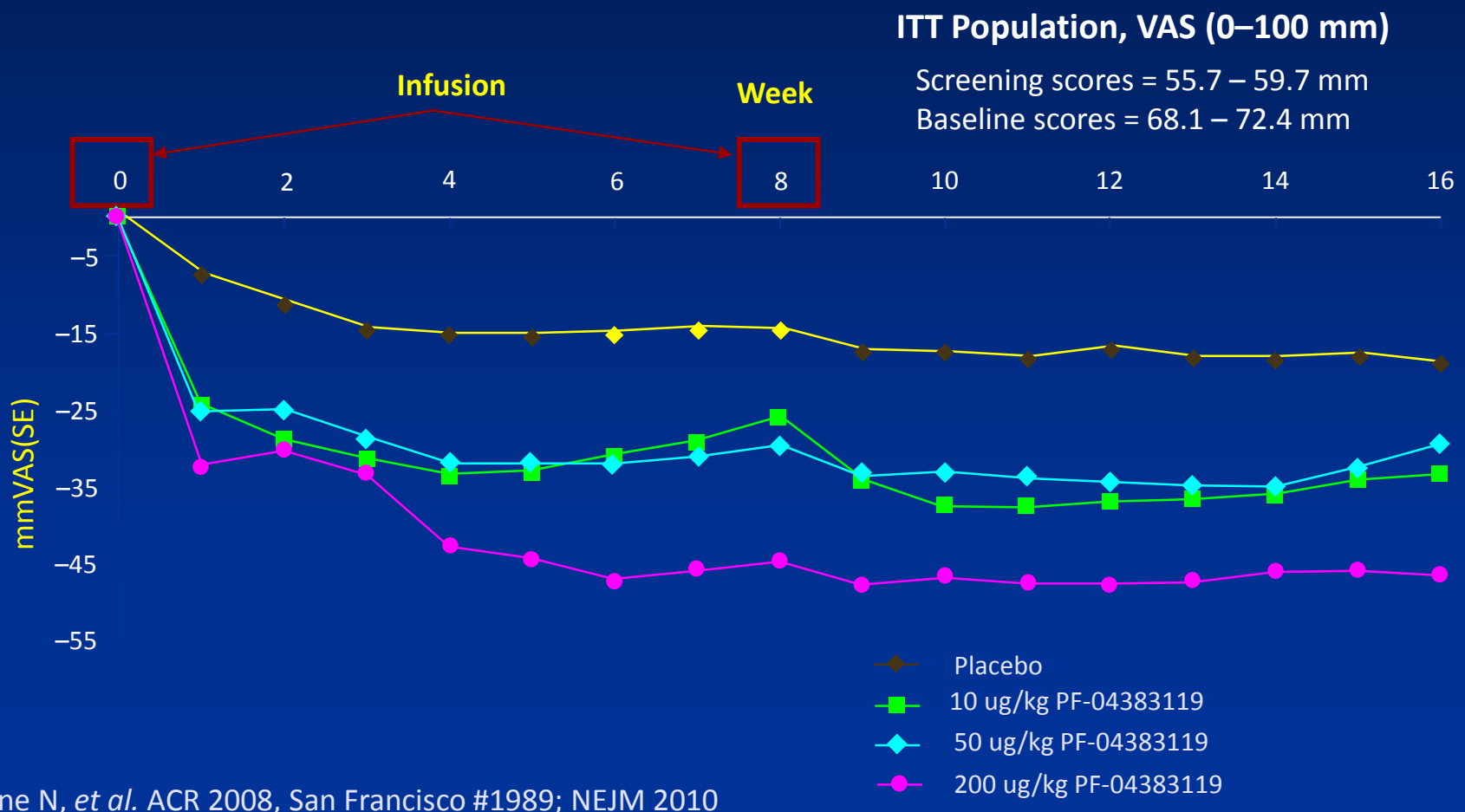
Tanezumab, a humanized anti-NGF antibody

- Tanezumab is a humanized IgG_2 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



Lane N, *et al.* ACR 2008, San Francisco #1989; NEJM 2010

Current Status of Anti-NGF development Program for Pain

- FDA put nearly all programs on clinical hold
- Some study subjects required total joint replacement.
- Questions of osteonecrosis and of higher rates of peripheral neuropathy.
- This issue is currently being studied by all pharmaceutical companies developing these agents

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

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- UC Davis Internal Medicine Department
- Mentors: Nancy Lane, Yuqing Zhang (both contributed some slides), Ellen Gold
- LEAP study
- MOST Study Participants