

A Review of Osteoarthritis Guidelines, their Application to Clinical Practice, and Populations at Risk

Stephen Brunton, MD, FAAFP
Professor
Department of Family and Preventive
Medicine
University of South Carolina

An adjunct offering for Global Pain Awareness Week

Sponsorship and Support

This presentation is sponsored by



PRIMARY CARE
EDUCATION
CONSORTIUM

and supported by an educational grant from
Haleon.

CME Information

In support of improving patient care, this activity has been planned and implemented by PCEC. PCEC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), the American Nurses Credentialing Center (ANCC), and the American Academy of PAs (AAPA) to provide continuing education for the healthcare team

Credit Designation: This activity is 1.25 credit hours.

Our faculty and disclosures

- Joel Block, MD, of Rush Medical College, discloses that he serves as a consultant for Sanofi, KM Medical Inc., Eupraxia, Inc., Novartis and Haleon, as well as the Chair, DSMB, NIH-funded Clinical Trials at Navitas Clinical Research.
- Stephen Brunton, Moderator, has no conflicts to report.
- All relevant financial relationships have been mitigated.
- If this CME activity includes discussion about medications not approved by the US Food and Drug Administration and uses of medications outside of their approved labeling, that will be plainly stated.

Learning Objectives

After viewing this webinar, participants should be able to...

Describe the guidelines for pain management in osteoarthritis.

Design strategies to improve pain management in clinical practice and individualize care.

Implement recommended approaches to pain management based on evidence and best practices.

Recognize and treat at-risk patient groups.

Now on to Dr. Joel Block for

A Review of the Osteoarthritis Guidelines and their Application to Clinical Practice

Musculoskeletal Pain: Background and Barriers to Effective RX

Joel A Block, MD, MACR

The Willard L. Wood, M.D. Professor and
Chief, Division of Rheumatology
Rush Medical College
Rush University Medical Center
Chicago, IL
jblock@rush.edu

Pain

- Definition and classification
- Sensitization and Pain
- Pain in the Musculoskeletal Diseases

Pain

• Definition:

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”



Hieronymus Bosch – Last Judgment (Wikimedia commons)

<https://www.iasp-pain.org/publications/iasp-news/iasp-announces-revised-definition-of-pain/>

Pain

- Historically, pain was considered a central component of inflammation (*Cardinal manifestations of inflammation: rubor; calor; dolor; tumor*).
- Currently, we recognize that not all pain is inflammatory.
- “Pain is both a sensory and an emotional experience and needs to be understood within its biopsychosocial context.” (Walsh DA and Malfait A-M, 2025, in press)

Pain

- **Nociceptive**
 - Activation of nociceptors by tissue injury, heat, multiple noxious stimuli.
 - Sharp, aching, throbbing
- **Inflammatory**
 - The “pain” of acute trauma or inflammation
 - Inflammatory mediators increase excitability; non-noxious stimuli cause pain (allodynia, hyperalgesia)
- **Neuropathic**
 - Nerve damage and remodeling in CNS and PNS perpetuates the pain sensation.
 - Burning, numbness, paresthesia, “heavy” sensation
 - Chronic, may intensify over time
- **Nociplastic / Dysfunctional**
 - Absence of obvious nerve damage or tissue injury
 - Absence of detectable inflammation
 - Often chronic

Pain

- Treatment focusing solely on inflammatory or nociceptive pain will be inadequate. Attention must be paid to the type(s) of pain individual patients are experiencing.

Pain

- Definition and classification
- Sensitization and Pain
- Pain in the Musculoskeletal Diseases

Pain

- Nociceptors (pain receptors) are normally stimulated by noxious stimuli.
- Sensitization: In pathological conditions, nociceptors can be sensitized to activate by normally non-noxious stimuli, hence transmit pain from normally non-painful stimuli.
- Sensitization occurs both peripherally and centrally: As pain becomes chronic, the PNS and CNS undergo alterations via neuroplasticity, and the pain may be felt more systemically and becomes complex.

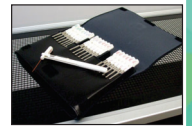
Pain

- Markers of sensitization:
 - Hyperalgesia: a painful stimulus elicits exaggerated pain.
 - Allodynia: normally non-painful stimuli are perceived as painful
- Quantitative Sensory Testing (QST): clinical measure of sensitization

Evidence for neuroplasticity in humans with knee osteoarthritis: Functional neuroplasticity

In experimental models

- Knee Hyperalgesia
- Mechanical Allodynia



In patients – quantitative sensory testing (QST):

- Pain Pressure Threshold
- Mechanical Allodynia
- Temporal summation (wind up)



Courtesy Prof A-M Malfait, MD, PhD

Sensitization in human subjects with OA

- Osteoarthritis patients have signs of nervous system sensitization
 - Lower pain pressure thresholds and increased temporal summation
 - At the osteoarthritic joint, and at sites distant from the joint
- Sensitization measures have been associated with osteoarthritis knee pain severity
 - Pressure pain threshold and mechanical temporal summation
- Joint replacement is often (~80%) associated with reversal of both sensitization and pain, suggesting that sensory input from the joint drives ongoing sensitization and pain
- Pressure pain sensitivity at the knee is a risk factor for developing persistent knee pain over a 2-year period.

Dua *et al*, BMC Musculoskelet Disord 2018; Neogi, Osteoarthritis and Cartilage 2013; Fingleton *et al*, Osteoarthritis and Cartilage 2015; Neogi *et al*, Ann Rheum Dis 2015; Groven-Nielsen *et al*, Arthritis Rheum 2012; Kosek *et al*, Pain 2000; Petersen *et al*, Pain 2015; Arendt-Nielsen *et al*, Pain, 2010; Roos *et al* 1999, Purser *et al* 2012, Ettinger *et al* 1994; Carlesso *et al*, Arthr Rheum 2019; Arant *et al*, OAC 2021.

Pain

- Definition and classification
- Sensitization and Pain
- Pain in the Musculoskeletal Diseases

Sources of Pain in Rheumatic Disease

Table II. Sources of Pain in Rheumatic Disease^a.

Mechanisms		
Inflammation	Damage	Pain processing and perception ^b
Rheumatoid arthritis	Osteoarthritis	Fibromyalgia
Psoriatic arthritis	Rheumatoid arthritis	TMJ disorder
Spondyloarthritis	Psoriatic arthritis	Rheumatoid arthritis
Osteoarthritis		Osteoarthritis
		Spondyloarthritis
		SLE

^aThe table presents a categorisation of clinical conditions in terms of mechanisms of pain that likely contribute to patient symptomatology and have been investigated in clinical studies. These conditions are listed as examples to emphasise that pain mechanisms are diverse and may interact in the individual patient.

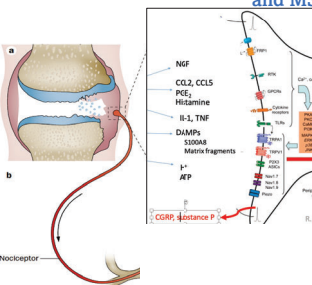
^bIncludes peripheral and central sensitisation and related issues considered under the terminology of fibromyalgia. Also includes genetic polymorphisms related to neurophysiological pathways for pain.

Sorensen DG, Hassett AL, Pincus DS. Clin Exp Rheum 2017

Neuroplasticity in the brain and in the periphery

- Other types of arthritis?
- Disease-specific pathways?

Arthritis as a source of pain: it is unknown at this time how mechanisms underlying pain may overlap or differ between different types of rheumatic and MSK diseases.



Different types of arthritis have different peripheral triggers: will engage the nervous system differentially.

For example:

- Osteoarthritis is a mechanically driven degenerative disease with low level inflammation/innate immune system
- Rheumatoid arthritis- an inflammatory auto-immune disease; adaptive immune system
- SpA/Psoriatic arthritis – inflammatory disease; bone involvement-different distribution of affected joints

Courtesy Prof A-M Malfait, MD, PhD

- Currently:
 - Each type of pain may be present in any of the arthritides.
 - Failure to address the type(s) of pain a patient is experiencing will result in inadequate pain control.
- As pain becomes more chronic, central processing (sensitization) occurs, and becomes much more difficult to ameliorate.

Pain, an Unmet Need in RA: 2000 - 2022

Report:	RAPID3 (1)	CORRONA (2)	BRASS (2)	Rodwell (3)	Schmukler (4)
Years data collection	2005-2019	2000-2019	2003-2021	2021	2022
N	285	48,255	1343	173	104
Measure:	Mean (SD)	Mean(SD)	Mean (SD)	Mean (SD)	Mean (SD)
SJC	3.7(4.1)	2.7 (4.4)	6.2 (7.1)	1.8 (3.2)	1.4 (3.0)
TJC	3.6(5.2)	3.4(5.4)	7.0 (7.7)	3.9 (5.7)	2.4 (4.5)
Pain	3.5(2.7)			4.6 (2.9)	4.7 (3.1)
PATGL	3.1 (2.5)	3.3(2.7)	3.3(2.5)	4.5 (3.0)	4.4 (3.2)
CDAI	12.3(10.6)	11.2(11.5)	19.5 (16.5)	13.8(10.6)	12.0 (10.3)
RAPID3	8.7(6.6)	8.2(6.3)	7.6 (5.5)	11.6 (7.3)	12.1 (8.6)

SJC = swollen joint count
TJC = tender joint count
PATGL = patient global

1. Pincus, Sweevingen, Bergman, Yazici. J Rheumatol. 2008;35(11):2136-47.
2. Kremer, Pappas, Greenberg, et al. J Rheumatol. 2021;48(12):1776-83.
3. Rodwell, Hassett, Gibson, Pincus, et al., ACR Open Rheumatol. 2023;5(10):511-21.
4. Schmukler, Li, Pincus. Rheumatol Adv in Pract. 2024;8(2):rkae057

Courtesy T. Pincus MD

Pain: Summary

- There are multiple types of pain. These may overlap in any patient.
- Attention to nociplastic and neuropathic pain, in addition to nociceptive and inflammatory pain, is essential to adequately address musculoskeletal pain.
- As neuroplasticity proceeds in the presence of chronic pain, sensitization can be assessed (and quantified) clinically by QST.
- Chronic pain is more refractory to treatment and requires a multimodality approach.
- Pain remains a substantial unmet need in the rheumatic diseases.

Osteoarthritis: Current and Emerging Therapy, 2024

Management of OA in 2024

- The Burden of OA
- Definitions
- Current Guidelines-based Management
- Emerging and Popular Approaches

Prevalence of Arthritis in U.S.

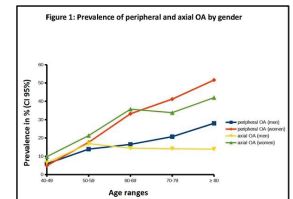
- 54.4 million Americans (23% of adults) have doctor-diagnosed arthritis (CDC, 2019: www.cdc.gov/arthritis/data_statistics/national-statistics.html)
 - 40 million have clinical osteoarthritis
 - 1.3 million have rheumatoid arthritis (↓ from 2.1 million in '80's!) (A&R '08 58:15)
- Prevalence expected to increase to 78 million by 2040
 - high prevalence of arthritis in the elderly
 - projected increase in the number of elderly people (CDC '19; A&R '06 54:226; A&R '08 58:15)

OA Prevalence: WORLD

India: 28.7% of population > 40 y/o
(Pal CP, et al, Indian J Orthop 50:518, 2016)

S. Africa: 33.1% Knee OA
(Usenbo A, et al, PLOS ONE, 2015, DOI:10.1371/journal.pone.0133858)

Spain: 29.35% of population > 40 y/o
(Blanco FJ, et al: Reumatol Clin, 2020 <https://doi.org/10.1016/j.reuma.2020.01.008>; ACR 2020)



Prevalence of Arthritis: WORLDWIDE

Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021

Summary
Osteoarthritis is the most common form of arthritis in adults, characterised by chronic pain and loss of mobility. Osteoarthritis most frequently occurs after age 40 years and prevalence increases strongly with age. WHO has designated 2020 as the decade of healthy ageing, which highlights the need to address diseases such as osteoarthritis, which severely affect functional ability and quality of life. Osteoarthritis can impact life and negatively affect other

Findings Globally, 595 million (95% uncertainty interval 535–656) people had osteoarthritis in 2020, equal to 7.6% (95% UI 6.8–8.4) of the global population, and an increase of 132.2% (130.3–134.1) in total cases since 1990. Compared with 2020, cases of osteoarthritis are projected to increase 74.9% (59.4–89.9) for knee, 48.6% (35.9–67.1) for hand, 78.6% (57.7–105.3) for hip, and 95.1% (68.1–135.0) for other types of osteoarthritis by 2050. The global age

age-standardised rate of YLDs for total osteoarthritis was 20.8 YLDs (95% UI 17.7–23.9) per 1000 in 2020, a 75.2% increase from 1990 (11.9 YLDs per 1000). In the adult aged 75 years and older, osteoarthritis was the most common cause of YLDs. Age-standardised prevalence in 2020 was more than 7% in all world regions, ranging from 6.0% (95% UI 5.0–7.0) per 1000 in southeast Asia to 8.0% (95% UI 6.8–9.2) in high-income regions. The highest prevalence rates were observed in high-income regions, which are projected to increase further by 2050.

Interpretation Age-standardised YLD attributable to osteoarthritis are continuing to rise and will lead to substantial increases in total disability burden of population growth and ageing, and burden due to its effect on the osteoarthritis. The demand on health systems for care of patients with osteoarthritis, including pain management, which is highly effective for low-severity osteoarthritis in hip and knee, will rise in all regions. Ageing for care of such and lead to further health inequity for individuals and countries unable to afford them. Much more can and should be done to prevent people getting to that stage.

Research WHO & Médecins Sans Frontières, Institute of Bone and Joint Research, and Global Alliance for Musculoskeletal Health.

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

OA: the most **DISABLING** form of arthritis

- The W.H.O. *Global Burden of Disease* estimates that 242 million people in the world have “symptomatic and activity-limiting” OA of the hip and/or knee.
- 75% increase in OA YLDs* from 1990 to 2013, the 3rd most rapidly rising disease-associated disability (behind diabetes at 135% and dementia at 84%).
- These represent a significant underestimate of the true global burden of OA, as these rates only consider hip and knee OA, and not OA at other sites.

*YLD: years lived with disability

Sources: WHO GBD, OARSI

Jin Z et al, ARD, 79:1014, 2020

OA: Disease Severity

Table 1 Mean MDHAQ Patient Scores in Patients with Four Rheumatic Diseases

Variable (range)	All (205)	RA (50)	SLE (66)	OA (67)	FM (32)	P-value
Physical Function (0 to 10)	2.5 (1.9)	2.4 (2.0)	1.8 (1.7)	2.9 (1.9)	3.6 (1.9)*	p = 0.0002
Pain (0 to 10)	5.7 (3.0)	5.1 (3.1)	4.3 (3.2)	6.8 (2.2)*	7.6 (1.7)†	p < 0.0001
Patient Global Estimate (0 to 10)	5.0 (3.0)	4.5 (3.2)	4.0 (3.0)	5.4 (2.8)	7.1 (1.9)†	p < 0.0001
RAPID3 (0-30)	13.0 (7.2)	11.4 (7.4)	9.9 (7.3)	15.1 (5.8)	18.2 (4.4)‡	p < 0.0001
Fatigue (0 to 10)	5.0 (3.0)	4.6 (3.2)	4.4 (3.1)	5.2 (3.0)	6.7 (1.8)*	p = 0.0067
Number of Symptoms (0-50)	11.1 (8.5)	8.1 (8.5)	10.4 (8.2)	11.1 (7.1)	17.9 (8.2)‡	p < 0.0001

Numbers are mean (standard deviation) *p < 0.05 †p < 0.01 ‡p < 0.001 (p-values using RA as reference group).

Table 2 Mean RheuMetric Physician Estimates in Four Rheumatic Diseases

Variable (range)	All (205)	RA (50)	SLE (66)	OA (67)	FM (32)	P-value
Patient Global Estimate (PATGL) (0 to 10)	3.9 (2.1)	3.9 (2.2)	2.9 (2.1)	4.5 (1.6)	4.9 (1.8)	p < 0.0001
Inflammation (DOCDNF) (0 to 10)	1.5 (1.8)	2.4 (2.4)	1.4 (1.6)	1.0 (0.5)	0.8 (1.2)†	p = 0.0003
Damage (DOCDAM) (0 to 10)	2.8 (2.1)	2.6 (2.2)	1.8 (1.8)	4.4 (1.6)	1.9 (1.8)	p < 0.0001
Distress (DOCDSTR) (0 to 10)	2.1 (3.0)	0.6 (1.9)	1.1 (2.3)	2.1 (3.1)	5.4 (2.2)‡	p < 0.0001

Numbers are mean (standard deviation) *p < 0.05 †p < 0.01 ‡p < 0.001 (p-values using RA as reference group).

Castrejón I, Gibson KA, Block JA, et al
Bull Hosp Joint Dis 2015;73:178-84

Castrejon I, Shakoor N, Chua JR, Block JA
Rheumatol Intl 2018; 38:2137-45

Management of OA in 2024

- The Burden of OA
- Definitions
- Current Guidelines-based Management
- Emerging and Popular Approaches

Management of OA in 2024

- The Burden of OA
- Definitions
 - What is OA?
- Current Guidelines-based Management
- Emerging and Popular Approaches

Arthritis: Inflammatory vs. Non-inflammatory

	Inflammatory (RA)	Non-inflammatory (OA)
Joint swelling:	Soft tissue / synovitis	Hard bony swelling
Joint appearance:	Warm Joints / Warm effusions	Cool joints / Cool effusions
Joints of the hand:	MCPs, PIPs, Wrist	DIPs, PIPs, 1 st MCP
Age of onset:	Young to middle aged	Middle aged to elderly
Systemic inflammation:	Abundant	No

What is OA?

A painful disease of the entire joint:

A painful degenerative process affecting all joint tissues with progressive deterioration of articular cartilage and alterations of subchondral bone and surrounding joint structures; local inflammation may be present but is not the primary source of joint dysfunction.

- Block & Malfait, 2023, Rheumatology, 8th Ed. (Hochberg et al, eds.)

Management of OA

- Definitions
 - What is OA?
 - What are the goals of OA Treatment?
- Evidence-based Management in 2024
- Emerging and Popular Approaches

Goals of OA Treatment:

- Retain function and independence
- Alleviate pain
- Delay structural progression & return to anatomic normal

Goals of OA Treatment:

- Retain function and independence
- Alleviate pain
- ~~Delay structural progression & return to anatomic normal~~

Goals of OA Treatment:

- Retain function and independence
- Alleviate pain
- ~~Delay structural progression & return to anatomic normal~~

In 2024, there are no therapeutic strategies shown to alter OA progression (structure/pain) in humans

Pain

- Nociceptive
- Inflammatory
- Neuropathic
- Nociplastic/Dysfunctional

Pain

- Nociceptive
 - Activation of nociceptors by tissue injury, heat, multiple noxious stimuli.
 - Sharp, aching, throbbing
- Inflammatory
- Neuropathic
- Nociplastic/Dysfunctional

Pain

- Nociceptive
 - Activation of nociceptors by tissue injury, heat, multiple noxious stimuli.
 - Sharp, aching, throbbing
- Inflammatory
 - The "pain" of acute trauma or inflammation
 - Inflammatory mediators increase excitability; non-noxious stimuli cause pain (allodynia, hyperalgesia)
- Neuropathic
- Nociplastic/Dysfunctional

Pain

- **Nociceptive**
 - Activation of nociceptors by tissue injury, heat, multiple noxious stimuli.
 - Sharp, aching, throbbing
- **Inflammatory**
 - The “pain” of acute trauma or inflammation
 - Inflammatory mediators increase excitability; non-noxious stimuli cause pain (allodynia, hyperalgesia)
- **Neuropathic**
 - Nerve damage and remodeling in CNS and PNS perpetuates the pain sensation.
 - Burning, numbness, paresthesia, “heavy” sensation
 - Chronic, may intensify over time
- **Nociplastic/Dysfunctional**

Pain

- **Nociceptive**
 - Activation of nociceptors by tissue injury, heat, multiple noxious stimuli.
 - Sharp, aching, throbbing
- **Inflammatory**
 - The “pain” of acute trauma or inflammation
 - Inflammatory mediators increase excitability; non-noxious stimuli cause pain (allodynia, hyperalgesia)
- **Neuropathic**
 - Nerve damage and remodeling in CNS and PNS perpetuates the pain sensation.
 - Burning, numbness, paresthesia, “heavy” sensation
 - Chronic, may intensify over time
- **Nociplastic/Dysfunctional**
 - Absence of obvious nerve damage or tissue injury
 - Absence of detectable inflammation
 - Often chronic

OA Pain

- **Formerly:**
 - Thought to be primarily nociceptive, related to local inflammation, injury
- **Currently:**
 - OA is a Chronic Pain Syndrome (CPS), with nociceptive and chronic (neuropathic and nociplastic) pain components.
- **Most troubling aspect to patients themselves**

Management of OA in 2024

- **The Burden of OA**
- **Definitions**
- **Current Guidelines-based Management**
- **Emerging and Popular Approaches**

Management of OA:
Evidence-based Recommendations (2014)

- **ACR**
- **OARSI**
- **AAOS**
- **NICE**
- **Multiple other organizations**

Table 1 Recommendations for non-operative treatment of knee osteoarthritis*				
Treatment modality	OARSI ¹	NICE ²	ACR ³	AAOS ⁴
Nonpharmacological				
Exercise regimens			Yes, for all patients	
Weight reduction, if overweight			Yes, for all patients	
Self management and education			Yes, for all patients	
Biomechanical (braces, medial wedges, etc.)			In appropriate circumstances	
Pharmacological				
Topical NSAIDs			In appropriate circumstances	
Topical capsaicin	In appropriate circumstances		Not recommended	Not addressed
Acetaminophen	In appropriate circumstances	In appropriate circumstances	In appropriate circumstances	Uncertain
Tamoxifen	Uncertain	Not addressed	In appropriate circumstances	
Oral NSAIDs or COX-2 inhibitors			In appropriate circumstances	
Opioids	In appropriate circumstances	Not addressed	Uncertain	Not addressed
Opoids	Uncertain	In appropriate circumstances	Uncertain	Uncertain
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances	In appropriate circumstances	Uncertain
Intra-articular hyaluronans	Uncertain	Not recommended	Uncertain	Not recommended
Complementary				
Acupuncture	Uncertain	Not recommended	In appropriate circumstances	Not recommended
Glucosamine and/or chondroitin sulfate	Uncertain	Not recommended	Not recommended	Not recommended
TENS	Uncertain	In appropriate circumstances	Uncertain	
Therapeutic ultrasound	Uncertain	Not addressed	Not addressed	Uncertain

*This table summarizes the main recommendations of evidence-based clinical practice guidelines for the management of knee osteoarthritis. ACR, American Academy of Orthopaedic Surgeons; COX-2, cyclooxygenase 2; NICE, National Institute for Health and Care Excellence; OARSI, Osteoarthritis Research Society International; NSAID, nonsteroidal anti-inflammatory drug; TENS, transcutaneous electrical nerve stimulation.

New Guidelines: 2020

Kolasinski SL, et al: 2019 ACR/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip and Knee. Arthritis Rheum. 72:220-233, 2020. PMID: 31908163.

ACR

What's New?

Bannuru RR, et al: OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 27:1578-1589, 2019. PMID: 31278997.

OARSI

Recent FDA Approvals for OA

- Drugs Approved in 2014
- Drugs Approved in 2015
- Drugs Approved in 2016
- Drugs Approved in 2017
- Drugs Approved in 2018
- Drugs Approved in 2019
- Drugs Approved in 2020
- Drugs Approved in 2021
- Drugs Approved in 2022
- Drugs Approved in 2023

Sources: <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals>; <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/8/musculoskeletal>

Recent FDA Approvals for OA

- Drugs Approved in 2014
- Drugs Approved in 2015
- Drugs Approved in 2016
- Drugs Approved in 2017
- Drugs Approved in 2018
- Drugs Approved in 2019
- Drugs Approved in 2020
- Drugs Approved in 2021
- Drugs Approved in 2022
- Drugs Approved in 2023

Frunevetmab (Solensia), cat anti NGF mAb approved for feline OA

Sources: <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals>; <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/8/musculoskeletal>

Recent FDA Approvals for OA

- Drugs Approved in 2014
- Drugs Approved in 2015
- Drugs Approved in 2016
- Drugs Approved in 2017
- Drugs Approved in 2018
- Drugs Approved in 2019
- Drugs Approved in 2020
- Drugs Approved in 2021
- Drugs Approved in 2022
- Drugs Approved in 2023

Frunevetmab (Solensia), cat anti NGF mAb approved for feline OA

Bedinvetmab, dog anti NGF mAb approved for canine OA

Sources: <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals>; <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/8/musculoskeletal>

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	Yes, for all patients
Physical therapy	Yes, for all patients	Yes, for all patients, preference for tai chi
Weight reduction, if overweight	Yes, for all patients	Yes, for all patients
Self management and education	Yes, for all patients	Yes, for all patients
Biomechanical (cane etc.)	Recommended	Recommended
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	Conditionally recommended
Balance training	Conditionally recommended	Conditionally recommended
Cognitive behaviour therapy	Conditionally recommended	Conditionally recommended
Pharmacological		
Topical NSAIDs	Strongly recommended	Strongly recommended
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Quilates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	Strongly recommended against
Mesenchymal stem cell therapy	Strongly recommended against	Strongly recommended against
Anti-NGF therapy	Not addressed	Not addressed
Complementary & Alternative		
Acupuncture	Uncertain	In appropriate circumstances
Glucosamine and/or chondroitin sulfate	Strongly recommended against	Strongly recommended against
TENS	Strongly recommended against	Strongly recommended against
Therapeutic ultrasound	Not recommended	Conditionally recommended
Kinesiotaping	Not recommended	Conditionally recommended

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022.

I am NOT unbiased regarding the guidelines

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	Yes, for all patients
Physical therapy	Yes, for all patients	Yes, for all patients, preference for tai chi
Weight reduction, if overweight	Yes, for all patients	Yes, for all patients
Self management and education	Yes, for all patients	Yes, for all patients
Biomechanical (cane etc.)	Recommended	Recommended
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	Conditionally recommended
Balance training	Conditionally recommended	Conditionally recommended
Cognitive behaviour therapy	Conditionally recommended	Conditionally recommended
Pharmacological		
Topical NSAIDs	Strongly recommended	Strongly recommended
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Quilates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	Strongly recommended against
Mesenchymal stem cell therapy	Strongly recommended against	Strongly recommended against
Anti-NGF therapy	Not addressed	Not addressed
Complementary & Alternative		
Acupuncture	Uncertain	In appropriate circumstances
Glucosamine and/or chondroitin sulfate	Strongly recommended against	Strongly recommended against
TENS	Strongly recommended against	Strongly recommended against
Therapeutic ultrasound	Not recommended	Conditionally recommended
Kinesiotaping	Not recommended	Conditionally recommended

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022.

Caveat: Guidelines are NOT Regulations

- Diseases are complex and heterogeneous
- Patients are complex and heterogeneous

Ergo the appropriate approach to any patient is complex, and NOT driven by guidelines.

- Guidelines are generic recommendations (a starting point) and should never be directive (notwithstanding third-party payers' desires).

Current OA Therapy

- Nonpharmacological

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	
Physical therapy	Yes, for all patients	
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi	
Weight reduction, if overweight	Yes, for all patients	
Self management and education	Yes, for all patients	
Biomechanical (cane etc.)	Recommended	
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	
Balance training	Conditionally recommended	
Cognitive behaviour therapy	Conditionally recommended	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022.

Exercise 2024

- Abundant evidence accrued regarding exercise and OA:

Exercise 2024

- Abundant evidence accrued regarding evidence and OA:
 - Exercise and Knee OA
 - Fransen M, et al, Cochrane Database of Systematic Reviews 2015

High quality evidence for pain, function: benefit at least 2-6 mos after completion of formal Rx, effect size comparable to NSAIDs

Exercise 2024

- Abundant evidence accrued regarding evidence and OA:
 - Exercise and Knee OA
 - Exercise and Hip OA
 - Fransen M, et al, Cochrane Database of Systematic Reviews 2014.

10 RCTs demonstrated that therapeutic exercise benefits pain and function; this lasts at least 3-6 mos after completion of formal Rx

Exercise 2024

- Abundant evidence accrued regarding evidence and OA:
 - Exercise and Knee OA
 - Exercise and Hip OA
 - Exercise and Hand OA
 - Østerås N, et al, Cochrane Database of Systematic Reviews 2017.
- 5 studies, low-quality evidence for beneficial effects of exercise on pain, function, and stiffness.

Exercise 2024

Conclusion: The Science is settled!

Cumulative Metaanalysis:

42 Studies, N=6863 pts

- Risk of Bias low
- Overall effect estimate unaffected by subgrouping
- Essentially no heterogeneity
- Extended funnel plot: “an additional study has no or very limited impact to change the current effect estimate”

In OA: “Exercise is effective and clinically worthwhile in reducing pain.”

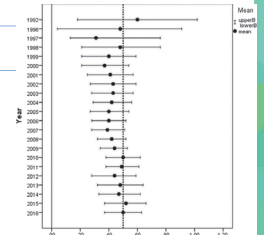


Fig. 1. Straight line: no effect. Dotted line: overall effect estimate.
Verhagen AP et al, Osteoarthritis and Cartilage 27 (2019) 1266e1269

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	
Physical therapy	Yes, for all patients	
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi	
Weight reduction, if overweight	Yes, for all patients	
Self management and education	Yes, for all patients	
Biomechanical (cane etc.)	Recommended	
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	
Balance training	Conditionally recommended	
Cognitive behaviour therapy	Conditionally recommended	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

Eastern Disciplines and OA

- Tai chi
 - Traditional Chinese practice, meditation with slow graceful movements, deep breathing, relaxation
 - Strongly recommended by ACR; “Effective and safe” for all patients with OA by OARSI
- Yoga
 - Traditional Indian mind-body practice combining physical postures, breathing techniques, meditation, relaxation
 - Conditionally recommended by ACR (Knee), no recommendation (Hip); “Effective and safe” by OARSI

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	
Physical therapy	Yes, for all patients	
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi	
Weight reduction, if overweight	Yes, for all patients	
Self management and education	Yes, for all patients	
Biomechanical (cane etc.)	Recommended	
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	
Balance training	Conditionally recommended	
Cognitive behaviour therapy	Conditionally recommended	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

Treatment modality	OARSI*	ACR*
Nonpharmacological		
Exercise	Yes, for all patients	
Physical therapy	Yes, for all patients	
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi	
Weight reduction, if overweight	Yes, for all patients	
Self management and education	Yes, for all patients	
Biomechanical (cane etc.)	Recommended	
Unloading knee braces	Not recommended	Recommended
Heat/therapeutic cooling	Conditionally recommended	
Balance training	Conditionally recommended	
Cognitive behaviour therapy	Conditionally recommended	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022



Unload Joint:

- cane
- walker
- wheelchair / motorized cart

Walking aids

- Canes
 - used on the contralateral side
 - Reduction in the PAddM of 7 to 10%
Kemp et al., 2008; Chan et al., 2005
- Bilateral walking sticks (hikers)
 - shown to be effective in reducing knee loading. Fregly et al., 2009



OA Therapy: Nonpharmacological Summary:

2014

2020

Table 1 Recommendations for non-operative treatment of knee osteoarthritis*				
Treatment modality	OARSI*	NICE*	ACR*	AAS*
Nonpharmacological				
Exercise	Yes, for all patients			
Physical therapy	Yes, for all patients			
Eastern disciplines (yoga, tai chi)	Yes, for all patients, preference for tai chi			
Weight reduction, if overweight	Yes, for all patients			
Self management and education	Yes, for all patients			
Biomechanical (cane etc.)	Recommended			
Unloading knee braces	Not recommended		Recommended	
Heat/therapeutic cooling	Conditionally recommended			
Balance training	Conditionally recommended			
Cognitive behaviour therapy	Conditionally recommended			

Block JA, Nat Rev Rheumatol 2014

Block JA & Cherny D, Med Clin N Am 2021.

OA Therapy: Pharmacological

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

Management of OA: Pain

A. Topicals

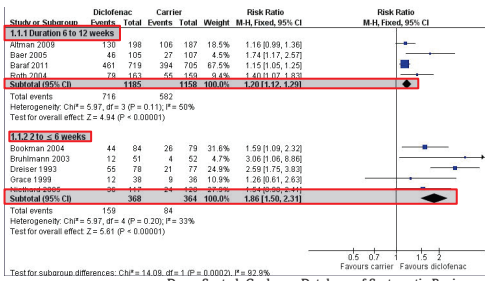
1. Topical NSAIDs

- Diclofenac: US FDA approved for Knee OA; salicylates available
- Outside USA and compounding pharmacies: ibuprofen, ketoprofen

Disclosure:
I served as a Consultant to this company

Topical Diclofenac

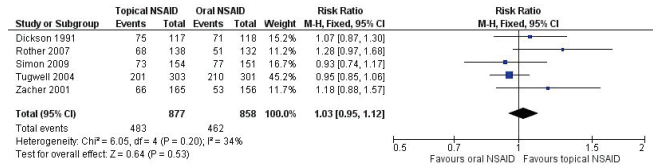
Forest plot of comparison: 8 Diclofenac versus carrier; outcome



Derry S, et al. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD007400.

Topical vs Oral Diclofenac

Forest plot of comparison: Topical NSAID versus oral NSAID, outcome: Clinical success.



Derry S, et al. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD007400.

Topical NSAIDs: safe and effective

- Zeng C, et al, “Comparative efficacy and safety of acetaminophen, topical and oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data” *Osteoarthritis Cartilage*, 2021; 29(9):1242–1251.
- “Topical NSAIDs are more effective and safer than acetaminophen for knee osteoarthritis.”
- “They are as effective as and safer than oral NSAIDs in both trial and real-world data.”

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Analgesics: Acetaminophen

- Acetaminophen** (APAP, N-Acetyl-Para-AminoPhenol)

- Until now, recommended for initial OA Rx by ACR, OARSI

BUT:

- NSAID >> APAP = PBO (12 wks)
Case JP, Baliunas AJ, Block JA, Arch Intern Med, 2003;163:169-178

- Cochrane Review 2016, Leopoldino, et al, OARSI: “the small effect sizes are unlikely to be clinically relevant.”

- APAP Toxicity:
 - almost ½ of fulminant hepatic failure in US (Rowden et al '05; Amar et al '07)

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Analgesics: Acetaminophen

- **Acetaminophen (APAP, N-Acetyl-Para-AminoPhenol)**

- Until now, recommended for initial OA Rx by ACR

BUT:

- NSAID >> APAP = PBO (12 wks)
Case JP, Baliunas AJ, Block JA, Arch Intern Med, 2010

- Cochrane Review 2016, Leopoldino, et al, OARSI: "the small effect sizes are unlikely to be clinically relevant."

- **APAP Toxicity:**

- almost 1/2 of fulminant hepatic failure in US (Rowden et al '05; Amar et al '07)

Not OARSI!
"...it has little to no efficacy in individuals with OA, with a signal for possible hepatotoxicity"

Analgesics: Acetaminophen

- **Acetaminophen (APAP, N-Acetyl-Para-AminoPhenol)**

- Until now, recommended for initial OA Rx by ACR

BUT:

- NSAID >> APAP = PBO (12 wks)
Case JP, Baliunas AJ, Block JA, Arch Intern Med, 2010

- Cochrane Review to be clinically rel

- **APAP Toxicity:**

- almost 1/2 of fulm

Not OARSI!
"...it has little to no efficacy in individuals with OA, with a signal for

ACR
".... conditionally recommended for patients with OA. ... Longer-term treatment is no better than treatment with placebo for most individuals.... For those with limited pharmacologic options due to intolerance or contraindications to the use of NSAIDs, acetaminophen may be appropriate for short term and episodic use."

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Analgesics: Tramadol

- *Cochrane Review* '06, '08: Reduced pain by 12%, overall improvement in 37% of subjects; high incidence of AEs. (Caution: more addictive than previously appreciated)
- *Cochrane Review* '19: No important mean benefit on pain or function, BUT more people taking tramadol group report a clinically important improvement (defined as 20% or more).
- *Arthr Care Res* '23, Zhang et al: Tramadol 100mg/d, 200mg/d, and 300mg/d all statistically better than PBO for Pain; only 300mg/d better than PBO for Function. AEs increase with dose.

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Agent	Usual dose	Maximum daily dose
Propionic acids		
Ibuprofen	400 - 800 mg tid or qid	2400 mg
Naproxen	250 - 500 mg bid	1500 mg
Ketoprofen	50 - 75 mg tid or qid	300 mg
Fenoprofen	300 - 600 mg tid or qid	1200 mg
Flurbiprofen	50 - 100 mg bid or tid	300 mg
Coxiprofen	600 - 1200 mg qid	1800 mg
Heteroarylacetic acids		
Diclofenac	50 - 75 mg bid	100 mg
Tolmetin	200 - 600 mg tid	1800 mg
Indoleacetic acids		
Etoricoxib	200 mg - 400 mg bid or tid	1000 mg
Indomethacin	25 - 50 mg bid or tid	200 mg
Sulindac	150 - 200 mg bid	400 mg
Naphthylalkanes		
Nabumetone	500 - 1500 mg qid	2000 mg
Oxicams		
Piroxicam	20 mg qid	20 mg
Meloxicam	7.5 mg	15 mg
Salicylates		
Diflunisal	500 mg bid	1500 mg
Salicylate	750 - 1500 mg bid or tid	3000 mg
COX-2 inhibitors		
Celecoxib	200 mg	200 mg

Kokebie and Block, '08

NSAIDs for OA

- NSAIDs and Coxibs
- Efficacy: Superior to PBO (and to pure analgesics), up to 2 years
 - E.g., Schnitzer Sem Arth Rheum 2011 (53 wks); Clegg NEJM (26 wks); Sheldon EA Clin Exp Rheumatol. 2008 Jul-Aug;26(4):611-9 (1 yr);
- No clear differences in efficacy among NSAIDs (Cochrane Reviews, hip OA and Knee OA)
- Safety: balance of risk and benefit
 - coxibs: political and medical-legal, not medical

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

OA Pain

- Formerly:
 - Thought to be primarily nociceptive, related to local inflammation, injury
- Currently:
 - OA is a disease involving Chronic Pain, with nociceptive and chronic (**neuropathic and nociplastic**) pain components.

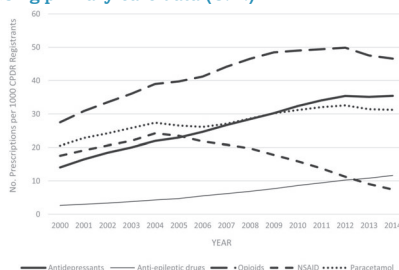
OA Pain: Complex and Neuropathic

• Neuroactive Rx:

- SNRIs – Duloxetine approved in U.S. for musculoskeletal pain including OA (Nov 2010)
(Representative Metaanalysis: Wang ZY, et al. Pain Medicine 2015; 16: 1373–1385)
- It is a class effect; there is reason to expect all SNRI's to be effective.
- Probably, also SSRI's, TCA's, anti-convulsants

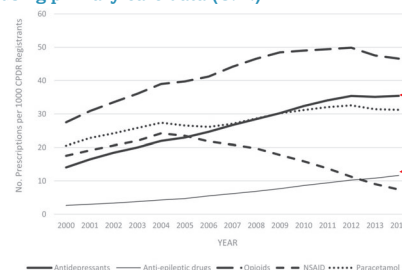
Note: These are not FDA-approved for this indication.

Analgesic utilization in people with knee osteoarthritis: A population-based study using primary care data (U.K.)



Taqi A, et al, Pain Practice, DOI: 10.1111/papr.13212, 2023

Analgesic utilization in people with knee osteoarthritis: A population-based study using primary care data (U.K.)



Taqi A, et al, Pain Practice, DOI: 10.1111/papr.13212, 2023

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

2024: Opiates no longer recommended

High rates of AE, especially in the elderly (falls, altered MS, etc.)

- Cochrane Update '14: Less significant pain relief with chronic use, higher rate of AEs:

"The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome ... observed effects were of questionable clinical relevance..."

2024: Opiates no longer recommended

High rates of AE, especially in the elderly (falls, altered MS, etc.)

- Cochrane Update '14: Less significant pain relief with chronic use, higher rate of AEs:

"The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome ... observed effects were of questionable clinical relevance..."

Welsch et al, Systematic Review Opioids in OA, Eur J Pain. 2020;24:685-703: No significant benefit.

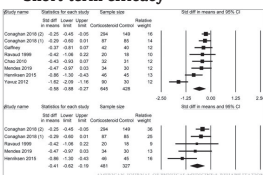
"...opioids provided no clinically relevant pain relief and no clinically relevant reduction in disability compared with placebo in chronic OA pain (hip, knee)."

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

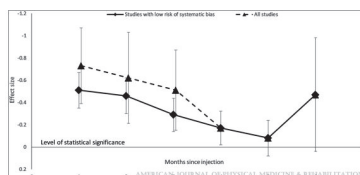
*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Intra-articular Glucocorticoids

• Short-term efficacy



Forest plots for all available time points and all corticosteroids.
Top, All of the included studies.
Bottom, Only studies with low risk of systematic bias



Pooled effect size (SMD) at different time points after the injection.

Intra-articular Glucocorticoids

• Potential harm to cartilage?

IA Glucocorticoid Toxicity

RCT: IA triamcinolone vs Saline q 12 wks X 2yrs.

- McAlindon TE, et al. *JAMA* 317:1967, 2017

Intraarticular triamcinolone acetate vs placebo in patients with knee osteoarthritis [†]			
Outcomes	Mean change from baseline to 2 y	Mean difference between groups (95% CI)	P value
Triamcinolone Saline			
Cartilage thickness (mm)	-0.21	-0.11 (-0.20 to -0.03)	0.01
WOMAC pain subscore [‡]	-1.2	-0.64 (-1.6 to 0.29)	0.17

† WOMAC = Western Ontario and McMaster Universities; CI defined in Glossary.
‡ Score range 0 to 20; 0 = no pain, 20 = extreme pain; minimal clinically important improvement 3.94 points.

Table: Hart LE, Ann Int Med, ACP Journal Club, 2017
doi:10.7326/ACPJC-2017-167-6-027

- **Structural Outcome:** IA triamcinolone yielded sig greater cartilage loss than PBO.
- **Pain/Function Outcome:** No difference, no advantage

Intra-articular Glucocorticoids

- Potential harm to cartilage? BUT:

Bucci J et al, *Arthritis Rheumatol*, 74:223-226, 2022. <https://doi.org/10.1002/art.42031>

- OAI & MOST data sets: steroid vs HA
- N= 791 steroid, N= 162 HA
- **Outcome:** Progression of K-L grade, JSN, or TKA

- **Results:**
Steroid = HA.
No increased risk of IA steroids

Table 2. Risk of radiographic progression of OA in knees treated with GC injections versus knees treated with HA injections[†]

	Rate ratio (95% CI) [‡]
Joint space narrowing	1.00 (0.83–1.21)
Kellgren/Lawrence grade	1.03 (0.83–1.29)
Medial joint space width [‡]	1.03 (0.72–1.48)

* 95% CI = 95% confidence interval.

† Difference in rates of osteoarthritis (OA) progression in knees treated with glucocorticoid (GC) injections versus knees treated with hyaluronic acid (HA) injections. A value >1 indicates higher progression with GC injections. Analyses were adjusted for age, sex, body mass index, study of origin (Osteoarthritis Initiative or Multicenter Osteoarthritis Study), and baseline Kellgren/Lawrence grade.

‡ Medial joint space width (determined by measuring the joint space width 250) was calculated using only Osteoarthritis Initiative data. Progression was defined as a difference of >0.5 mm.

Intra-articular Glucocorticoids

My conclusion:

- Whatever risk there is with the use of these agents, it is likely quite small, and in any case is likely negligible relative to the risks associated with other intraarticular therapies.”

Block, J.A. (2022), Are Intraarticular Glucocorticoids Safe in Osteoarthritis?. *Arthritis Rheumatol*, 74: 181-183. <https://doi.org/10.1002/art.42032>

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.

Block JA & Cherry D. *Rheum Dis Clin North Am*. 48:549-567, 2022

Digression: OA Pain Studies

OA Pain

- The most debilitating and problematic aspect of OA to patients
- Not adequately controlled with most traditional strategies:

Modalities recommended by OARSI and by the ACR in their updated treatment guidelines for knee OA have effect sizes in the range of 0.2 – 0.4; none was even close to a “large effect” (0.8)

- Block, *Nature Rev Rheum* 2014

OA Pain

- The most debilitating and problematic aspect of OA to patients
- Not adequately controlled with most traditional strategies:

Modalities recommended by OARSI and by the ACR in their updated treatment guidelines for knee OA have effect sizes in the range of 0.2 – 0.4; none was even close to a “large effect” (0.8)

- Block, Nature Rev Rheum 2014

But these are compared to PLACEBO

Pain in OA: Disease Modification

- Extraordinarily susceptible to “placebo” effect:
- Expect > 40% placebo response in OA Pain trials.
Effect size 0.51 – 0.77 (Doherty & Dieppe, OAC 17:1255, 2009)
- Placebo response is very durable, > 1 year.

Placebo Effect and OA

- Effect size of PBO increases with increasing invasiveness.
 - Oral < Injection
(Bannuru et al, Ann Intern Med, 2015; Dieppe et al, Osteoarthritis Cart, 2016)
- The Relative Contribution of PBO to OA treatments
(Zou, et al, Ann Rheum Dis, 2016)
 - Effect Sizes of “Active” and “PBO” arms in 215 OA trials
 - Determine proportion of the Effect of each Rx due to PBO
 - For OA Meds: “On average, 75% of pain reduction was attributable to [PBO effect]”

Hyaluronans

- Originally developed as “viscosupplementation” to repair joint function (lower friction) and improve cartilage
- No effect on structure or function....

Hyaluronans

- Originally developed as “viscosupplementation” to repair joint function (lower friction) and improve cartilage
 - No effect on structure or function....
- Approved by the US FDA only for pain relief.

Hyaluronans

Table: FDA Approved HA Preparations for OA of the Knee

Product	Source	Size, characteristics	Weekly injections	Cost*
Durotone (Bioventus)	Bacterial	High MW NASHA cross-linked	1	\$875.00
Supartz (Ferring)	Bacterial	2.4-3.6X106 kDa	3	\$1,019.00
Gen-One (Zimmer-Biomet)	Chicken comb	High MW cross-linked dimers	1	\$998.00
GenSyn-3 (Bioventus)	Bacterial	1100 kDa	3	\$1,035.00
GenVisc 850 (Orthogenics)	Bacterial	620-1170 kDa	5	\$1,350.00
Hyalgan (Sanofi-Schering-Plough)	Chicken comb	500-730 kDa	3 or 5	\$950.00
Hyovis (Fidia)	Bacterial	500-730 kDa	2	\$872.00
Monovisc (DePuy)	Bacterial	1000-2900 kDa, Cross-linked	1	\$1,360.00
Orthovisc (DePuy Mitek)	Chicken comb	1100-2900 kDa	3 or 4	\$1,388.00
Supartz/Supartz FX (Smith and Nephew)	Chicken comb	620-1170 kDa	3 or 5	\$1,151.50
Suproptil (Teva)	Not specified	2500 kDa	3	N.A.
Synvisc (Synvisc-One) (Genzyme Biosurgery)	Chicken comb	>6000 kDa Cross-linked Hyalans	3 (1)	\$1,284.10
TriVise (Orthogenics)	Bacterial	Not specified	3	N.A.
Visco3 (Zimmer Biomet, Bioventus)	Chicken comb	620-1170 kDa	3	\$790.00

N.A. Not Available

* Average wholesaler acquisition cost for one dosage regimen (Source: The Medical Letter on Drugs and Therapeutics, 2018;50(1554): 142-4)

Richardson R, Plaas AHK, Block JA, Rheum Dis Clin N Amer, 2019

Hyaluronans

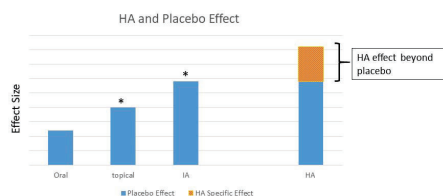


Figure. The effect size of placebo increases with the invasiveness of the delivery. Topical placebo has a significantly higher effect size than oral, and intraarticular is higher than topical. The placebo effect accounts for more than 70% of the total therapeutic effect of HA. (Bannuru, et al 2015; Zou, et al 2016)

HA= hyaluronan

* Statistically significant

Richardson R, Pias AHK, Block JA, Rheum Dis Clin N Amer, 2019

Intra-articular Injections

- Hyaluronans
 - Several products approved for use.
 - Effective; controversy regarding significance over Placebo

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.

Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Platelet-Rich Plasma (PRP): what is it

- Definition: PRP is an autologous plasma sample whose platelet count is higher than that in the circulating blood, i.e., enriched for platelets.
- Originally developed as chondroprotective agent, and for disease-modification

PRP Approval (U.S.)

- 510(k) Clearance: may be used to obtain permission to market devices that are considered low risk.
- Considered “substantially equivalent” to a previously cleared device
- 510(k) clearances focus on safety and technical performance of a device, and do not typically require supportive clinical data.

PRP Approval (U.S.)

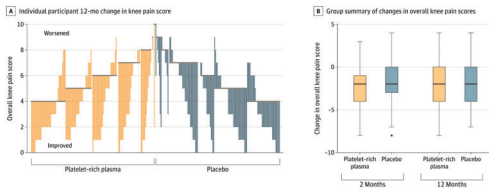
- The preparation of PRP is cleared for use in humans:
 - PRP systems are considered to be safe; the Plt preparation is not hazardous.
 - The performance is similar to a predicate device, i.e., it effectively isolates Plts and plasma from whole blood.
- There is no formal indication for use.

Beitzel K, et al, US Definitions, Current Use, and FDA Stance on Use of Platelet-Rich Plasma in Sports Medicine. J Knee Surg 2015; 28:29

PRP and Knee OA

Table 2. Continuous Outcomes at Baseline and 12 Months by Treatment Group*

Outcomes	Platelet-rich plasma (n = 144)			Placebo (n = 144)			Difference in change between groups, mean (95% CI)†	P value
	Baseline	12 mo	Within-group change	Baseline	12 mo	Within-group change		
Primary outcomes								
Overall knee pain score ^{a,d}	5.7 (1.5)	3.5 (2.6)	-2.1 (2.7)	5.7 (1.5)	3.9 (2.6)	-1.8 (2.5)	-0.4 (-0.9 to 0.2)	.17
Annual change in medial tibial cartilage volume, % ^{b,c}	-1.4 (7.2)	-1.4 (7.2)	-1.4 (7.2)	-1.2 (6.8)	-1.2 (6.8)	-1.2 (6.8)	-0.2 (-1.9 to 1.5)	.81



Bennell KL, et al, JAMA. 2021;326(20):2021-2030. doi:10.1001/jama.2021.19415

115

PRP and Human OA: Pain / Function

“Despite an increased focus on ‘orthobiologics’ in recent years, studies continue to demonstrate nonsuperiority to comparison groups.”

Delanois RE, et al: Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review, J Arthroplasty, 37:2480-2506, 2022

PRP: Cost vs. Patient satisfaction

- Cost: single PRP injection mean \$714 (95% CI: \$691–737, n=153).
- Pt Satisfaction: mean 76% (95% CI: 73.5–78.3%, N=84).



Fig. 3. Correlation between PRP injection marketed price and claimed clinical efficacy. PRP, platelet-rich plasma.

Pizzuti NS, et al, J Knee Surg. 2019; PMID: 30189436

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.

Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Mesenchymal Stem Cells

- Pluripotent cells, harvested from multiple tissues; adult as well as fetus
- Potential to provide reliable cell source
- Chondrocytic phenotypic differentiation, elaboration of matrix, formation of neocartilage plugs.

Richardson SM, et al, J Cell Physiol, 2010

MSC Injections and OA

- Animal Models
- Systematic Review of Structural and Pain-related behavior outcomes:
 - “gross morphology, histological analysis, immunohistochemical analysis, radiological evaluation or behavior analysis... For all outcomes, the evidence quality was low or very low.”
 - Xing D, et al, “Intra-articular injection of mesenchymal stem cells in treating knee osteoarthritis: a systematic review of animal studies,” OA&C 26:445, 2018

MSC Injections and OA: Structure

- Bone Marrow-derived Stem Cells (15 studies)
 - BMSC vs. Saline (3 studies): No difference MRI T2 mapping
 - MicroFx vs BMSC (1 study): No difference radiographic outcome
 - I.A. vs Subchondral injection: No difference in WOMS
- Adipose-derived Stem Cells (10 studies)
 - ADSC (multiple doses) vs Saline: No differences in MRI Knee OA Score or Outerbridge or WOMS, but cartilage defect size decreased in 1 study.
 - ADSC (multiple doses) ± PRP vs. Saline: No differences in T2 mapping at 48 wks.
 - 1 study had increased cartilage volume after ADSC.

Delanois RE, et al: Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review, J Arthroplasty, 37:2480-2506, 2022

MSC Injections and OA: Structure

- Bone Marrow-derived Stem Cells (15 studies)
 - BMSC vs. Saline (3 studies): No difference MRI T2 mapping
 - MicroFx vs BMSC (1 study): No difference radiographic outcome
 - I.A. vs Subchondral injection: No difference in WOMS
- Adipose-derived Stem Cells (10 studies)
 - ADSC (multiple doses) vs Saline: No differences in MRI Knee OA Score or Outerbridge or WOMS, but cartilage defect size decreased in 1 study.
 - ADSC (multiple doses) ± PRP vs. Saline: No differences in T2 mapping at 48 wks.
 - 1 study had increased cartilage volume after ADSC.

Delanois RE, et al: Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review, J Arthroplasty, 37:2480-2506, 2022

MSC Injections and OA: Structure

- Bone Marrow-derived Stem Cells (15 studies)
 - BMSC vs. Saline (3 studies): No difference MRI T2 mapping
 - MicroFx vs BMSC (1 study): No difference radiographic outcome
 - I.A. vs Subchondral injection: No difference in WOMS
- Adipose-derived Stem Cells (10 studies)
 - ADSC (multiple doses) vs Saline: No differences in MRI Knee OA Score or Outerbridge or WOMS, but cartilage defect size decreased in 1 study.
 - ADSC (multiple doses) ± PRP vs. Saline: No differences in T2 mapping at 48 wks.
 - 1 study had increased cartilage volume after ADSC.

Delanois RE, et al: Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review, J Arthroplasty, 37:2480-2506, 2022

MSC Injections and OA: Pain and Function

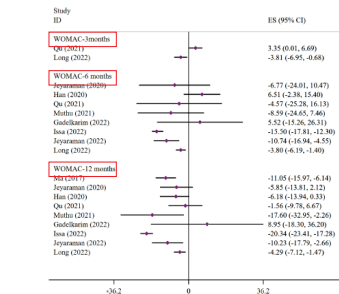
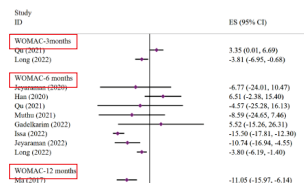


Fig 2 Meta analysis results of WOMAC

Shang et al. Stem Cell Research & Therapy 14:91, 2023. PMID: 37061744

MSC Injections and OA: Pain and Function



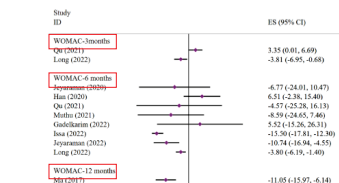
Conclusion:

Our analysis of 50 clinical studies and 13 SRs/MAs revealed that inconsistent effectiveness outcomes, potential safety risks, and poor evidence quality hinder any recommendation for stem cell product use in KOA patients... Clinical translation of stem cell therapies for KOA lacks sufficient support and should be approached cautiously until stronger evidence is available.

Fig 2 Meta analysis results of WOMAC

Shang et al. Stem Cell Research & Therapy 14:91, 2023. PMID: 37061744

MSC Injections and OA: Pain and Function



Conclusion:

Our analysis of 50 clinical studies and 13 SRs/MAs revealed that inconsistent effectiveness outcomes, potential safety risks, and poor evidence quality hinder any recommendation for stem cell product use in KOA patients... Clinical translation of stem cell therapies for KOA lacks sufficient support and should be approached cautiously until stronger evidence is available.

Fig 2 Meta analysis results of WOMAC

Shang et al. Stem Cell Research & Therapy 14:91, 2023. PMID: 37061744

MSCs vs Steroid Injection

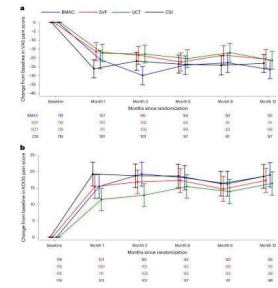
- RDBCT:
 - Autologous bone marrow aspirate vs. Autologous adipose stromal vascular fraction vs. Allogeneic human umbilical cord tissue-derived MSCs; **Comparator:** corticosteroid injection (CSI).
- N=480, Knee OA (K-L grade II-IV).
- Primary Endpoints: VAS and KOOS at 12 mos vs baseline.
- Secondary Endpoint: Change in MRI OA score compared to baseline.

Mautner, et al, Nat Med. 2023; 29(12): 3120–3126. Published online 2023 Nov 2. doi: 10.1038/s41591-023-02632-w

MSCs vs Steroid Injection

Results:

- None of the 3 forms of MSC injections was superior to another, or to the CSI control.
- None of the four groups showed significant change in MRI OA score compared to baseline.



Mautner, et al, Nat Med. 2023; 29(12): 3120–3126. Published online 2023 Nov 2. doi: 10.1038/s41591-023-02632-w

It's tough to measure the direct impact on a nation's changing economic landscape.

Start to relieve your pain today!

STEM CELL THERAPY

Regenerative Techniques & Stem Cell therapy will induce profound healing activity for:

- Osteoarthritis, degenerative cartilage
- Diabetes • Rheumatoid arthritis
- Emphysema • Parkinson's disease

www.aspen-regenerative-medicine.com

Call for a Consultation

Dr. Gordon Board certified in Sports Medicine and Anti-Aging & Regenerative Medicine. Former OLS team physician and Olympic team physician.

Aspen Institute
122 W. Main St. Aspen | 970-201-1332

STOP THE PAIN!

Do You Suffer From...

- Knee Pain • Neck Pain • Hip Pain
- Shoulder Pain • Neuropathy
- Low Back Pain • Joint Pain

STEM CELL Therapy for Pain

www.StemCellTherapyForPain.com

Regenerative medicine is a new medical field and is effective in relieving and even eliminating your pain without surgery or addictive medications.

Find Out If Regenerative Medicine Is Right For You!

Regenerative medicine uses your own cells to regenerate and repair tissues in your body that are damaged due to injury, age, disease and surgery. Stem cells have the power to do this. These stem cells are grown in a lab and injected into you.

SAFE • ETHICAL • EFFECTIVE

RESERVE YOUR SPOT TODAY

844-677-3740

Stem Cells: The Market

- 2016: 351 US companies were marketing stem cell interventions at 570 clinics.
 - Turner & Koepfler, Cell Stem Cell 19:154-157, 2016
- 2018: 700 – 750 clinics
 - Koepfler and Turner, Regen Med 13:19-27, 2018

Stem Cells

Table 1 Pricing information of stem-cell therapies marketed to consumers for knee osteoarthritis in the United States

U.S. stem-cell clinics providing pricing information for knee injection (n = 65)	Statistics
Average cost	\$5,156.43
Standard deviation	\$2,445.61
Margin of error	\$605.99
95% confidence interval	\$4,550.44–\$5,762.42
Price range (minimum–maximum)	(\$1,150.00–\$12,000)

Table 2 Patient satisfaction information of stem-cell therapies marketed to consumers for knee osteoarthritis in the United States

U.S. stem-cell clinics providing clinical efficacy information for stem-cell knee injection (n = 36)	Statistics
Average positive patient satisfaction	82.2%
Standard deviation	9.6%
Margin of error	3.2%
95% confidence interval	79.0–85.5%
Patient satisfaction range (minimum–maximum)	55.0–100.00%

Piuzzi NS, et al, J Knee Surg, 2017

Costs of Stem Cell Rx: 2024

- There are no updated systematic analyses.
- Twitter poll performed by Bioinformant, 4/1/2023, update: 2/12/2024 (<https://bioinformant.com/cost-of-stem-cell-therapy/>):
- (N=??)
 - 30% of the respondents undergoing stem cell treatments spent \$5,000 or less
 - 20% spent \$5,000 to \$10,000
 - 40% spent \$10,000 to \$25,000
 - 10% spent over \$25,000

Costs of Stem Cell Rx: 2024

- There are no updated systematic analyses.
- Twitter poll performed by Bioinformant, 4/1/2023, update: 2/12/2024 (<https://bioinformant.com/cost-of-stem-cell-therapy/>):
- (N=??)
 - 30% of the respondents undergoing stem cell treatments spent \$5,000 or less
 - 20% spent \$5,000 to \$10,000
 - 40% spent \$10,000 to \$25,000
 - 10% spent over \$25,000

133

Stem Cells

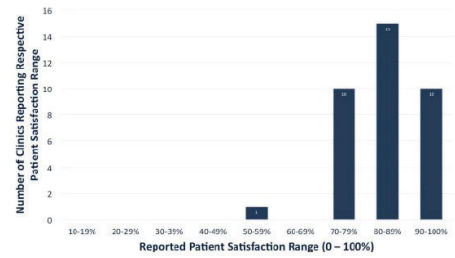


Fig. 2 Histogram of stem-cell treatment success rates reported by businesses to consumers.

Piuzzi NS, et al, J Knee Surg, 2017

Stem Cells

BOTTOM LINE: In choosing pain therapy, scientific data may not matter... People will do what helps them regardless of objective data, because "placebo" is palliative in OA.

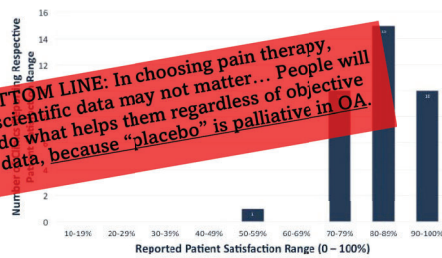


Fig. 2 Histogram of stem-cell treatment success rates reported by businesses to consumers.

Piuzzi NS, et al, J Knee Surg, 2017

Stem Cell Injections and OA

Summary:

- Intraarticular stem cell injections are widely offered.
- Individual patients appear to feel benefit, often with prolonged duration (PBO effect?)
- What is the evidence?
 - There is no good evidence of a specific pain advantage.
 - There is no good evidence of a structural advantage.

Pharmacological Rx of OA: 2024

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Pharmacological Rx of OA: 2024

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

Pharmacological Rx of OA: 2024

Treatment modality	OARSI*	ACR*
Pharmacological		
Topical NSAIDs	Strongly recommended	
Topical capsaicin	Not recommended	Not recommended
Acetaminophen	Conditionally not recommended	Conditionally recommended
Tramadol	Uncertain	Conditionally recommended
Oral NSAIDs or COX-2 inhibitors	In appropriate circumstances	Strongly recommended, if able
Duloxetine	In appropriate circumstances	In appropriate circumstances
Opiates	Not recommended	Conditionally not recommended
Intra-articular glucocorticoids	In appropriate circumstances	In appropriate circumstances
Intra-articular hyaluronans	Conditionally recommended	Conditionally not recommended
Platelet-rich plasma	Strongly recommended against	
Mesenchymal stem cell therapy	Strongly recommended against	
Anti-NGF therapy	Not addressed	

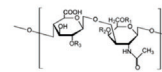
*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

Other Treatments

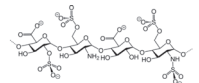
Treatment modality	OARSI*	ACR*
Complementary		
Acupuncture	Uncertain	In appropriate circumstances
Glucosamine and/or chondroitin sulfate	Strongly recommended against	
TENS	Strongly recommended against	
Therapeutic ultrasonography	Not recommended	Conditionally recommended
Kinesiotaping	Not recommended	Conditionally recommended

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherny D. Rheum Dis Clin North Am. 48:549-567, 2022

Chondroitin Sulfate



Heparin



<https://en.wikipedia.org/wiki/Heparin>

https://en.wikipedia.org/wiki/Chondroitin_sulfate

- Poorly absorbed from GI tract, 1-5%.
- Anti-inflammatory activity (COX independent) *in vitro* & in animal models.

Glucosamine

- > 90% absorbed orally.
- precursor sugar of GAGs
- claimed to have “special tropism for cartilage.”
- GlcN marketed as dietary supplement is unsulfated; it is the SO_4^{-2} salt.

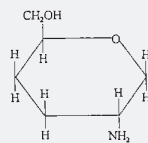


Figure 1. Chemical structure of glucosamine.

Block, et al. OA & Cart 2010

“GAIT” Trial

- “GAIT” = GlcN-CS Arthritis Intervention Trial
- NIH (NIAMS/NCCAM) sponsored
- RDBPC, 24 week trial in 1583 subjects with knee OA (with 2 year extension):
 - GlcN 1500 mg/d
 - CS 1200 mg/d
 - GlcN 1500 mg/d + CS 1200 mg/d
 - Celecoxib 200 mg/d
 - PBO
- Primary Outcome: 20% ↓ knee pain (WOMAC)
- Clegg, et al NEJM, 2006

“GAIT” Trial (cont.)

This was a Null Study,
with a primary outcomes P value for

Glucosamine: .30

Chondroitin Sulfate: .17

Glucosamine + Chondroitin Sulfate: .09

And Celecoxib : .008.

Clegg, et al NEJM '06

CS / GlcN Today

- All independently funded trials have been null.
- No change in GlcN or CS usage after GAIT results were widely publicized.
- Many individuals feel pain palliation with CS / GlcN, though this is not superior to placebo when assessed systematically.
- If the product is unadulterated (manufactured under GMP), side effects profile is good.

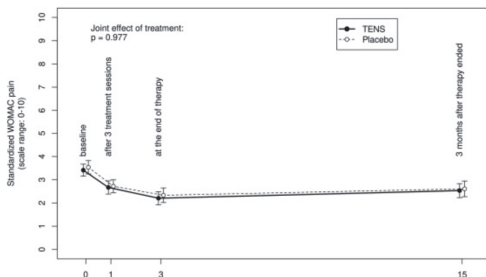
Treatment modality	OARSJ*	ACR*
Complementary		
Acupuncture	Uncertain	In appropriate circumstances
Glucosamine and/or chondroitin sulfate	Strongly recommended against	
TENS	Strongly recommended against	
Therapeutic ultrasonography	Not recommended	Conditionally recommended
Kinesiotaping	Not recommended	Conditionally recommended

*This table is not intended to represent a complete listing of the guidelines.
Block JA & Cherry D. Rheum Dis Clin North Am. 48:549-567, 2022

TENS

- Cochrane Collaboration
 - Rutjes AWS, et al, Cochrane Collaboration 2009: “we could not confirm that TENS is effective for pain relief [in OA]. The current systematic review is inconclusive, hampered by the inclusion of only small trials of questionable quality. Appropriately designed trials of adequate power are warranted.”
- Reichenbach S, et al, OAC 2022:
 - RDBPCT, N= 220, 15 wk trial, TENS vs PBO
 - Primary outcomes: WOMAC pain 3 wks
 - Secondary outcomes: WOMAC pain 15 wks, WOMAC physical function, safety
 - “The first adequately powered RCT of TENS vs PBO in a sufficient number of pts to detect a minimal clinically relevant difference between groups.”

TENS (cont.)



Reichenbach S, Jüni P, Hincapié CA, Schneider C, Meli DN, Schürch R, Streit S, Lucas C, Mebes C, Rutjes AWS, da Costa BR. Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRILKA randomized clinical trial. Osteoarthritis Cartilage. 2022 Mar;30(3):426-435. doi: 10.1016/j.joca.2021.10.015. Epub 2021 Nov 23. PMID: 34826572.

Management of OA

- Definitions
- Evidence-based Management in 2024
- Emerging and Popular Approaches

Disease Modification Strategies

- Pain Modification
- Structure Modification

Disease Modification Strategies

- Pain Modification
- ~~Structure Modification~~



Disease Modification Strategies

- Pain Modification
- Cannabinoids

Cannabinoids and OA

- Cannabinoid receptors (CB1, CB2, and several “non-classical”) are widely present in all joint tissue: chondrocytes, neurons, synoviocytes, bone.
- Endocannabinoids are present in OA joint tissue.
- Evidence that CB2 receptors regulate pain responses and central sensitization in the MIA rat model (Burstion JJ et al, PLOS One 2013), collagen-induced arthritis, aged guinea pigs (La Porta C, et al, Europ J Neurosci, 2014).

Reviewed in: Miller RJ and Miller RE, Clin Exp Rheum, 35:S59, 2017

Cannabinoids and OA: Human

- Systematic review found 4 RCTs of cannabinoids in rheumatic diseases (RA, OA, FM):
 - Reports of statistically significant improvement in pain and sleep
 - Side effects of altered perception, dizziness, drowsiness, GI effects
 - OA: a single study, and no positive effect (Huggins JP, et al, Pain 2012)

- For all:
- High risk of bias
 - Poor allocation concealment
 - Poor blinding

(Fitzcharles M-A, et al, Arthr Care Res, 68:681, 2016)

Cannabinoids and OA: Human

- Those data ended 2016.
- PubMed Search 1/18/2024:
 - Keywords: (Cannabinoids or cannabidiol or cannabis or THC) and osteoarthritis
- 2 additional trials in humans:
 - Vela J, et al: “Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial.” Pain, 2021 Aug 27, PMID: 34510141
 - Pramhas S, et al: “Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial.” Lancet Reg Health Eur. 2023 Nov 10;35:100777. PMID: 38033459

- Vela J, et al: "Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial." Pain, 2021 Aug 27, PMID: 34510141

"22% of patients receiving CBD and 21% receiving PBO experienced a reduction in pain intensity of more than 30 mm. We found neither clinically nor statistically significant effects of CBD for pain intensity in patients with hand OA and PsA when compared with PBO. In addition, no statistically significant effects were found on sleep quality, depression, anxiety, or pain catastrophizing scores."

- Vela J, et al: "Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial." Pain, 2021 Aug 27, PMID: 34510141

"22% of patients receiving CBD and 21% receiving PBO experienced a reduction in pain intensity of more than 30 mm. We found neither clinically nor statistically significant effects of CBD for pain intensity in patients with hand OA and PsA when compared with PBO. In addition, no statistically significant effects were found on sleep quality, depression, anxiety, or pain catastrophizing scores."

- Pramhas S, et al: "Oral cannabidiol (CBD) as add-on to paracetamol for painful chronic osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial." Lancet Reg Health Eur. 2023 Nov 10;35:100777. PMID: 38033459

"In KOA patients, oral high-dose add-on cannabidiol had no additional analgesic effect compared to adding placebo to continued paracetamol. Our results do not support the use of cannabidiol as an analgesic supplement in KOA."

Cannabinoids and Pain

• Current Investigations

- Clinicaltrials.gov, 3/12/2024

Keywords: Pain and cannabis, or cannabidiol:

• 133 Trials

- Principally chronic pain, widespread pain, FM, cancer pain, etc.

Cannabinoids and OA: Human

• Current Investigations

- Clinicaltrials.gov, 3/12/2024

Keywords: OA and (cannabinoids or cannabidiol or cannabis)

- 13 Total trials; 3 Active and relevant (the others completed or withdrawn):

Cannabinoid Profile Investigation of Vaporized Cannabis in Patients With Osteoarthritis of the Knee. (NCT02324777)

Vaporized THC vs PBO, 7 days, crossover, Unknown status

Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee. (NCT04992624)

RPCT Factorial Assignment THC vs CBD vs PBO in Knee OA; outcome IL-6 levels and fMRI, not pain. Ongoing

Osteoarthritis of the Knee Pain Study Using a CBD and THC Sublingual Tablet . (NCT04195269)
Open-label, single group, effects on pain. Unknown status

Cannabinoids and OA

Conclusion:

- No evidence at present that THC is helpful in OA.
- Systematic investigation is ongoing, but minimal.

Disease Modification Strategies

• Pain Modification

- Cannabinoids
- Neurolysis

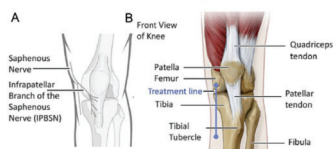
Neurolysis

- Originally used 1970's for trigeminal pain
- Longstanding use for post-operative pain, as well as chronic pain: craniofacial pain, LBP
- Mechanism of action: In theory, blocks nociceptive (A- δ and C-fibers) input to CNS without destroying motor or sensory (A- β)
- Axonal damage (Wallerian degeneration) without damage to neuronal cell body, and without local inflammation or fibrosis

Neurolysis

- Cryoneurolysis (cryoneuroablation, cryoanalgesia, cryogenic nerve blockade)
- Radiofrequency ablation (water-cooled radiofrequency neuroablation)
- Geniculate artery embolization

Neurolysis



- For knees:
 - U/S or fluoroscopic control; Genicular nerves (articular branches of several nerves)
 - Cryoneurolysis: infrapatellar branch of saphenous nerve
 - Transarterial embolization of the geniculate arteries
 - Radiofrequency ablation: also superolateral branch of femoral nerve; superomedial branch of saphenous nerve

Illustration: Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial
Radnovich, R. et al., Osteoarthritis and Cartilage, Volume 25, Issue 8, 1247 - 1256

Cryoneurolysis and OA: Results

- RDBPCT, n=180, 6-month trial
- Primary outcome: WOMAC pain improvement at day 30; also tracked through 6 mos

	Active treatment (n = 121) LS mean (SE) change from baseline	Sham treatment (n = 59) LS mean (SE) change from baseline	LS mean difference from sham (95% CI)*	P-value
WOMAC pain				
Day 30 (Primary endpoint)	-16.65 (1.26)	-9.54 (1.63)	-7.12 (-11.01 to -3.22)	0.0004
Day 60	-16.64 (1.24)	-11.98 (1.60)	-4.65 (-8.48 to -0.82)	0.0176
Day 90	-17.03 (1.30)	-11.37 (1.68)	-5.67 (-9.69 to -1.64)	0.0061
Day 120	-15.27 (1.28)	-12.45 (1.65)	-2.82 (-6.77 to 1.13)	0.161

Radnovich R, et al, OA&C 25:1247, 2017

Cryoneurolysis and OA: Results

- RDBPCT, n=180, 6-month trial
- Primary outcome: WOMAC pain improvement at day 30; also tracked through 6 mos

	Active treatment (n = 121) LS mean (SE) change from baseline	Sham treatment (n = 59) LS mean (SE) change from baseline	LS mean difference from sham (95% CI)*	P-value
WOMAC pain				
Day 30 (Primary endpoint)	-16.65 (1.26)	-9.54 (1.63)	-7.12 (-11.01 to -3.22)	0.0004
Day 60	-16.64 (1.24)	-11.98 (1.60)	-4.65 (-8.48 to -0.82)	0.0176
Day 90	-17.03 (1.30)	-11.37 (1.68)	-5.67 (-9.69 to -1.64)	0.0061
Day 120	-15.27 (1.28)	-12.45 (1.65)	-2.82 (-6.77 to 1.13)	0.161

Radnovich R, et al, OA&C 25:1247, 2017

Cryoneurolysis and OA: Results

- RDBPCT, n=180, 6-month trial
- Primary outcome: WOMAC pain improvement at day 30; also tracked through 6 mos

	Active treatment (n = 121) LS mean (SE) change from baseline	Sham treatment (n = 59) LS mean (SE) change from baseline	LS mean difference from sham (95% CI)*	P-value
WOMAC pain				
Day 30 (Primary endpoint)	-16.65 (1.26)	-9.54 (1.63)	-7.12 (-11.01 to -3.22)	0.0004
Day 60	-16.64 (1.24)	-11.98 (1.60)	-4.65 (-8.48 to -0.82)	0.0176
Day 90	-17.03 (1.30)	-11.37 (1.68)	-5.67 (-9.69 to -1.64)	0.0061
Day 120	-15.27 (1.28)	-12.45 (1.65)	-2.82 (-6.77 to 1.13)	0.161

Radnovich R, et al, OA&C 25:1247, 2017

Radiofrequency Ablation

5 RCTs provided data on pain scores at 6 months. A random effects model indicates that the RFA group experienced significantly greater pain reduction compared to the controls.

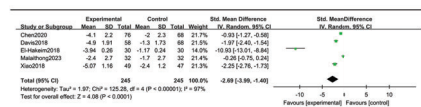


Figure 2. Meta-analysis of pain scores at 6 months.

4 RCTs provided data on pain scores at 12 months. The long-term effect of the RFA group compared to controls is uncertain.

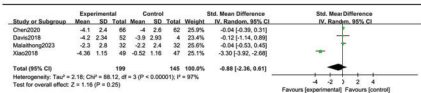


Figure 3. Meta-analysis of pain scores at 12 months.

Chen B, et al, Ann Med Surg (Lond). eCollection 2024 Jan. PMID: 38222705; doi: 10.1097/MS9.0000000000001509.

Transarterial Embolization for Pain

Table 1. Characteristics of included studies and summary of findings

Musculoskeletal Conditions Treated	Source	Age (y)	Duration of Follow-Up (Mo)	Main Findings/Comments
Knee Osteoarthritis				
	Ref. 8 (Bajo et al, 2019, US) N = 20	Range: 46-54 Mean: 59.4	6	100% technical success 49% mean reduction in WOMAC and 59% mean reduction in VAS at 6 months 0% major adverse events (no osteonecrosis, cartilage, or tendon injury)
	Ref. 9 (Kuno et al, 2017, Japan) N = 72 (55 joints)	Range: 46-79 Mean: 64.4	24	100% technical success 74% mean reduction in WOMAC and 74% mean reduction in VAS at 6 months 88% mean reduction in WOMAC and 81% mean reduction in VAS at 24 months 0% major adverse events MRI: significant reduction in synovitis at 24 months without osteonecrosis, tendinopathy, or cartilage loss
	Ref. 10 (Bhatia et al, 2019P, US and Japan) N = 21 (13 joints)	Range: 46-82 Mean cohort: 1.66 Mean cohort: 2.73	3	100% technical success 50% mean reduction in total WOMAC and 60% mean reduction in WOMAC pain score at 3 months 0% major adverse events No significant difference between administered (PM-CS and Embosphere embolic agent
	Ref. 11 (Lee et al, 2019, S. Korea) N = 41 (71 joints)	Range: 47-80 Mean: 67.2	6	100% technical success KL 1-3: 60% mean reduction in VAS at 3-6 months KL 4: 30% mean reduction in VAS at 1 month, but return to baseline at 3-6 months 0% major adverse events Lumbar baseline symptom duration in KL 4 patients

Kishore S, et al, ACR Open Rheumatology, 2022, DOI 10.1002/acr2.11383

170

Neurolysis and (Knee) OA

- Cryoneurolysis and radiofrequency ablation have been tested in small RCTs and there appears to be short-term benefit
- Geniculate embolization, by Interventional Radiology, does not yet have clear RCT evidence, but preliminary data are encouraging.
- NIH-sponsored RCTs are ongoing, and will have data in the next few years.

Summary

- OA management includes physical measures (exercise, PT) and mechanical measures (canes, walkers).
- Pharmacological management of OA is focused on pain palliation; structure modification remains an aspiration.
- Strategies for OA pain management must involve attention to nociceptive, neuropathic, and complex pain.

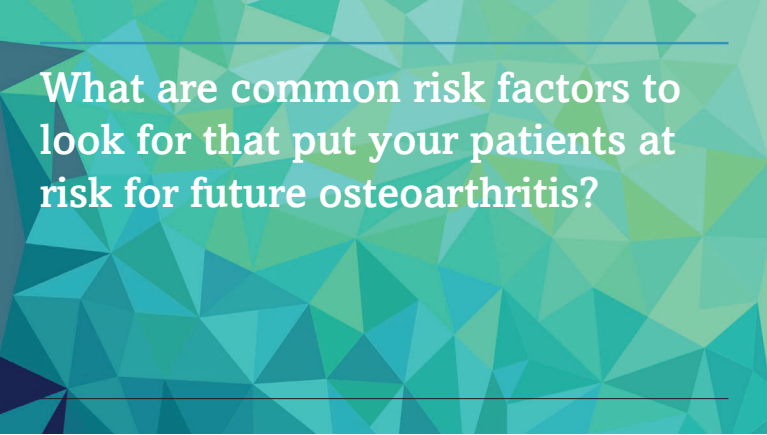
Summary (cont'd)

- Revised guidelines have been published by ACR and OARSI (largely similar to the older guidelines).
- Important differences:
 - APAP is recognized as largely ineffective.
 - Opiates (except, conditionally, tramadol) are no longer recommended.
 - Eastern Disciplines (Tai Chi, Yoga) are now recommended.
 - Topical NSAIDs are convenient and effective for superficial joints.

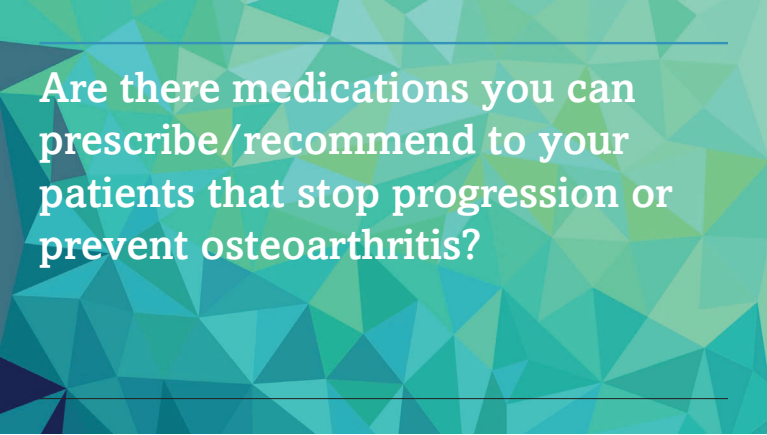
Summary (cont'd)

For OA in general, always

- Placebo is effective and durable for OA pain.
- Be wary of therapies that promise dramatic relief; they are unlikely to be real.
- This is especially true if they are expensive.



What are common risk factors to look for that put your patients at risk for future osteoarthritis?



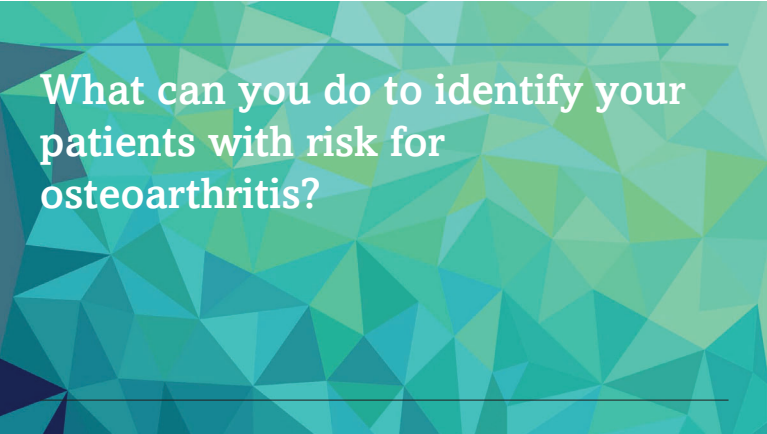
Are there medications you can prescribe/recommend to your patients that stop progression or prevent osteoarthritis?



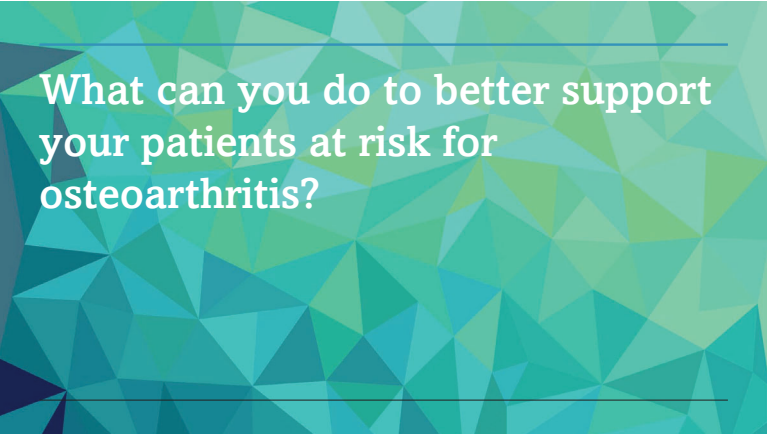
Are there other activities you can recommend to your patients to delay and/or reduce risk for osteoarthritis?



What are the concerns with progression of your patient's osteoarthritis?



What can you do to identify your patients with risk for osteoarthritis?



What can you do to better support your patients at risk for osteoarthritis?

To receive your credit, visit the QR code
to the right or this URL:

[https://www.pceconsortium.org/
survey/post/gpawpaintopics](https://www.pceconsortium.org/survey/post/gpawpaintopics)

