Aging in place: Management of OA

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Rocky Mountain Geriatrics Conference 2018

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Disclosures

- I will mention a few brand names and some non-FDA approved drugs and drugs under study
- My funding sources include NIH/NIAMS, CDC, Rheumatology Research Foundation
- Editorial Board of *Osteoarthritis & Cartilage* and a member of the ACR and OARSI
- Consultant to GSK
- I attended Overland HS in Aurora and got my BA from The Colorado College

COLORADO COLLEGE

Overview

- Osteoarthritis as a common chronic condition
- OA and aging, mobility, and independence
- The Johnston County OA Project overview
- OA management guidelines summary
- The OA Action Alliance: a resource for patients and providers
- Future directions in OA management

OA is a common chronic condition

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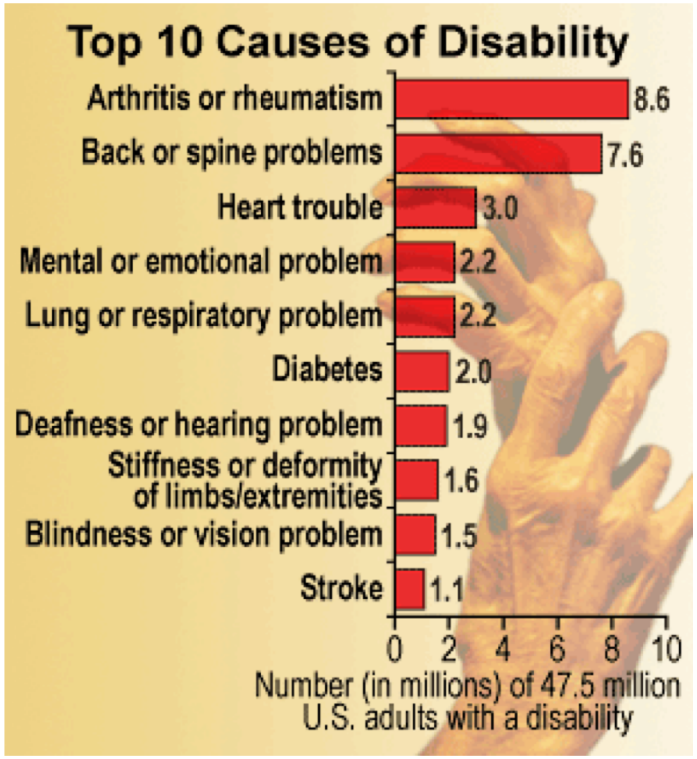
Prevalence of OA

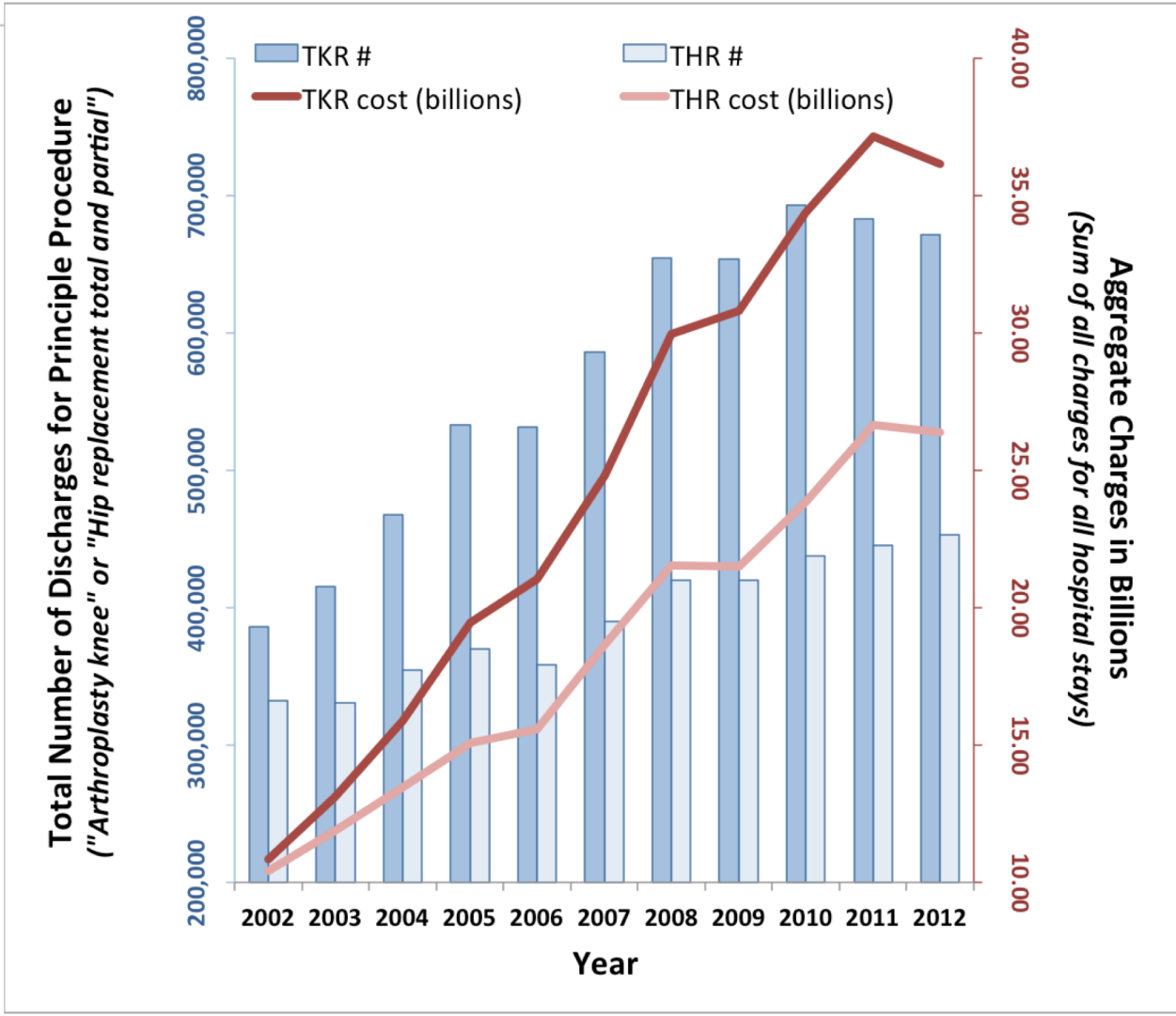
- Arthritis is the most common cause of disability (1) in the US
  - MSK disorders are 2nd globally
- OA is the most common form of arthritis
- Over 50 million in the U.S. were affected as of 2012 (2), projected >75 million by 2040
- Numbers continue to increase due to aging and obesity trends



1. CDC 2009; 2. Arthritis Rheumatol 2016;68:1582-7

Joint replacement for OA

- Most joint replacements are done for OA.
- Rates of joint replacement are on the rise and will soon outpace capacity.



http://hcupnet.ahrq.gov/HCUPnet.jsp

OA is a key factor in aging, mobility, and independence

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Aging and OA (Aging ≠ OA)

- **Age-related factors**
  - "Inflammaging"
  - Reduced muscle mass
  - Increased fat mass
  - Low grade inflammation
  - Altered mechanical properties of cartilage, meniscus, and ligaments
  - Altered function and composition of bone

- **Normal aging**
  - Intact but thin cartilage
  - Cartilage cross-linking by AGEs
  - Increased chondrocyte density overall
  - Reduced matrix activity
  - Decreased bone mass and density
- **OA**
  - Fibrillation of cartilage surface and focal loss of GAGs
  - Clusters of chondrocytes near tissue damage
  - Increased matrix activity
  - Synovial inflammation
  - Subchondral bone thickening

Loeser, Nat Rev Rheumatol 2016;12(7):412-20.

Burden of chronic disease on HRQL

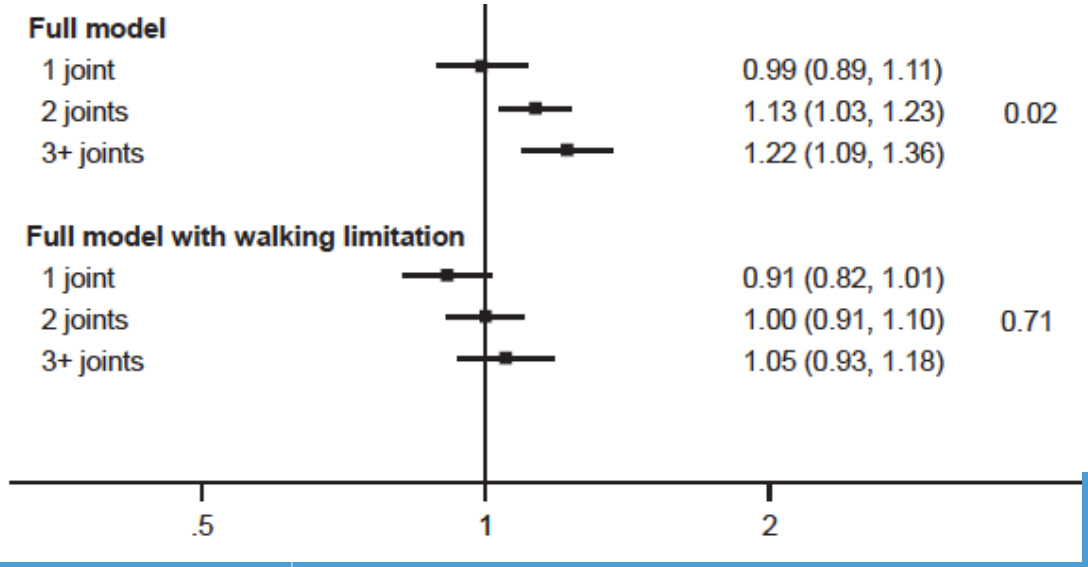
- 5849 UK participants, mean age 74, ½ male, 1/3 with one and ¼ with 2 or more morbid conditions
- The greatest and clinically significant negative impacts on HRQL were seen for:
  - **osteoarthritis (-0.08)**
  - neurologic disease (-0.17)
  - depression (-0.27)
- *Smaller* declines were seen from htn, CHF, cancer, RA, diabetes, and CAD

Parker, Family Practice 2014;31(5):557-63.

OA and mobility: The Ontario Hip and Knee Cohort

Kendzerska, Osteoarthritis Cartilage 2017;25:1771-80.

- >18,000 respondents, median age 68, 60% female, median BMI 26
  - 10% had hip, 15% had knee, 16% had hand OA
  - ¼ reported walking limitation
- Over 13-year follow-up, 32% had 1+ CV event
  - Dose-response relationship between # joints and CV risk
  - *Fully attenuated* by adjustment for walking limitation



63% of people with knee/hip OA had walking limitations compared with 17% of those without OA

OA and mobility: The Ontario Hip and Knee Cohort

- Among those with hip or knee sx OA **and** self-reported physician diagnosed diabetes (n=359)
  - Mean age 71, 2/3 women, median of moderate to severe walking disability at baseline
- Over 6 years follow-up, ½ were hospitalized for a diabetes complication
- Time to complications was shorter for those who were older, had pre-existing CV disease, and *greater* ***difficulty walking*** *including use of walking aids*

Hawker, Osteoarthritis Cartilage 2017;25:67-75.

Multimorbidity, OA, and participation restriction

- Adults from UK, median age 65, 2/3 female, **with lower extremity OA** (n=1053)
- 17% had incident participation restriction at 3 years
  - Limitations in social activity, volunteering, working, etc.
- **2-3x higher odds of PR** with multimorbidity
- Locomotor disability and depression had the greatest mediation effect and are potentially modifiable

Wilkie, Arthritis Care Res 2013;65(6):910-9.

Mobility outside the home

Wilkie, BMJ Open 2017;7:e012826.

- 1802 UK adults, mean age 66, 56% female
- 13% had restricted mobility (RM) at 3-year follow-up
- Associated with health and environmental factors
- Associations between health conditions and RM were greater in the presence of environmental factors

	Frequency of the onset of restricted mobility outside the home at 3-year follow-up	Crude	Associations adjusted for confounders*
	%	OR (95% CI)	Adjusted OR (95% CI)
Walking disability and hills and steep slopes			
No walking disability, no hills and steep slopes	6.8	1	1
Walking disability, no hills and steep slopes	29.3	5.71 (4.00 to 8.13)	3.60 (2.43 to 5.32)
No walking disability, hills and steep slopes	29.2	5.69 (3.69 to 8.78)	4.55 (2.89 to 7.16)
Walking disability, and hills and steep slopes	47.9	12.67 (8.05 to 19.94)	7.66 (4.64 to 12.64)

Environmental barriers to participation

- Data from MOST (n=322): associations between environmental barriers (Home and Community Environment Q) and participation restriction (Late Life Disability Index) in those with/at risk for knee OA
  - Mean age 70, 93% white, 69% female
- 18% had developed participation restriction @ 30mo, increasing to 27% at 60mo
- Those with high community mobility barriers* had **2x risk of participation restriction** at 5 years

  *Uneven sidewalks, lack of parks, benches, curb ramps

Vaughn, Arthritis Care Res 2017;69(7):952-8.

Long term value of improved mobility

- Combined data (clinical trial and 2012 MEPS) to model the effects of improved QoL and mobility on health economic outcomes
- Compared status quo to **improvement of ~550 steps/day**
- Over 18-year simulation, improved mobility resulted in:
  - 7.4 million fewer patient years of ADL limitations
  - 6% fewer patients each year with ADL limitations
  - Medical savings of $44 billion (over half to Medicare)
  - 2.8% reduction in nursing home utilization
  - 1.2 million employed patient-years, $78 billion in earnings
  - A total “value to society” of ~$482 billion

Kabiri, Value Health 2018;21(7):792-8. doi: 10.1016/j.jval.2017.12.021

Summary

- Aging and OA are related but not synonymous
- OA along with other comorbidities reduces QoL
- Reduced mobility due to OA contributes to morbidity and mortality, including participation restriction
- Restricted mobility and participation restriction are associated with environmental factors
  - Poor walking conditions, unsafe, lack of seating
- Modification of these factors could improve individual and societal outcomes

The Johnston County OA Project

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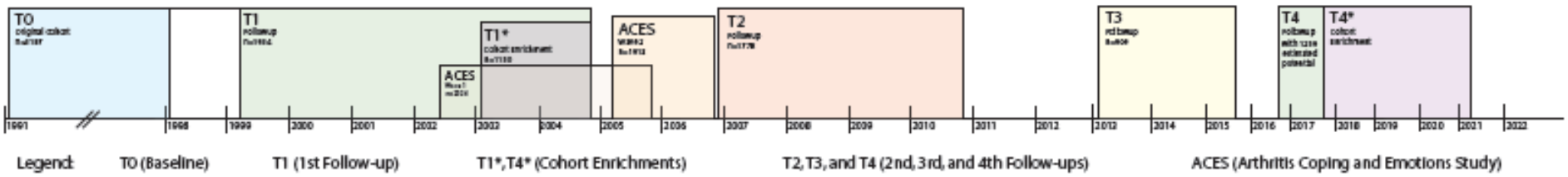
The Johnston County OA Project

Dr. Joanne Jordan,
PI 1990-2017

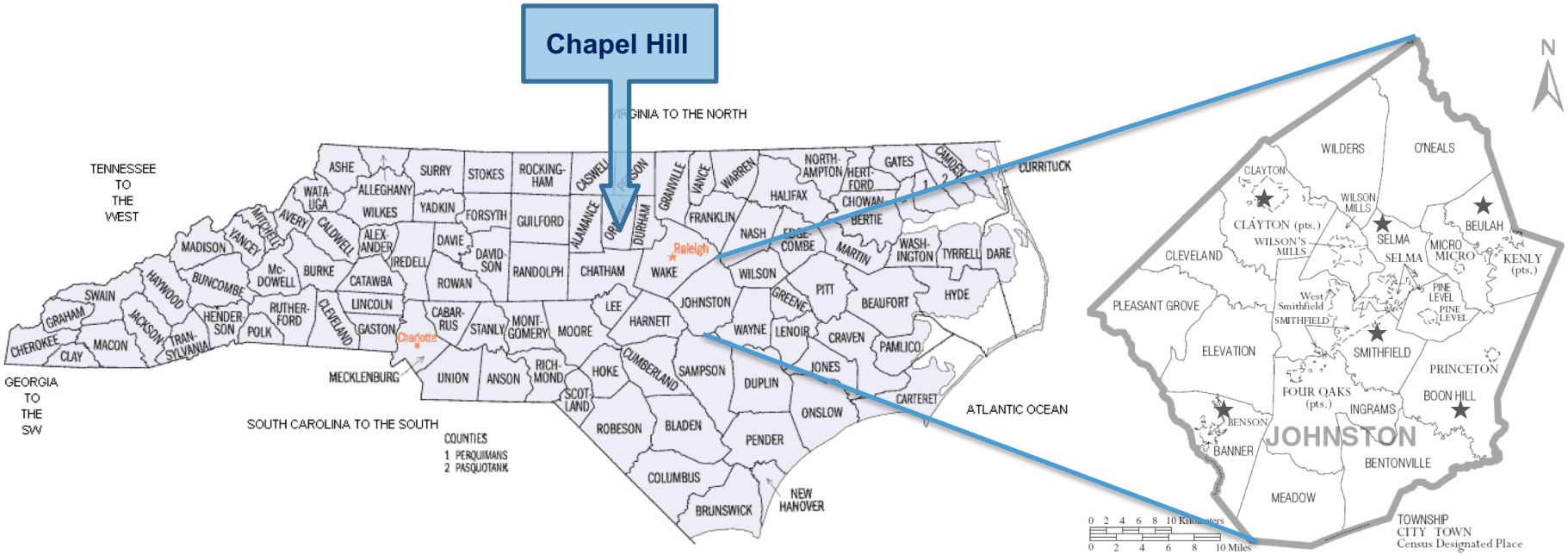
Drs. Amanda Nelson and
Yvonne Golightly, Co-PIs 2017-

The Johnston County OA Project

- prospective, population-based cohort study
- non-institutionalized adults 45+ years
- African American and white, men and women
- Began in 1990 and has involved more than 4000 individuals over ~25 years
- follow-up approximately every 5 years



The Johnston County OA Project



- Recruited from 6 townships
- Over-sampled African Americans

The Johnston County OA Project

- All participants provide/undergo:
  - self-report data via questionnaires
    - general health, comorbidities, function, pain, psychosocial, etc.
  - physical examination
  - radiography (hips, knees; later hands, spine, feet)
  - blood and urine samples
  - performance-based functional assessment

The Johnston County OA Project

- In general, participants:
  - range from 45 to over 90 years of age
  - have a mean BMI around 30 kg/m^2
  - are 1/3 women
  - are 1/3 African American

The Johnston County OA Project

- A sampling of findings…

The Johnston County OA Project

- Population-based OA prevalence

KNEE	Symptoms	Radiographic	Symptomatic
African American	47.1%	32.4%	19.0%
White	42.4%	26.8%	15.9%

HIP	Symptoms	Radiographic	Symptomatic
African American	37.1%	32.1%	12.0%
White	36.0%	26.6%	9.2%

Jordan, et al. J Rheumatol 2007;34:172-80; Jordan et al. J Rheumatol 2009;36:809-15

The Johnston County OA Project

Annual Incidence Rates (IR) per 1000 person-years, age and sex-standardized

- Population-based OA incidence

KNEE	Symptoms	Radiographic OA	Symptomatic OA
Overall	58	36	24
African American	68	37	28
White	55	35	23

HIP	Symptoms	Radiographic OA	Symptomatic OA
Overall	38	24	17
African American	28	7	7
White	39	24	15

Murphy, et al. Arthritis Care Res 2016:55-65; Moss et al. Osteoarthritis Cartilage 2016:1518-27.

Lifetime risk of symptomatic OA

- Estimated risk by 85 years of age:
  - 40% for **hand** OA (higher for women and whites)[1]
  - 25% for **hip** OA (no differences)[2]
  - 45% for **knee** OA (higher for obesity, injury)[3]

1. Qin, Arthritis Rheumatol 2017;69:1204-12; 2. Murphy, Osteoarthritis Cartilage 2010;18:1372-9; 3. Murphy, Arthritis Rheumatol 2008;59:1207-13.

JoCo OA: OA outcomes and function

- Knee pain is more significantly associated with difficulty performing HAQ activities compared with radiographic OA[1]
- A composite score of symptoms (pain/aching/stiffness in multiple sites) was strongly related to gait speed and HAQ while radiographic measures were not[2]

1. Jordan, J Rheumatol 1997;24(7):1344-9; 2. Nelson, Disabil Rehabil 2014;36(4):300-6; .

Fall risk and OA

- Baseline to 6 year follow up, mean age 62, mean BMI 31, 1/3 African American and 1/3 men
- The odds of self-reported falls increased with an increasing number of symptomatic OA joints
- Higher odds of falls for whites, women, older participants, and those with prior falls

Table 2. Associations between number of lower-extremity joints with symptomatic OA, covariates, and future falls*

Characteristic	Adjusted OR (95% CI)
No symptomatic OA joints†	1.00
1 symptomatic OA joint	1.53 (1.10–2.14)
2 symptomatic OA joints	1.74 (1.19–2.53)
3–4 symptomatic OA joints	1.85 (0.96–3.55)
White	1.39 (1.05–1.84)
Female	1.36 (1.04–1.77)
Age, per year	1.02 (1.01–1.04)
BMI, per kg/m^2	1.01 (0.99–1.03)
Falls at baseline	2.37 (1.80–3.12)
Lung problems	1.50 (1.12–2.01)
Neurologic problems	1.63 (1.07–2.49)
Narcotic use	1.88 (0.99–3.57)

* OA = osteoarthritis; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index.
† Symptomatic OA is defined as radiographic evidence of OA and pain, aching, or stiffness in the same joint.

Dore, et al. Arthritis Care Res 2015;67(5):633-9

Mortality and Knee OA

	No Knee rOA or Pain	Knee Pain Only	Knee rOA Only	Both Knee rOA and Pain
Deaths/Cohort	511/1271	264/561	497/1173	550/1177
All-Cause Deaths§	ref.	0.95 (0.83-1.09)	**1.19 (1.04-1.35)**	**1.17 (1.03-1.34)**
Deaths/Cohort	189/1271	88/561	178/1173	222/550
CVD Deaths*	ref.	0.96 (0.76-1.23)	1.11 (0.89-1.38)	1.21 (0.97-1.51)

§ Adjusted for birth cohort, age, sex, race, education, enrollment cohort, hip rOA, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depressive symptoms, physical activity, obesity, diabetes, cardiovascular disease

* Adjusted for birth cohort, age, sex, race, education, enrollment cohort, hip rOA, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depressive symptoms, physical activity, obesity, diabetes

Mortality and Hip OA

	No Hip rOA or Pain	Hip Pain Only	Hip rOA Only	Both Hip rOA and Pain
Deaths/Cohort	560/1321	382/787	509/1156	311/655
All-Cause Deaths§	ref.	1.04 (0.91-1.17)	**1.33 (1.17-1.51)**	1.01 (0.87-1.18)
Deaths/Cohort	205/1321	142/787	199/1156	115/655
CVD Deaths*	ref.	1.01 (0.82-1.24)	1.22 (0.99-1.50)	1.01 (0.80-1.28)

§ Adjusted for birth cohort, age, sex, race, education, enrollment cohort, knee rOA, hip injury, cancer, non-steroidal anti-inflammatory drug use, high blood pressure, smoking, liver disease, alcohol use, depressive symptoms, physical activity, body mass index, diabetes, cardiovascular disease

*Adjusted for birth cohort, age, sex, race, education, enrollment cohort, knee rOA, hip injury, cancer, non-steroidal anti-inflammatory drug use, high blood pressure, smoking, liver disease, alcohol use, depressive symptoms, physical activity, body mass index, diabetes

OA management guidelines

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OA Management Guidelines

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative

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[g] Department of Orthopaedics, University of North Carolina, Chapel Hill, NC

Nelson, et al. Sem Arthritis Rheum 2014;43(6):701-12

Guidelines Review

- MEDLINE 2003-2013: 188 articles, 16 included in final synthesis
- Quality of guidelines assessed using AGREEII
- Generated summary statements regarding recommendations (following slides)
- Found high levels of agreement across guidelines, indicating that suboptimal uptake is more likely due to lack of dissemination and utilization in practice

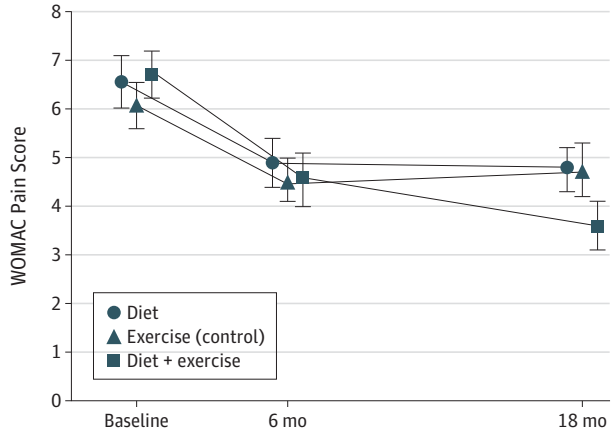
Non-pharmacologic 1

- **Education and self-management**
  - Provide or refer pts to self-management programs, provide education, regular contact to promote self-care, joint protection strategies, and individualized treatment plans to OA pts
- **Exercise and weight loss**
  - Encourage pts to engage in low-impact aerobic exercise and if overweight to lose weight. Consider ROM/flexibility and/or endurance/strengthening exercises, combination exercise with manual therapy, and PT/OT referral.

Evidence: Exercise and Weight Loss

- The IDEA trial
  - Compared a restrictive diet to an exercise intervention and the combination
  - Combination group vs. Exercise alone at 18 months:
    - 50% reduction in pain
    - 40% had little or no pain
    - Better WOMAC function scores
    - Reduced knee joint loads
    - Reduced plasma IL-6 levels
    - Improved walking speeds

Figure 2. Mean WOMAC Pain Scores Across the 18-Month Intervention Period



No. of patients	Baseline	6 mo	18 mo
Diet	152	115	124
Exercise	149	119	127
Diet + exercise	152	130	120

Messier et al, JAMA 2013;310(12):1263-73

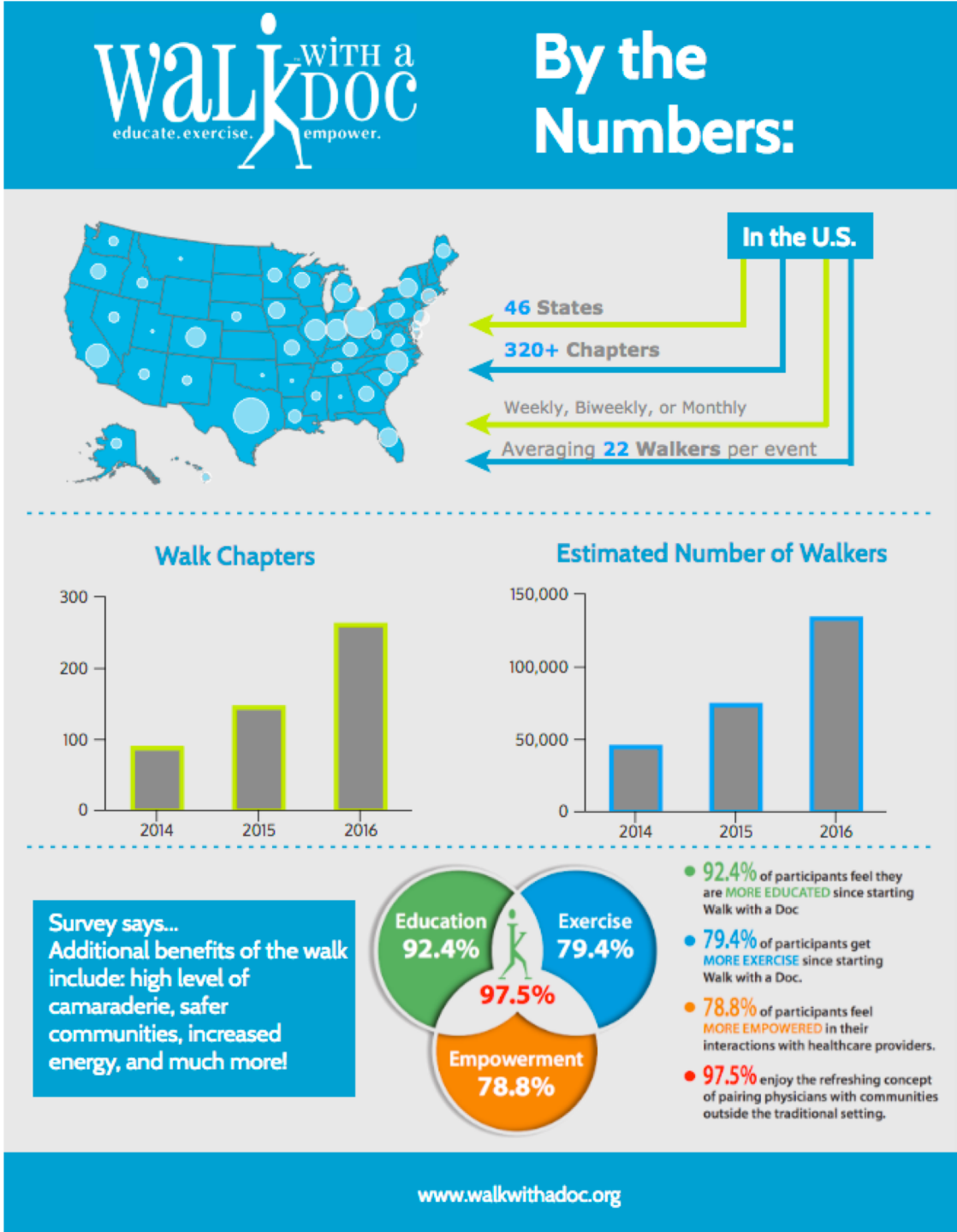
WALK WITH A DOC

dispensing health and happiness

www.WALKwithaDOC.org

http://walkwithadoc.org/our-locations/chapel-hill-north-carolina/

We were the first arthritis-based group to have a chapter.



Non-pharmacologic 2

- **Assistive devices, bracing, taping**
  - Walking aids (cane, crutch) and other assistive devices for ADLs recommended as needed (PT/OT)
  - Inconclusive evidence for bracing, heel wedges, thumb splints
- **Alternative and complementary modalities**
  - Thermal modalities are recommended. Therapeutic ultrasound is not, and insufficient evidence for acupuncture, Tai Chi, or TENS
- **Surgical**
  - Joint replacement is recommended when appropriate. Arthroscopy with debridement is not recommended*.

*Moseley et al, NEJM 2002;347:81-88; Kirkley et al, NEJM 2008;359:1097-1107; Katz et al, NEJM 2013;368:1675-84

Pharmacologic

- **First line**
  - Acetaminophen up to 3 grams/day
  - Topical NSAIDs (especially in 75+ or with comorbidities)
- **Second line**
  - Oral NSAIDs (with appropriate risk stratification, GI prophylaxis)
  - COX-2 inhibitor with or without gastroprotection
  - Intra-articular corticosteroids (knee and hip)
- **Other** (refractory disease)
  - Tramadol (recommended)
  - +/- Opioid analgesics (consider, along with AE's)
  - +/- Duloxetine (less evidence)
- **Controversies**
  - Glucosamine/chondroitin
  - Intra-articular hyaluronan

Core recommendations (always recommended):

- ✓ Self-management programs
- ✓ Education
- ✓ Individualized treatment plans
- ✓ Weight loss or maintenance
- ✓ Exercise (land or water-based)

Recommended for most situations (if appropriate for clinical situation, comorbidities, etc.):

- ✓ Intra-articular corticosteroid injection
- ✓ Topical non-steroidal anti-inflammatory medications (NSAIDs)
- ✓ Acetaminophen
- ✓ Oral NSAIDs or COX-2 inhibitors
- ✓ Walking aids and assistive devices
- ✓ Thermal modalities
- ✓ Physical or Occupational therapy referral

Consider in some situations (e.g. specific patient populations or presentations):

- ✓ Duloxetine
- ✓ Capsaicin
- ✓ Mind and body therapies (e.g. yoga, Tai Chi, acupuncture)
- ✓ Splinting and bracing
- ✓ Transcutaneous electrical nerve stimulation (TENS)
- ✓ Surgical intervention (specifically joint replacement)

Not recommended:

- ☒ Therapeutic ultrasound
- ☒ Needle lavage
- ☒ Arthroscopy with debridement

Controversial across guidelines, insufficient data, or not addressed:

- Intra-articular hyaluronic acid injection
- Other intra-articular treatments (e.g. platelet rich plasma, stem cells)
- Glucosamine/chondroitin
- Other surgical interventions (e.g. osteotomy, partial joint replacement)
- Herbal or botanical treatments

Nelson, NCMJ 2018;78(5):332-6.

McAlindon et al, OAC 2014;22:363-88.

OARSI 2014

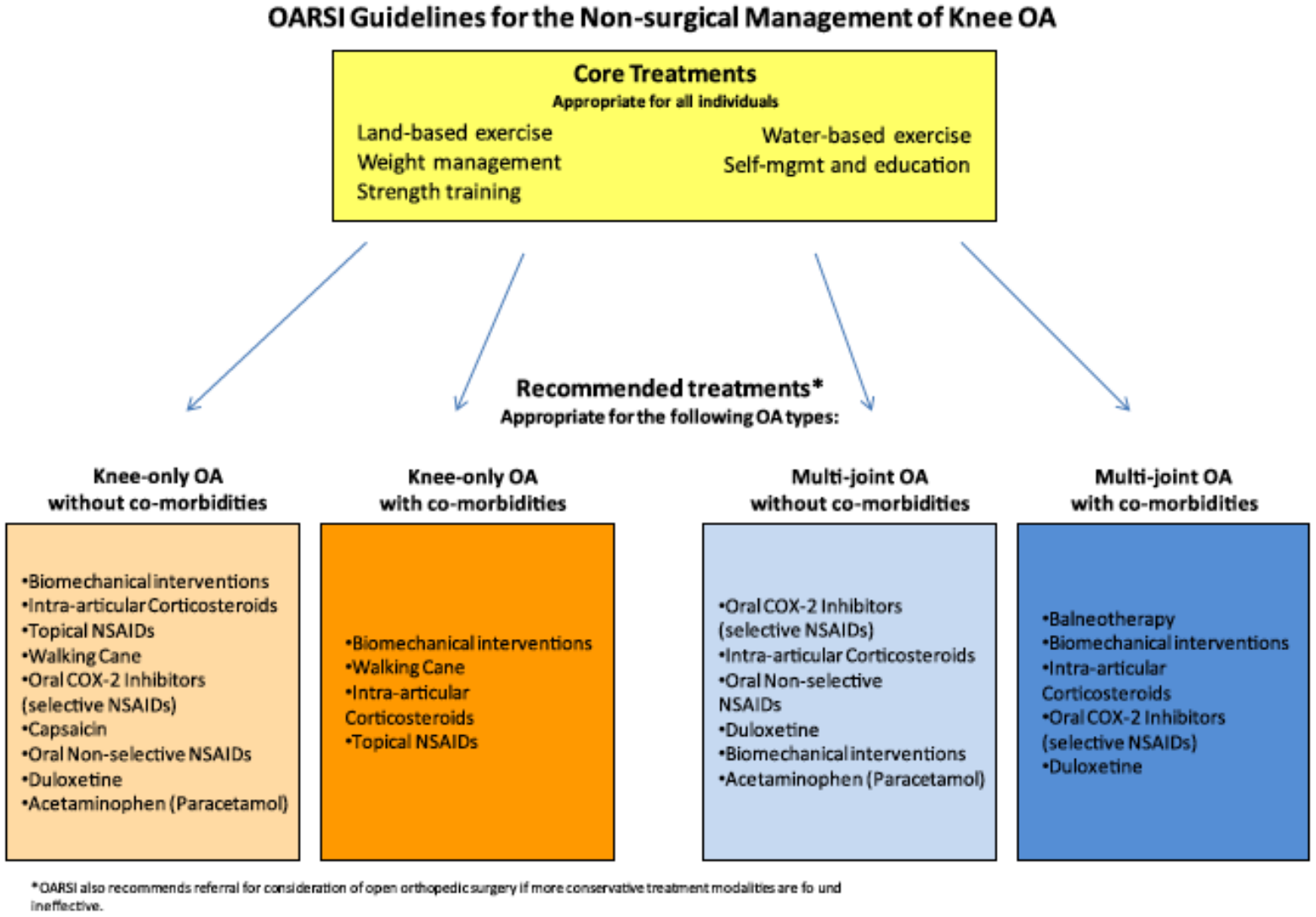
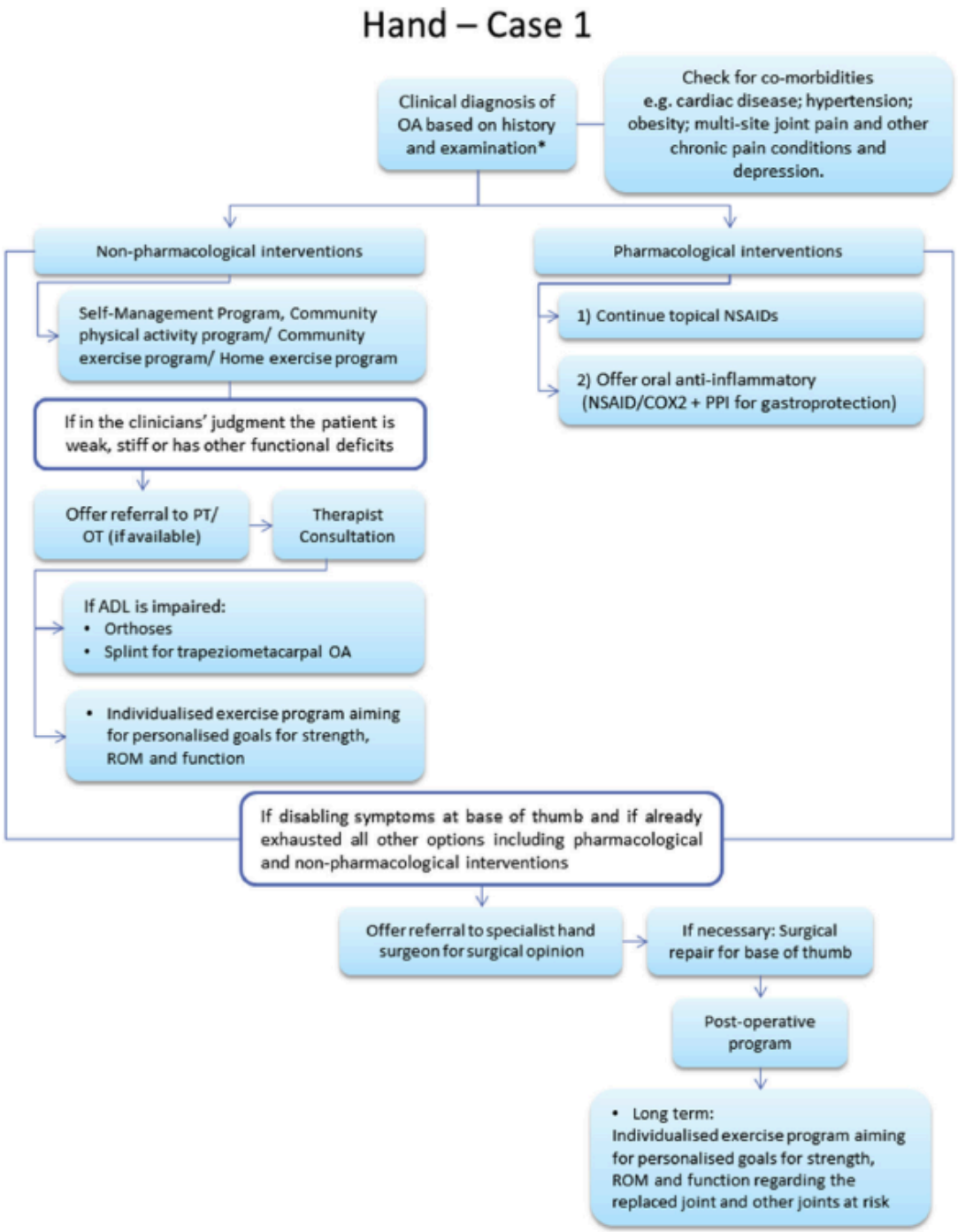


Fig. 1. Appropriate treatments summary.

OA algorithms

- Used prior systematic review to inform example algorithms



Meneses, OAC 2016;24:1487-99

Arthritis Foundation: Living with Arthritis

- http://blog.arthritis.org/living-with-arthritis

March 5, 2018: 6 tips for adapting your house when you have arthritis

1. Identify the issues
   - Consider an OT Certified Aging-in-Place Specialist or Certified in Environmental Modification
2. Conserve energy
   - Keep items at counter-height, downsize items, sit to wash dishes
3. Avoid falls
   - Transfer aids, seats for bathroom
4. Stair and hallway safety
   - Slip grips on stairs, cane, guard rail, lighting, remove rugs
5. Kitchen habits
   - Keep cookware/appliances on counter, replace heavy pans, ergonomic utensils
6. Change locations
   - Move bedroom downstairs, mini-fridge for medications, relocate laundry facilities

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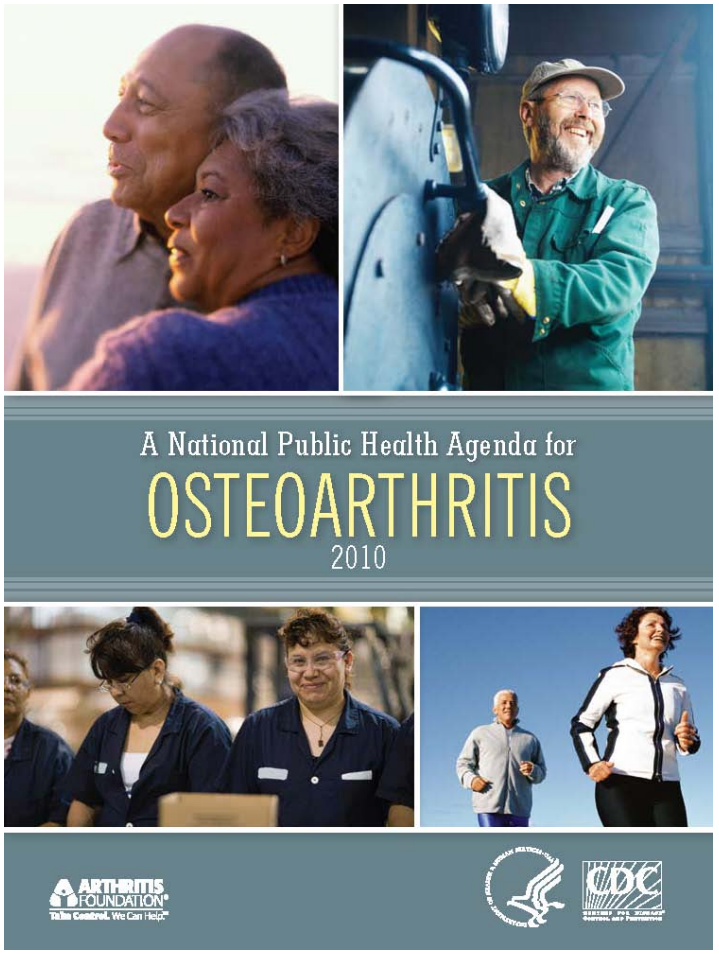
OA | OSTEOARTHRITIS ACTION ALLIANCE

oaaction.unc.edu

OA Action Alliance

- The **OA Action Alliance** is a national coalition of over 90 member organizations.

- Advancing the recommendations outlined in the **National Public Health Agenda for Osteoarthritis** (2010), or the **OA Agenda.**



OAAA Workgroups

OSTEOARTHRITIS ACTION ALLIANCE

- **Policy & Advocacy** – educating federal and state level legislators about OA, OAAA, importance of evidence-based programs
- **Community + Healthcare + Individuals** – WWE mini-grant program; developing value propositions for health systems and large employers; WWE health messaging to encourage participation
- **OA Prevention**
  - *Weight Management* – childhood obesity, physical activity, joint health
  - *Injury Prevention* – training strategies to minimize risk for lower limb injury and maintain joint health

OAAA: Connecting

OSTEOARTHRITIS ACTION ALLIANCE

OAAction.unc.edu

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Osteoarthritis Action Alliance

Osteoarthritis Action Alliance

CONTACT US

OAAction@unc.edu

#StandUp2OA

OAAA: Community Programming

- Physical activity can decrease pain and improve physical function by about 40% and may reduce healthcare costs.
  - **BUT** *1 in 3 adults with arthritis are inactive*
- Adults with arthritis also can reduce their symptoms by participating in disease management education programs.
  - **BUT** *only 1 in 10 have taken part in these programs*

CDC Vital Signs, March, 2017. www.cdc.gov/vitalsigns/arthritis

Walk With Ease

- Walking program
- 2 formats: Group/Instructor-led OR self-directed
- 1 hour; 3x/week; 6 weeks
- Includes:
  - Pre-walk discussion covering a specified topic related to exercise and arthritis
  - 10- to 40-minute walk (includes warm-up and cool-down)
- Trained group exercise leaders

www.arthritis.org/living-with-arthritis/tools-resources/walk-with-ease/

Future directions in OA management

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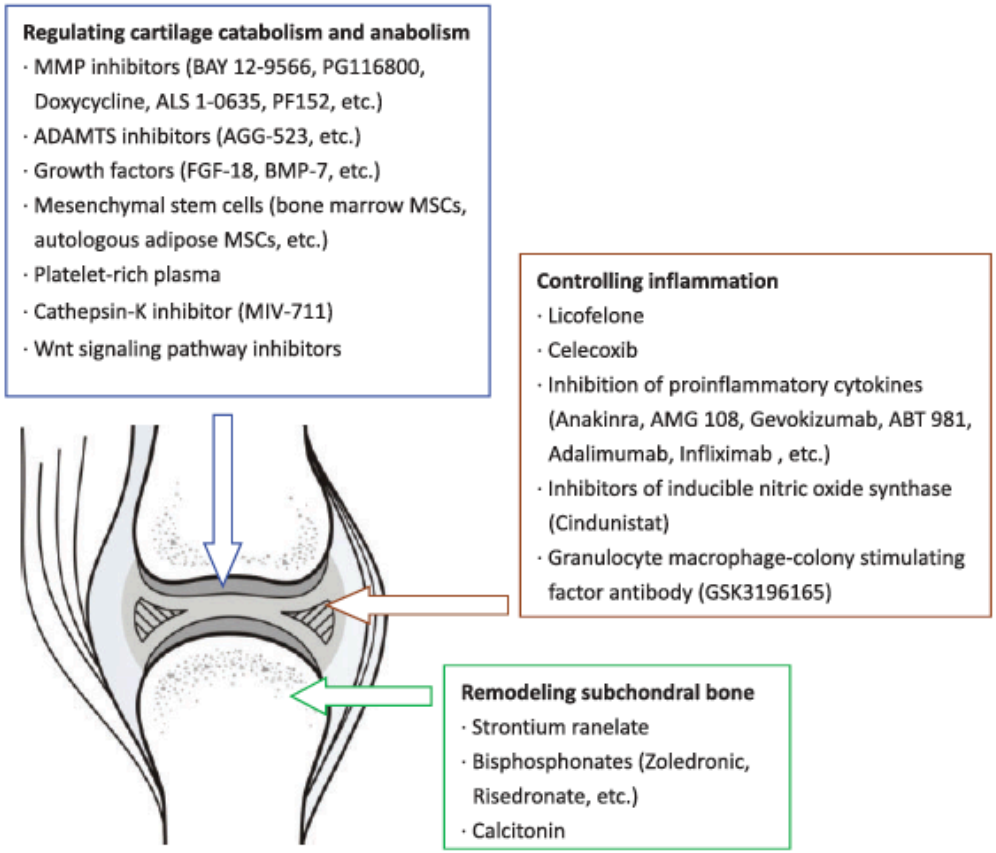
Future directions in management

- Anti-NGF
- Sprifermin/FGF-18
- TissueGene
- Joint distraction
- MSC/PRP

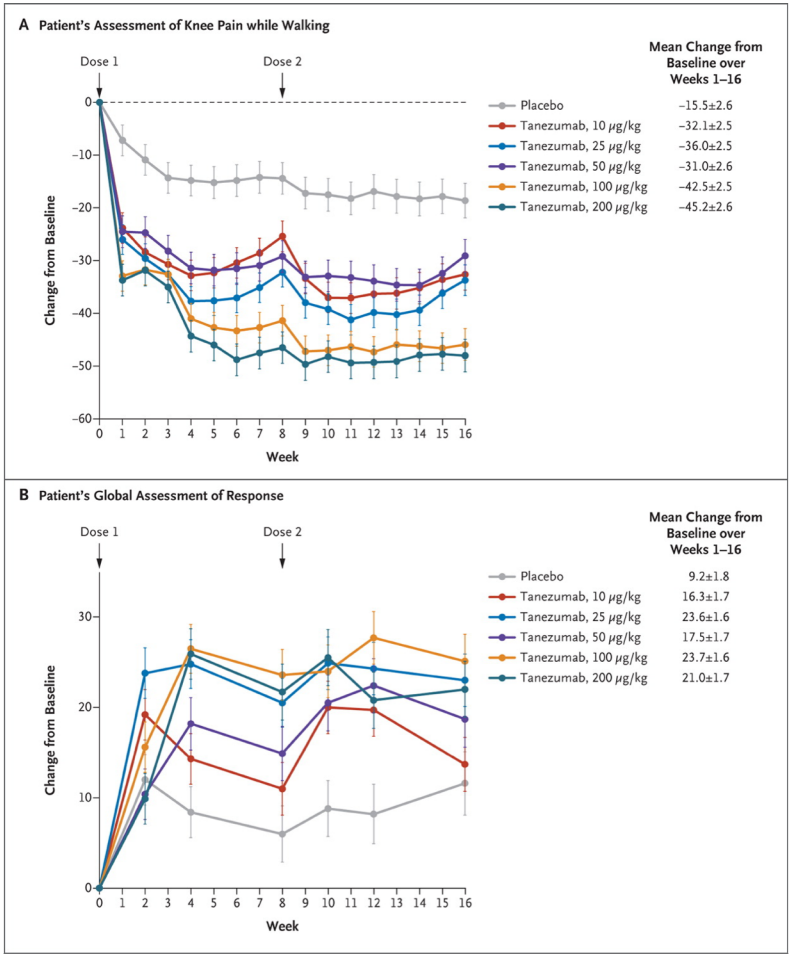
Fig. 1 Therapies targeting joint structures in OA



Huang et al Rheumatology 2018;57(iv):108-23.

Anti-NGF

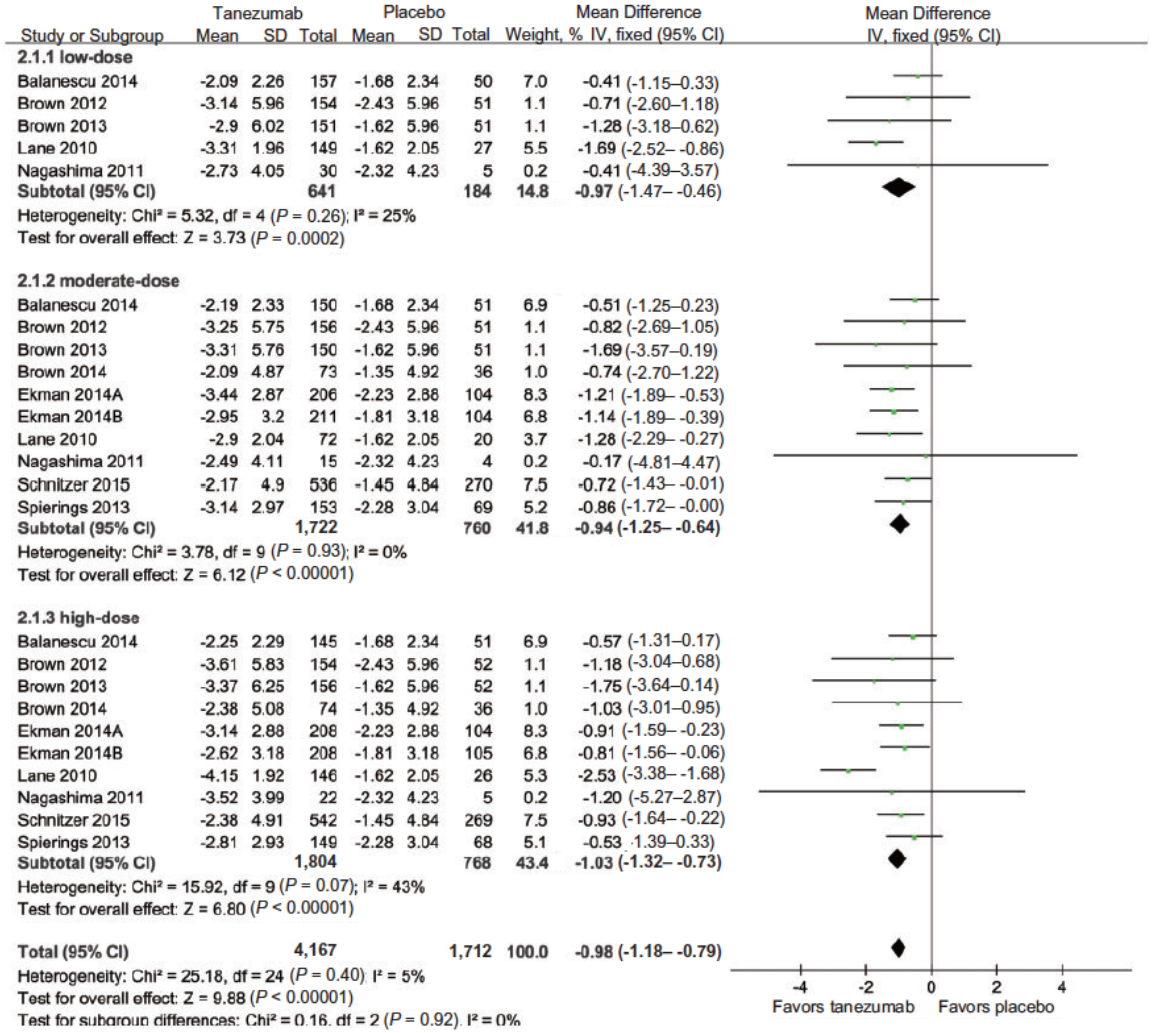
- Higher levels of NGF=more pain via nociceptor sensitization
- Tanezumab: Anti-nerve growth factor
- Highly significant improvements at 16 weeks in 2010 clinical trial



Lane et al NEJM 2010;363:1521-31.

Meta-analysis of anti-NGF in OA

- 10 RCTs with over 7000 participants
- Similar effect size for pain and function, smaller for PGA
- More AE for tx
- ?RPOA



Study or Subgroup	Tanezumab Mean	SD	Total	Placebo Mean	SD	Total	Weight, %	Mean Difference IV, fixed (95% CI)
2.1.1 low-dose								
Balanescu 2014	-2.09	2.26	157	-1.68	2.34	50	7.0	-0.41 (-1.15–0.33)
Brown 2012	-3.14	5.96	154	-2.43	5.96	51	1.1	-0.71 (-2.60–1.18)
Brown 2013	-2.9	6.02	151	-1.62	5.96	51	1.1	-1.28 (-3.18–0.62)
Lane 2010	-3.31	1.96	149	-1.62	2.05	27	5.5	-1.69 (-2.52– -0.86)
Nagashima 2011	-2.73	4.05	30	-2.32	4.23	5	0.2	-0.41 (-4.39–3.57)
Subtotal (95% CI)			**641**			**184**	**14.8**	**-0.97 (-1.47– -0.46)**
Heterogeneity: Chi² = 5.32, df = 4 (*P* = 0.26); I² = 25%								
Test for overall effect: Z = 3.73 (*P* = 0.0002)								
2.1.2 moderate-dose								
Balanescu 2014	-2.19	2.33	150	-1.68	2.34	51	6.9	-0.51 (-1.25–0.23)
Brown 2012	-3.25	5.75	156	-2.43	5.96	51	1.1	-0.82 (-2.69–1.05)
Brown 2013	-3.31	5.76	150	-1.62	5.96	51	1.1	-1.69 (-3.57–0.19)
Brown 2014	-2.09	4.87	73	-1.35	4.92	36	1.0	-0.74 (-2.70–1.22)
Ekman 2014A	-3.44	2.87	206	-2.23	2.88	104	8.3	-1.21 (-1.89– -0.53)
Ekman 2014B	-2.95	3.2	211	-1.81	3.18	104	6.8	-1.14 (-1.89– -0.39)
Lane 2010	-2.9	2.04	72	-1.62	2.05	20	3.7	-1.28 (-2.29– -0.27)
Nagashima 2011	-2.49	4.11	15	-2.32	4.23	4	0.2	-0.17 (-4.81–4.47)
Schnitzer 2015	-2.17	4.9	536	-1.45	4.84	270	7.5	-0.72 (-1.43– -0.01)
Spierings 2013	-3.14	2.97	153	-2.28	3.04	69	5.2	-0.86 (-1.72– -0.00)
Subtotal (95% CI)			**1,722**			**760**	**41.8**	**-0.94 (-1.25– -0.64)**
Heterogeneity: Chi² = 3.78, df = 9 (*P* = 0.93); I² = 0%								
Test for overall effect: Z = 6.12 (*P* < 0.00001)								
2.1.3 high-dose								
Balanescu 2014	-2.25	2.29	145	-1.68	2.34	51	6.9	-0.57 (-1.31–0.17)
Brown 2012	-3.61	5.83	154	-2.43	5.96	52	1.1	-1.18 (-3.04–0.68)
Brown 2013	-3.37	6.25	156	-1.62	5.96	52	1.1	-1.75 (-3.64–0.14)
Brown 2014	-2.38	5.08	74	-1.35	4.92	36	1.0	-1.03 (-3.01–0.95)
Ekman 2014A	-3.14	2.88	208	-2.23	2.88	104	8.3	-0.91 (-1.59– -0.23)
Ekman 2014B	-2.62	3.18	208	-1.81	3.18	105	6.8	-0.81 (-1.56– -0.06)
Lane 2010	-4.15	1.92	146	-1.62	2.05	26	5.3	-2.53 (-3.38– -1.68)
Nagashima 2011	-3.52	3.99	22	-2.32	4.23	5	0.2	-1.20 (-5.27–2.87)
Schnitzer 2015	-2.38	4.91	542	-1.45	4.84	269	7.5	-0.93 (-1.64– -0.22)
Spierings 2013	-2.81	2.93	149	-2.28	3.04	68	5.1	-0.53 -1.39–0.33)
Subtotal (95% CI)			**1,804**			**768**	**43.4**	**-1.03 (-1.32– -0.73)**
Heterogeneity: Chi² = 15.92, df = 9 (*P* = 0.07); I² = 43%								
Test for overall effect: Z = 6.80 (*P* < 0.00001)								
Total (95% CI)			**4,167**			**1,712**	**100.0**	**-0.98 (-1.18– -0.79)**
Heterogeneity: Chi² = 25.18, df = 24 (*P* = 0.40); I² = 5%								
Test for overall effect: Z = 9.88 (*P* < 0.00001)								
Test for subgroup differences: Chi² = 0.16, df = 2 (*P* = 0.92), I² = 0%								

Figure 2 Forest plots of mean baseline-to-end point change in Western Ontario and McMaster Universities Osteoarthritis Index pain after tanezumab treatment vs placebo (mean ± SD).

Chen et al Pain Med 2017;18:374-85.

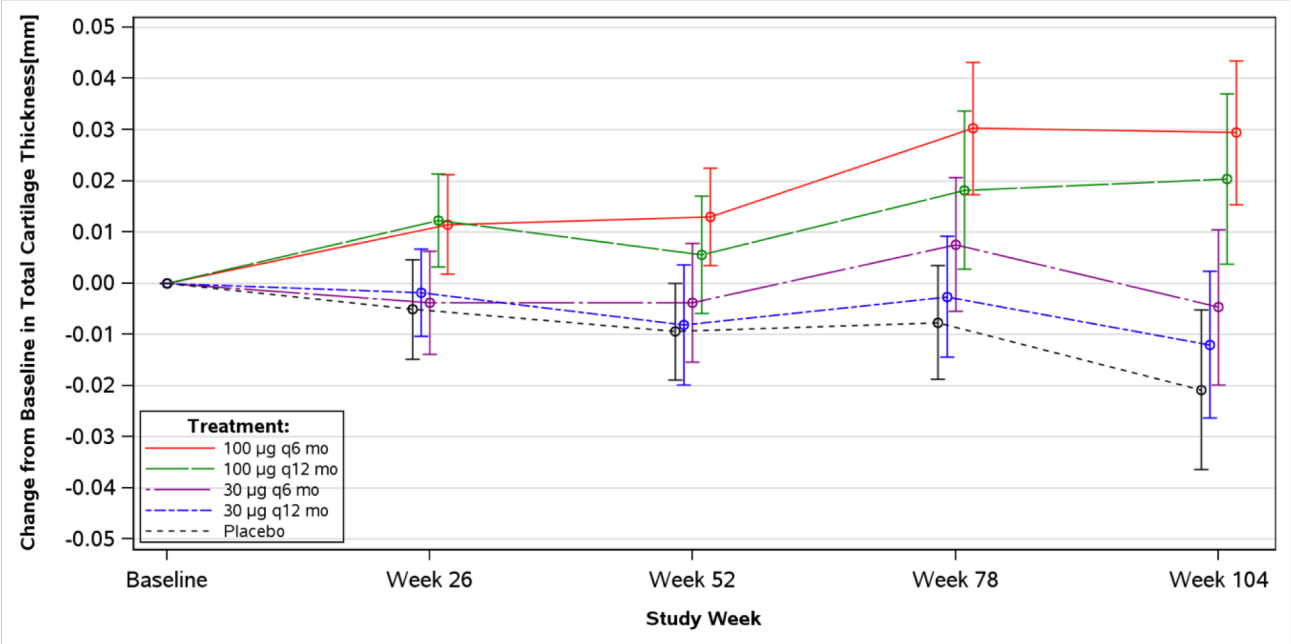
Sprifermin/FGF-18

- Fibroblast growth factor 18 (FGF-18) is a signal for chondrocyte proliferation, osteoblast differentiation, and matrix production
- Sprifermin is a recombinant, truncated, non-glycosylated form given intra-articularly
- The first-in-human study (1) showed no safety concerns and possible benefit to cartilage[1]
- Subsequent abstracts on phase II work suggest prevention of cartilage loss (by MRI, next slide) at 2 and 3 years with no difference in symptoms[2,3]

1. Dahlberg, Clin Exp Rheumatol 2016;34:445-50; 2. Hochberg ACR 2017 1L; 3. Hochberg OARSI 2018, 32.

Sprifermin 2 year cartilage thickness

Figure 2. Primary endpoint: change from baseline in cartilage thickness in the TFJ over 2 years (qMRI)



Analysis population: modified ITT (all subjects with BL and ≥1 post-treatment qMRI in the double-blind treatment period); error bars = 95% CI.

Total qMRI cartilage thickness= total volume divided by total surface area (i.e. average cartilage thickness)

At baseline, qMRI total cartilage thickness was similar in all treatment arms and averaged ~ 1.8 mm.

CI, confidence interval; q6mo, every 6 months; q12 mo, every 12 months; qMRI, quantitative magnetic resonance imaging; TFJ, total femorotibial joint

Hochberg ACR 2017;69 (suppl10), 1L.

TissueGene

- Currently phase III
- IA injection of genetically engineered chondrocytes transduced with TGF-beta 1 (TGF-B stimulates PG synthesis, chondrocyte proliferation)
- Modest benefits in pain and IKDC
- No clear safety signals

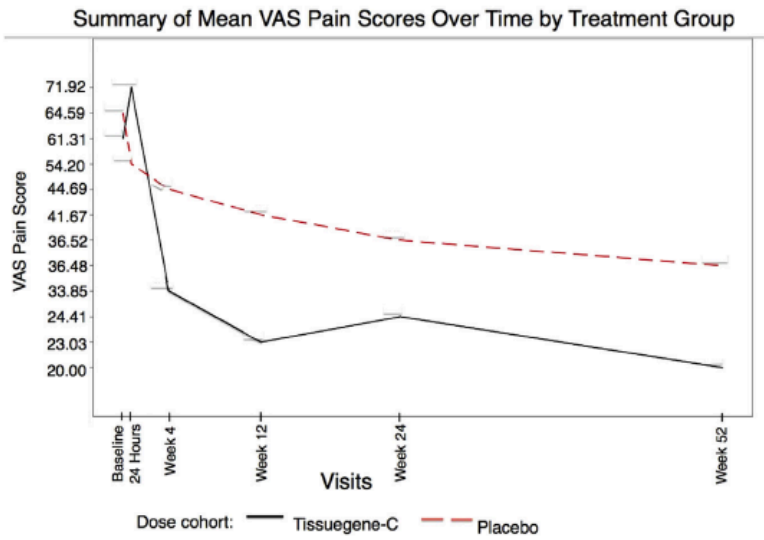
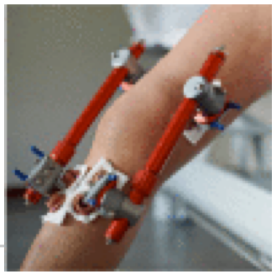


Fig. 3. Mean VAS pain scores over time by treatment group.

Cherian, Osteoarthritis Cartilage 2015;23;2109-18.

Joint Distraction



- External fixation to distract the joint
- Knee oint distraction for ~6 weeks demonstrated increased joint space width at 1-2 year follow-up[1,2]
  - Improved collagen synthesis:breakdown, reduced pain
  - Pain still better at 5 years, reduced progression
- May reduce secondary inflammatory and resultant cartilage degeneration and bone remodeling
- Most troubling AE is pin tract infection

1. Intema, Ann Rheum Dis 2011;70:1441-6; 2. Wiegant, Osteoarthritis Cartilage 2013;21:1660-7; 3. van der Woude Cartilage 2017;8:263-71.

MSCs and PRP

- MSCs: Mesenchymal stem cells
- PRP: Platelet-rich plasma
- Given IA, both have theoretical benefits (and risks!) on cartilage and joint tissues
- Suffer from lack of standardization and sound RCTs
- Neither recommended by any guidelines, high quality studies are needed
- Many active studies are listed on clinicaltrials.gov

Huang et al Rheumatology 2018;57(iv):108-23; Osborne, Br J Sports Med 2016;50:1237-44.

Ongoing trials

- As of 8/6/18, there were 733 studies active or recruiting on ClinicalTrials.gov
- These included behavioral, biomechanical, topical, IA, and drug interventions as well as device trials
- A few examples:
  - Senolytic in phase I
  - Longer duration IA corticosteroids
  - Drugs to enhance chondrogenesis (IA), phase I-II
  - Novel analgesic pathways (neurotrophin)
  - RFA for geniculate nerves
  - Geniculate artery embolization

Take Home Points

- Osteoarthritis is common, increasing in prevalence, and debilitating
- OA in relation to other common chronic diseases significantly affects QoL and mobility
- The JoCo OA Project has provided unique insights
- OA management is primarily through lifestyle and behavioral interventions
  - Resources are available including WWAD, AF, OAAA
- There are several promising treatments under study

Acknowledgments

Thank you!

Rheumatology Research Foundation

Advancing Treatment | Finding Cures

National Institute of Arthritis and Musculoskeletal and Skin Diseases