IV CONGRESSO NAZIONALE

SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE
DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

Antimo Moretti

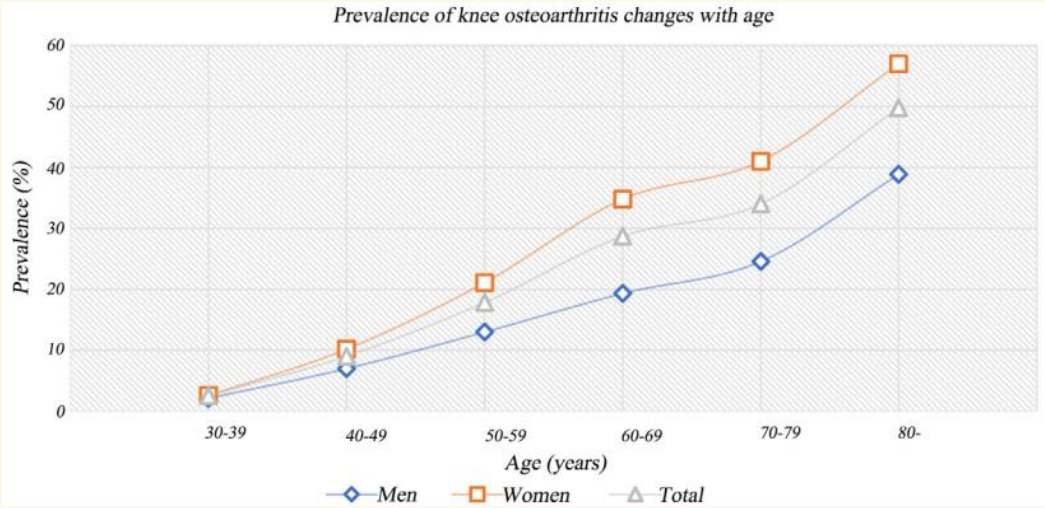
Nuove acquisizioni nella terapia farmacologica dell'osteoartrosi

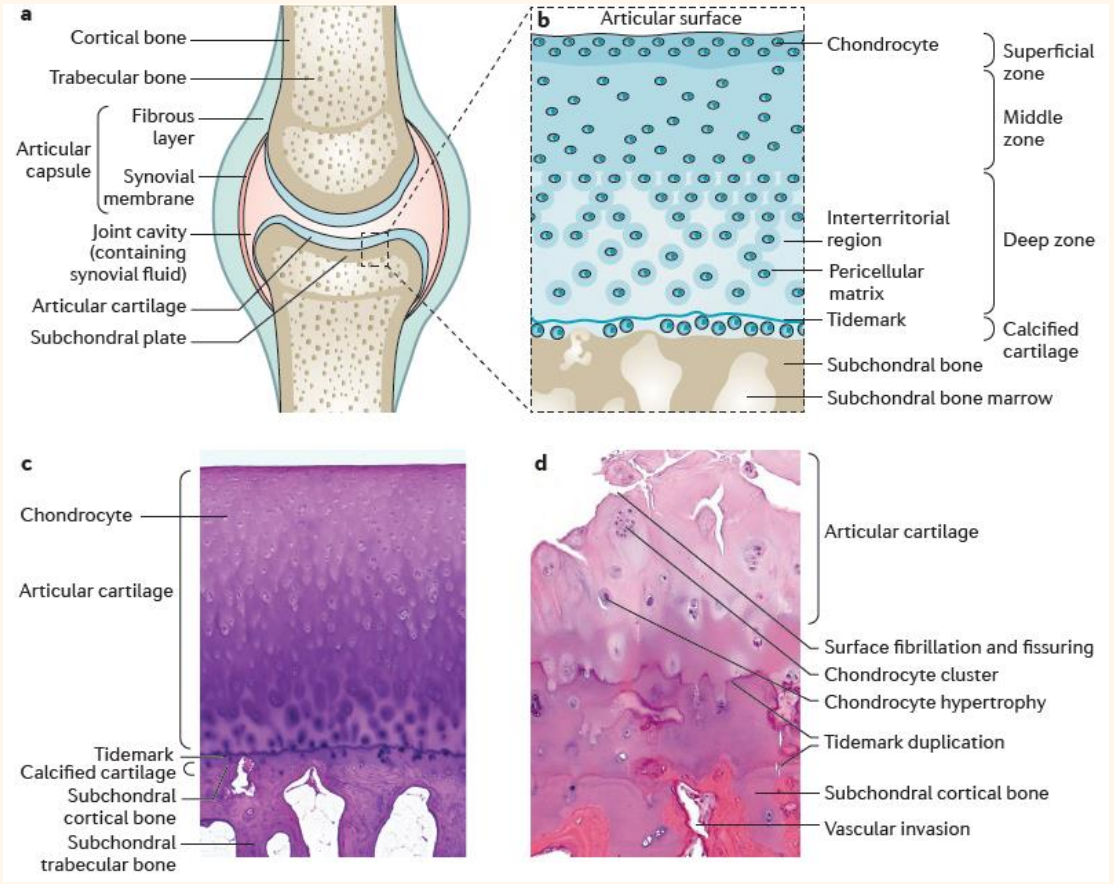
Centro Congressi Unione Industriali

TORINO 11-13 MAGGIO 2023

Osteoarthritis: progress and pitfalls

- Complex multifactorial and heterogeneous disease
- Joint impairment as a result of articular cartilage degeneration, subchondral bone sclerosis, joint deformation and synovial inflammation
- Continuing to be prevalent in adults and older people

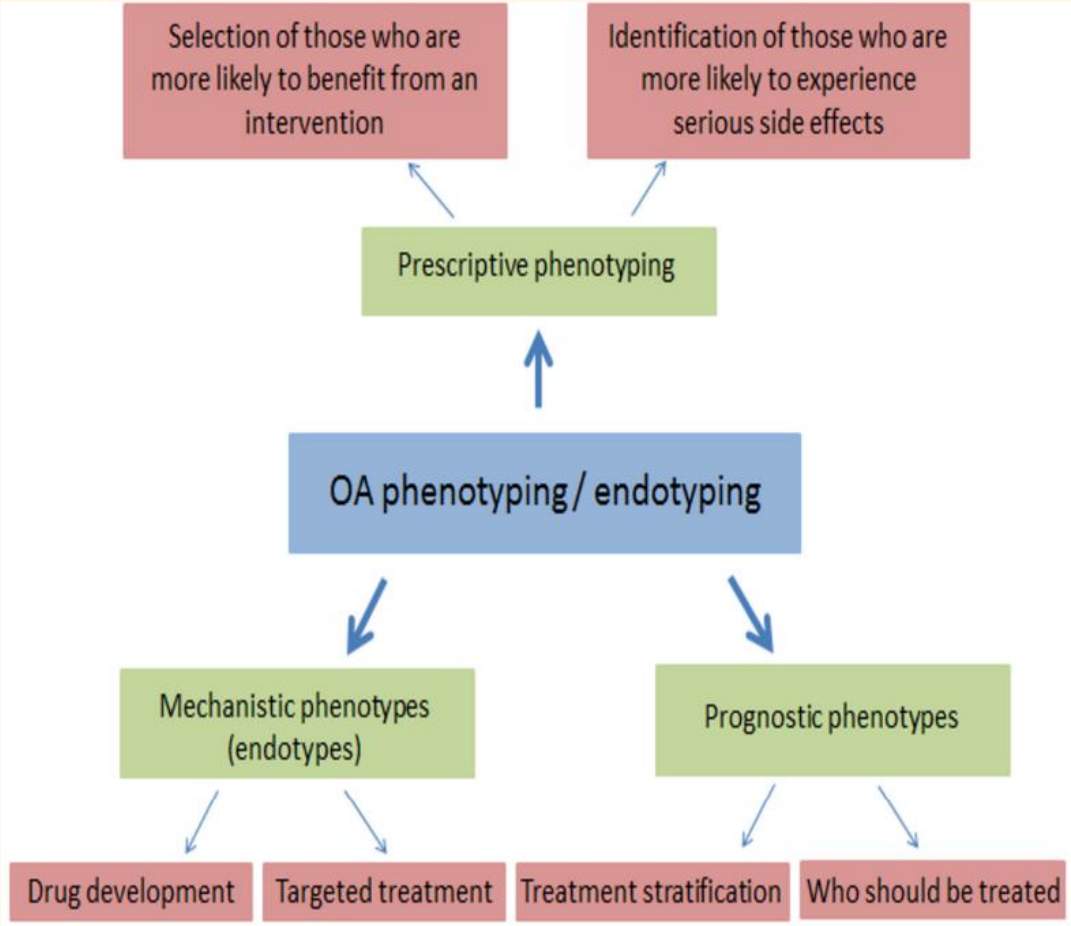




N Schäfer et al. Nat Med 2022
Martel-Pelletier, J et al. Nat Rev Dis Primers 2016
Cui A et al. EClinicalMedicine. 2020

Osteoarthritis therapy: progress and pitfalls

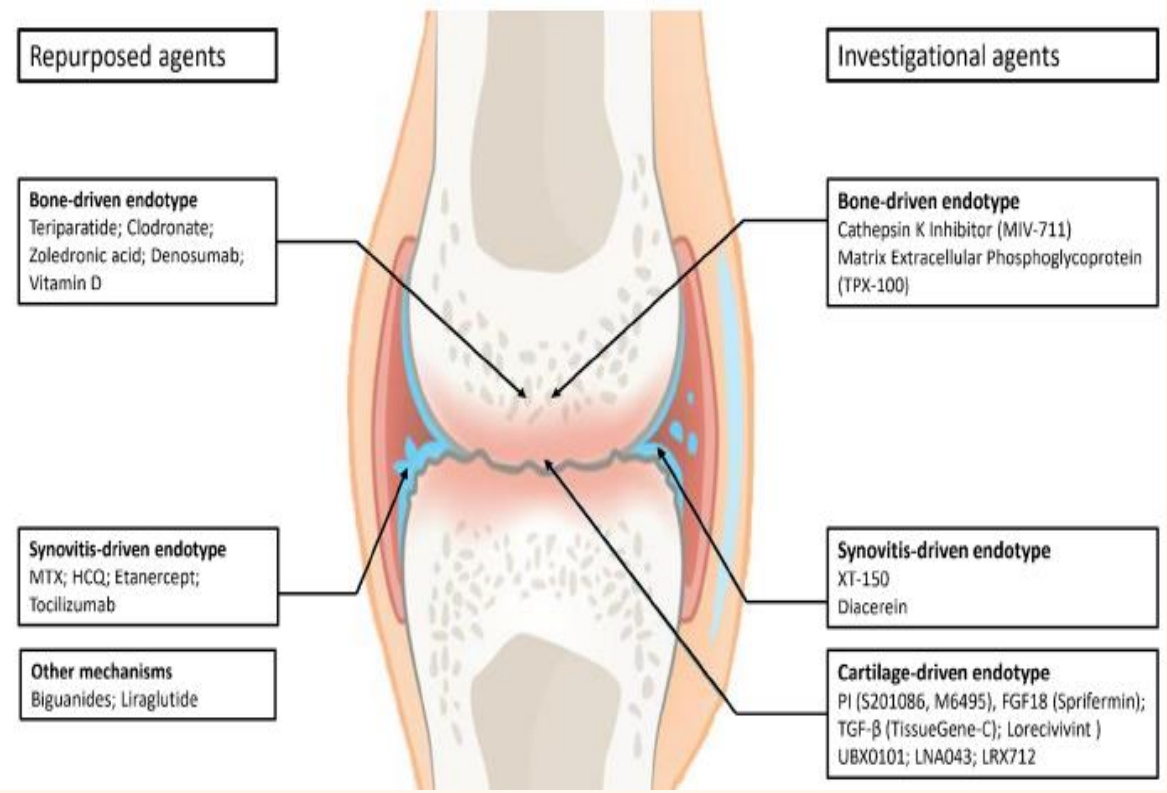
- No therapy succeeded in modifying disease progression— unmet need for novel DMOADs or regenerative therapies
- Consider
  - Pathophysiology and treatment goals
  - Current and emerging treatments



van den Bosch, M. H. J. Et al. Osteoarthritis Cartilage 2021
Deveza, L. A et al. Clin. Exp. Rheumatol. 2019

Disease-modifying OA drugs (DMOADs)

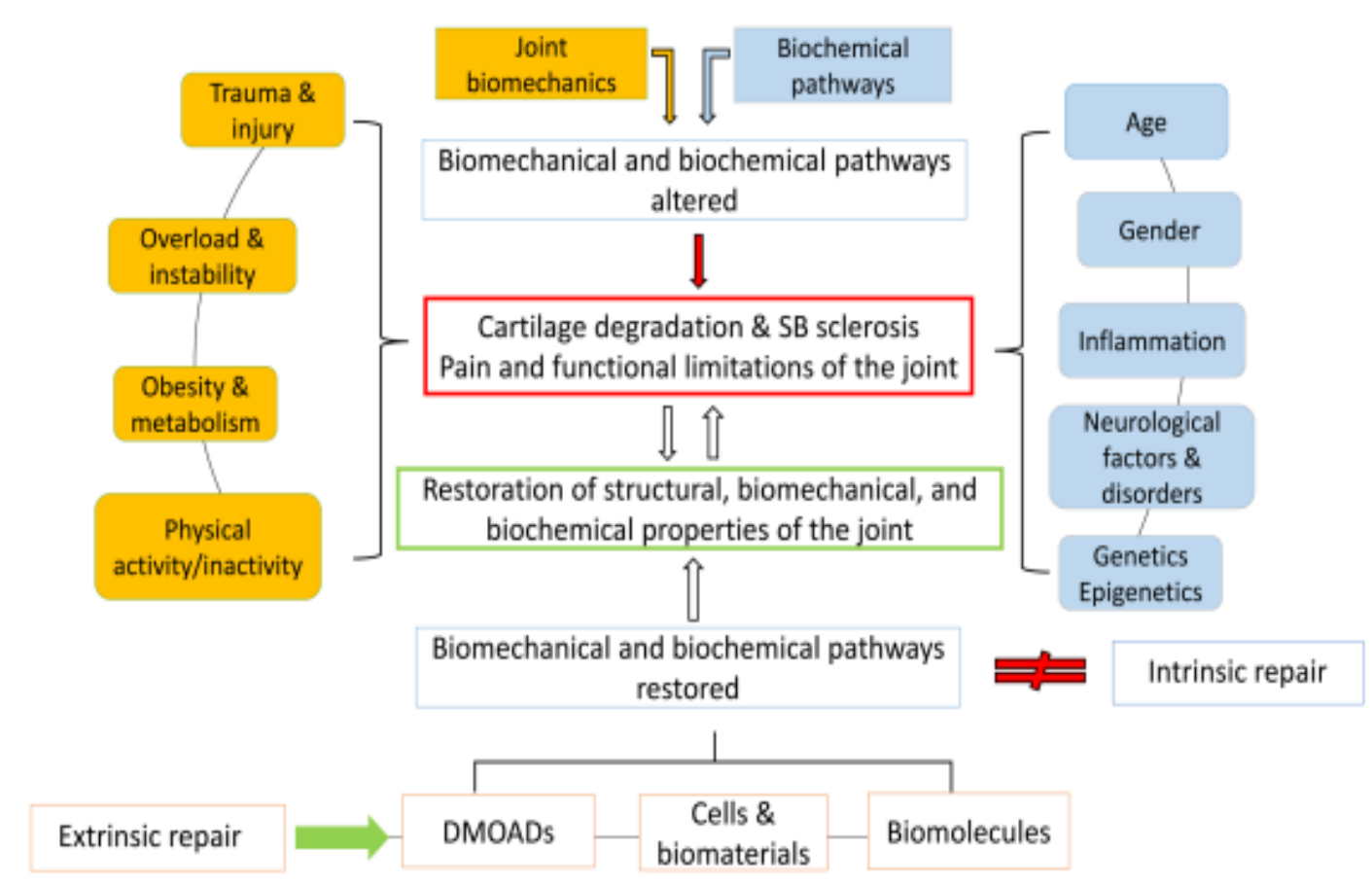
- To delay or reverse the progression of joint structural damage, leading to clinical translation of improvement in symptoms (pain/function)
- Both structural and symptomatic benefits needed
- New IMP and drug repurposing (cost savings for preclinical and phase I/II fo about US$300 million)



Oo, W. M Ther. Adv. Musculoskelet. Dis. 2022

Osteoarthritis therapy: progress and pitfalls

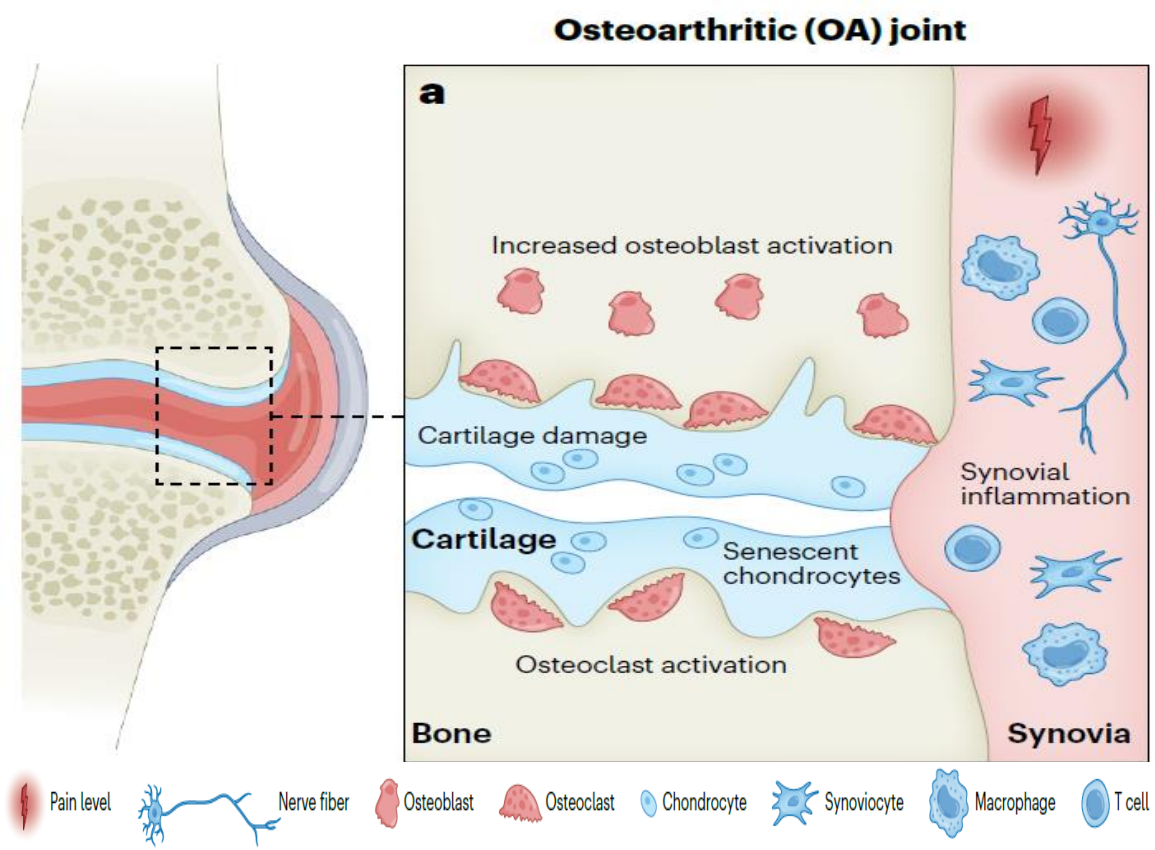
- OA is not a single disease — many pathways and risk factors lead to mechanical failure — identifying and targeting pathways in early-stage OA would be advantageous.



Grässel, S et al. F1000Res 2020

Osteoarthritis therapy: progress and pitfalls

- Defining patient subgroups according to pathobiology is challenging – but will enable trials to identify who may benefits from a drug
- Phenotypes can possess several molecular endotypes
  - ➢ Cartilage-driven
  - ➢ Bone-driven (e.g., BMLs in MRI)
  - ➢ Inflammation (synovitis)-driven

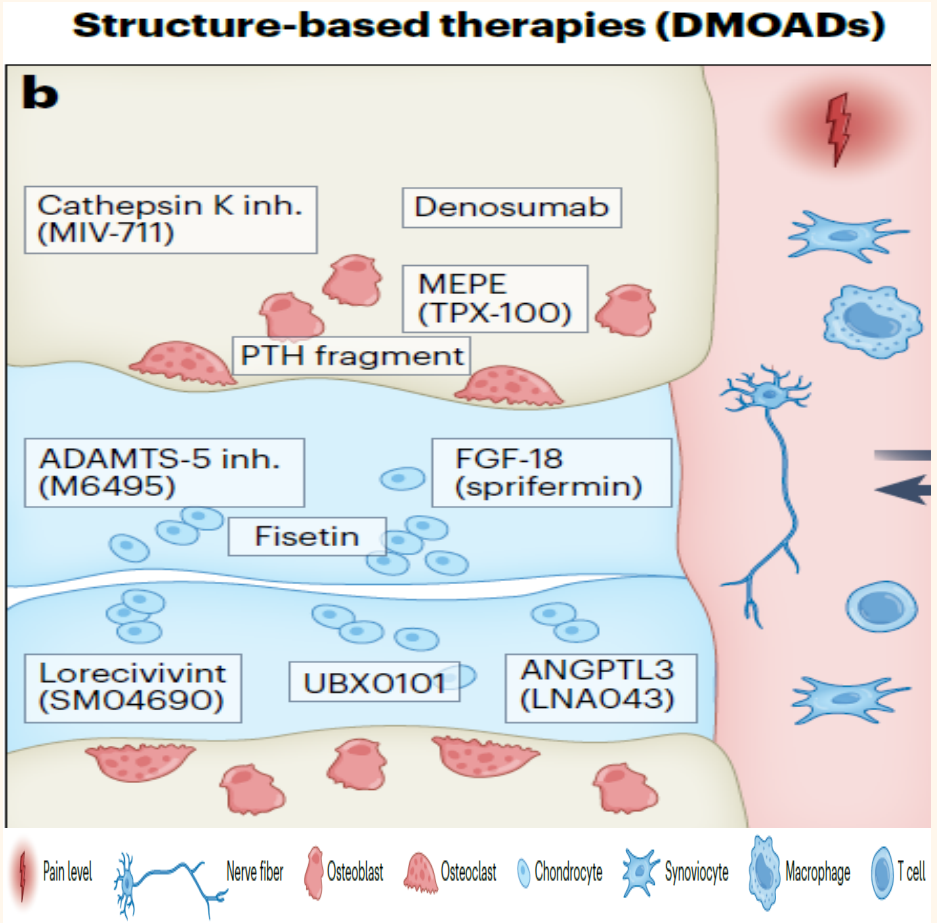


N Schäfer et al. Nat Med 2022

Osteoarthritis therapy: cartilage-driven

Most DMOADs

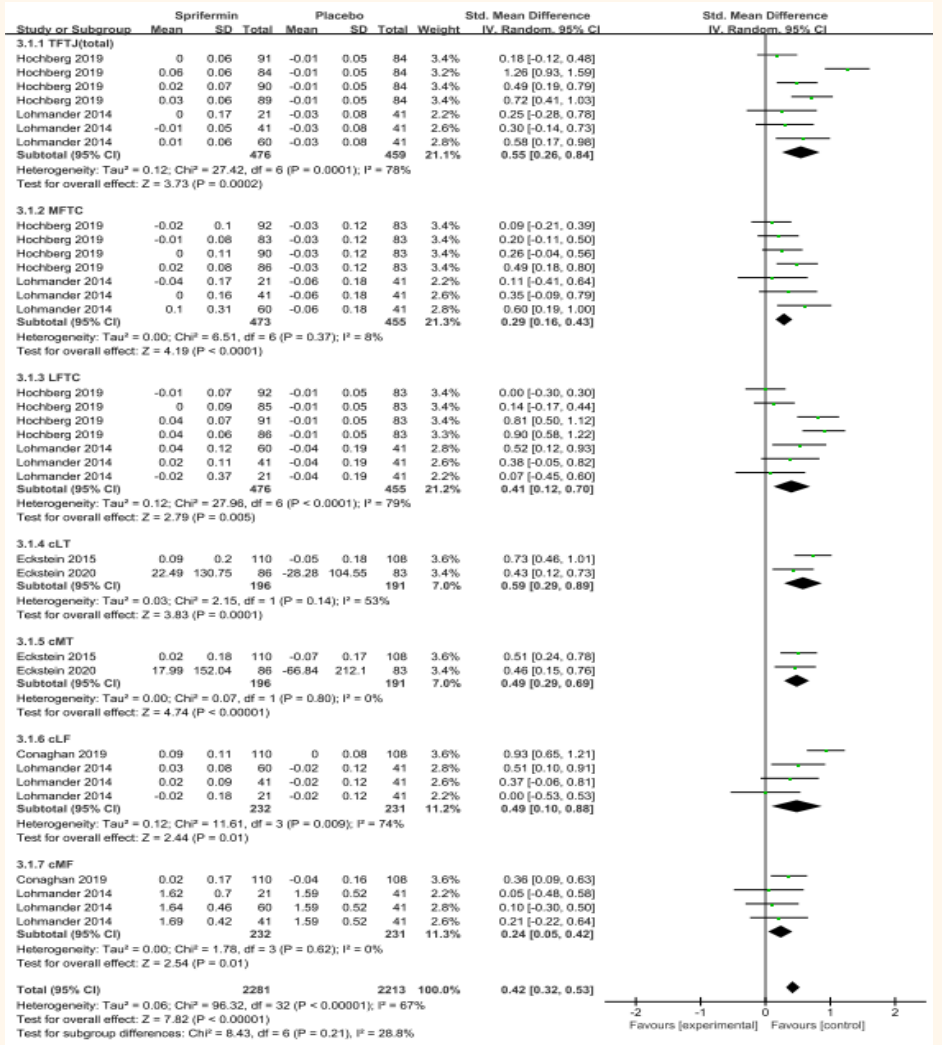
- Chondrogenesis and ECM production
  - ADAMTS-5 inhibitors, rFGF18 , LNA043
- Cartilage catabolism:
  - Lorecivivint (small-molecule DMOAD, phase 2/3), inhibits WNT–β-catenin signaling decreasing MMPs expression
- Senolytic therapies:
  - Hydrogel miR-29b-5p (aging-related miRNA) promotes recruitment of synovial stem cells and their differentiation into chondrocytes (animal model)



N Schäfer et al. Nat Med 2022
Oo, W. M Ther. Adv. Musculoskelet. Dis. 2022

Osteoarthritis therapy: cartilage-driven

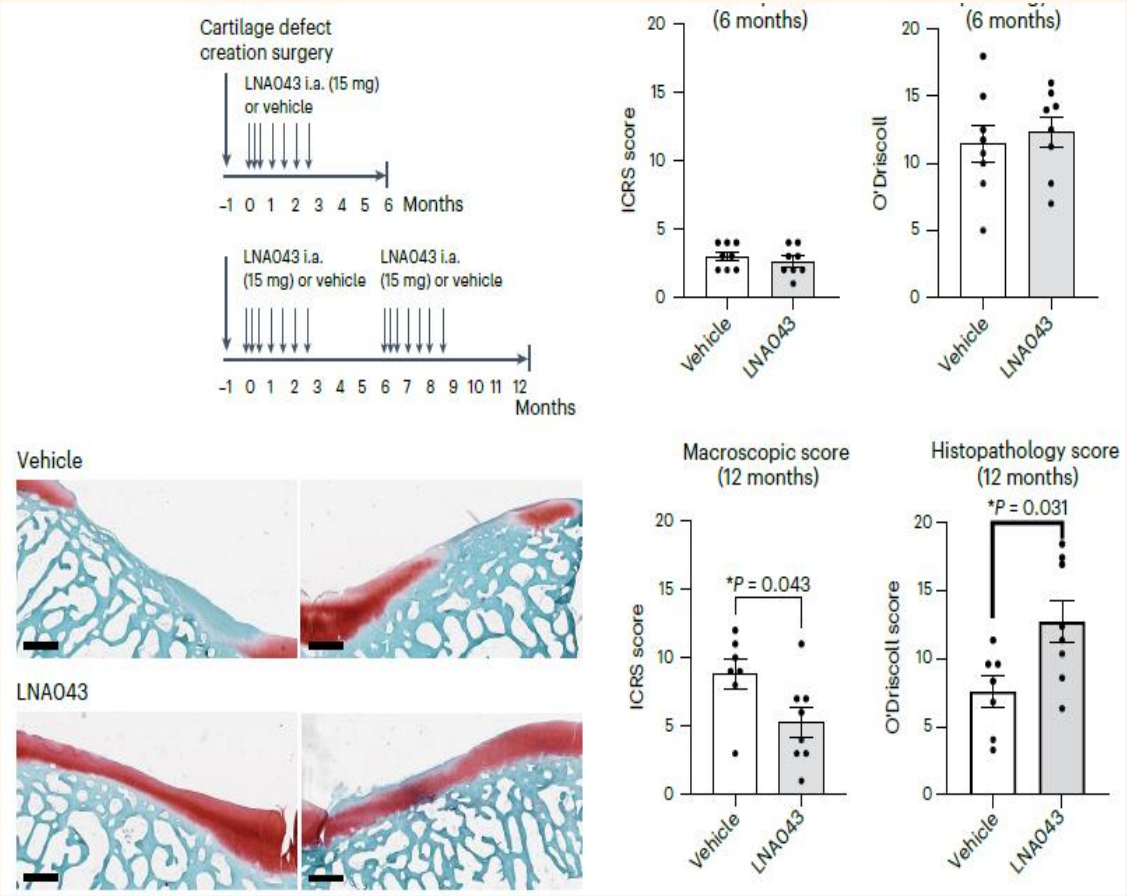
- Sprifermin (rFGF) increased synthesis of ECM (animal studies)
- 5-y FORWARD study (n=494): maintenance of structure-protective effects of 2-y administration (100 µg every 6 months) despite a treatment-free period of 3 y, good safety profile
  - ➢ Symptomatic improvement (WOMAC) in subgroup at risk (SAR) of progression: baseline minimum radiographic JSW 1.5–3.5mm and WOMAC pain 40–90
- Meta-analysis confirmed disease-modifying properties (cartilage thickness, volume and morphology)
  - ➢ Structure-protective effects may prevent or delay KOA patients from reaching levels of debilitating pain in the long term



Zeng N et al. Arthritis Res Ther. 2021

Osteoarthritis therapy: cartilage-driven

- LNA043 derivative of angiopoietin-like 3 (ANGPTL3), potent inducer of chondrogenesis and hyaline cartilage regeneration through binding to the fibronectin receptor (integrin α5β1) on MSC and chondrocytes.
  - ➢ Chondroprotective effects during inflammation in candidates for TKR (currently phase 2b)
  - ➢ Reversed OA transcriptome vs placebo: induced expression of cartilage ECM components involved in anabolic signaling (lubricin, DKK1, collagen II), suppressed OA mediators (ALP, LEP)

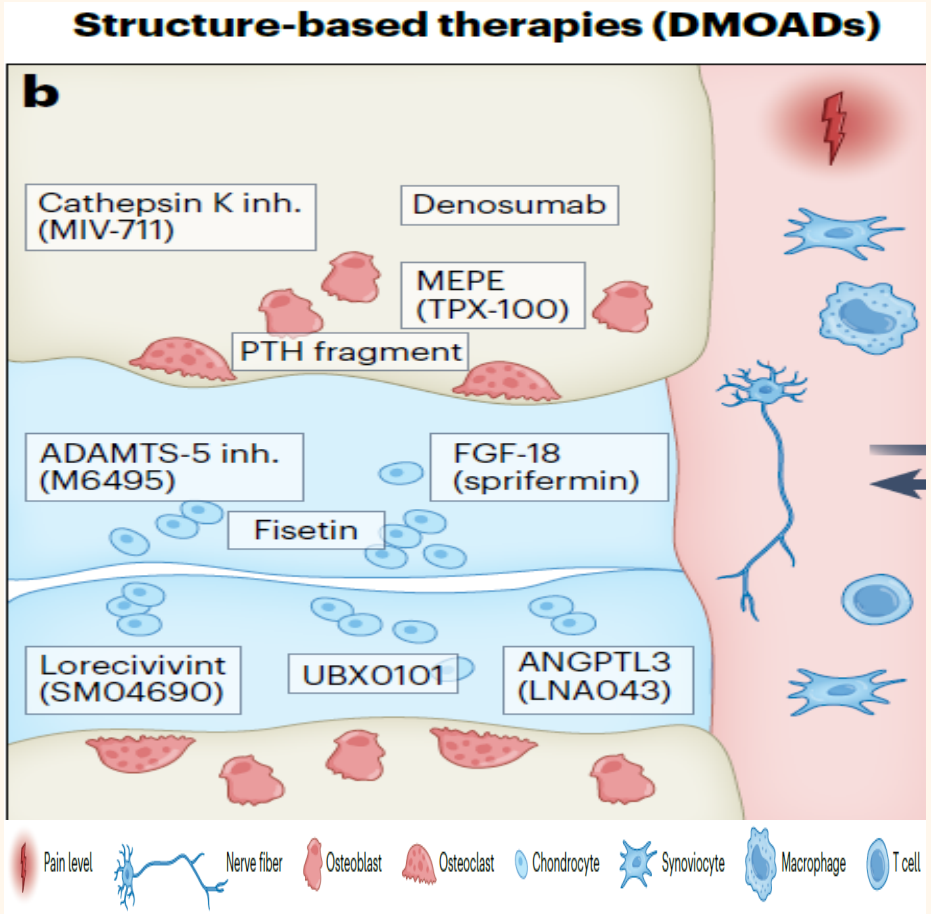


Gerwin, N. et al. Nat. Med 2022

Osteoarthritis therapy: (subchondral)bone-driven

Several phase 2/3 trials

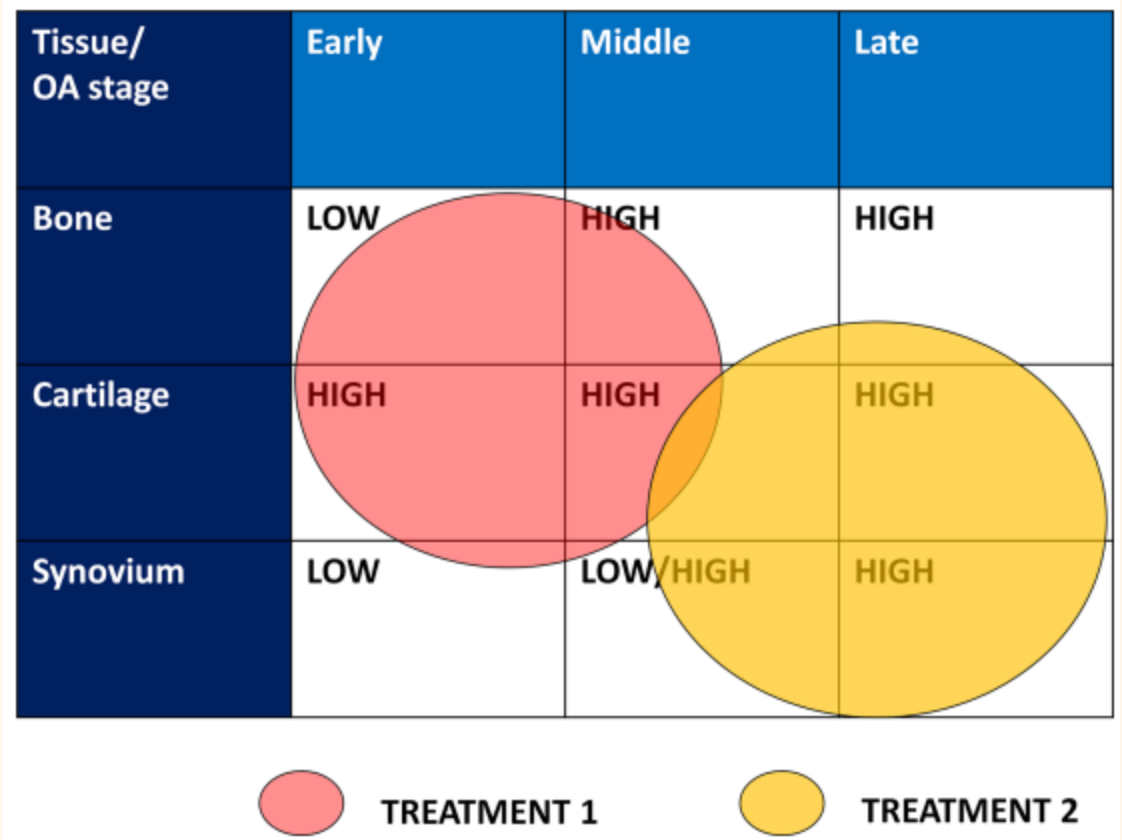
- Cathepsin K inhibitor: reduce cartilage loss but no pain
- Anti-resorptives: reduce bone remodeling and chondroprotective
- Vitamin D
- Anabolic peptide fragments (PTH and ECM phosphoglycoprotein (MEPE)): symptomatic improvement, in a few knees changes in cartilage and SB
  - ➢ Both cartilage and SB (PTH)
  - ➢ SB (MEPE)



N Schäfer et al. Nat Med 2022
Burr DB et al. Nat Rev Rheumatol. 2012

Osteoarthritis therapy: (subchondral)bone-driven

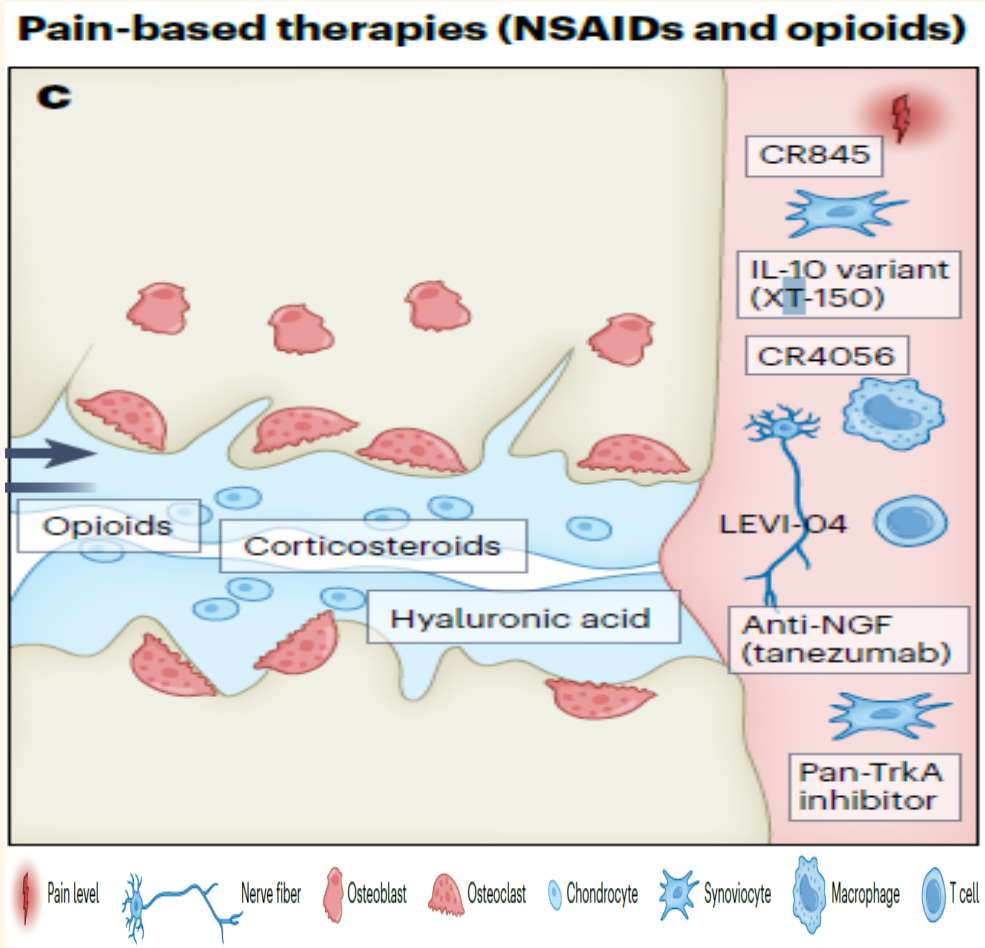
- Non-overweight female patients (BMI<25) with early radiographic KOA (baseline KL<2) revealed a 51% reduction of 2-year radiographic progression after BPs (90% ALN or RSN) (propensity-matched retrospective cohort analysis of the OA Initiative - OAI; n=346)
- No significant effects in patients with advanced OA



Hayes KN et al. JBMR 2020
Karsdal MA et al. Ann Rheum Dis 2014

Osteoarthritis therapy: synovitis-driven

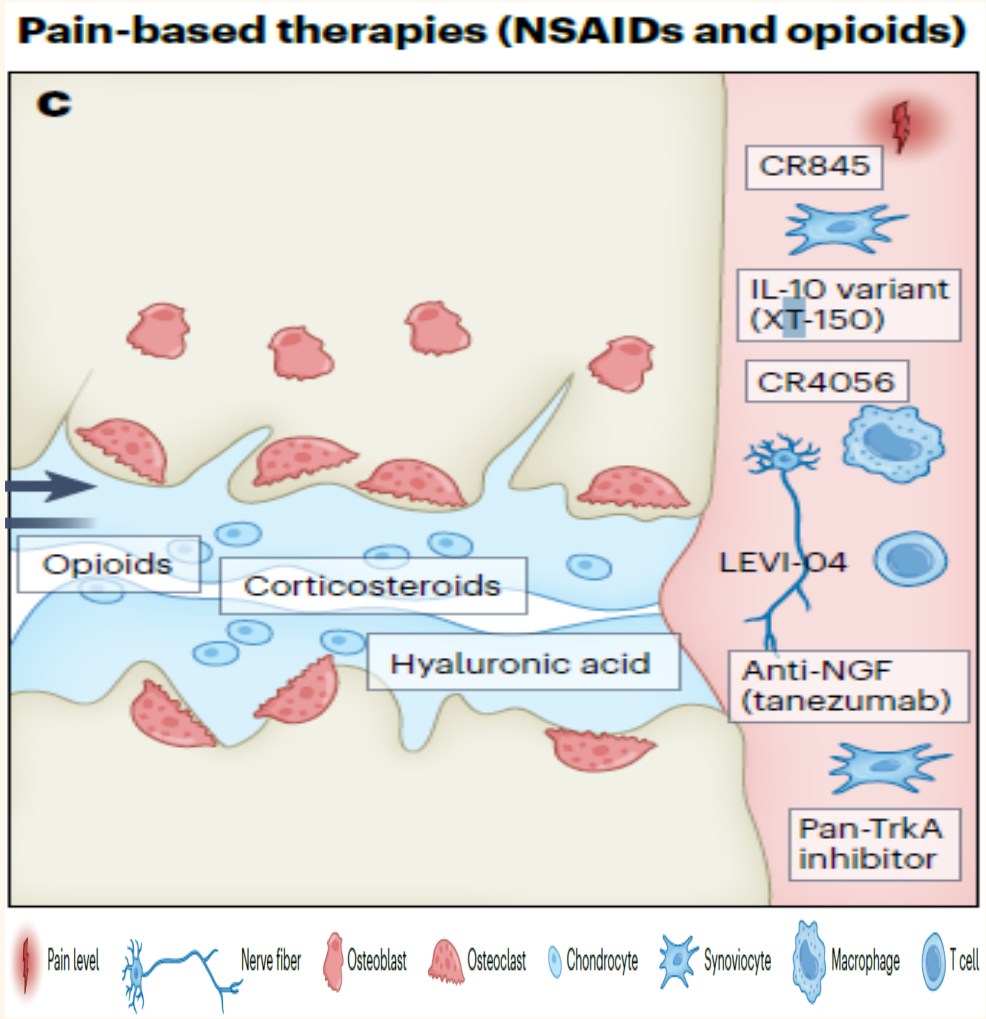
- Critical for perpetuating OA progression.
- Anti-inflammatory drugs for rheumatic diseases repurposed to OA
- However, most trials targeting cytokines failed
- One promising DMOAD (an IL-10 variant, phase 2) suppresses pro-inflammatory cytokines, chondroprotective and pain relief



N Schäfer et al. Nat Med 2022
Schäfer N et al. Peptides. 2022

Osteoarthritis therapy: pain-based

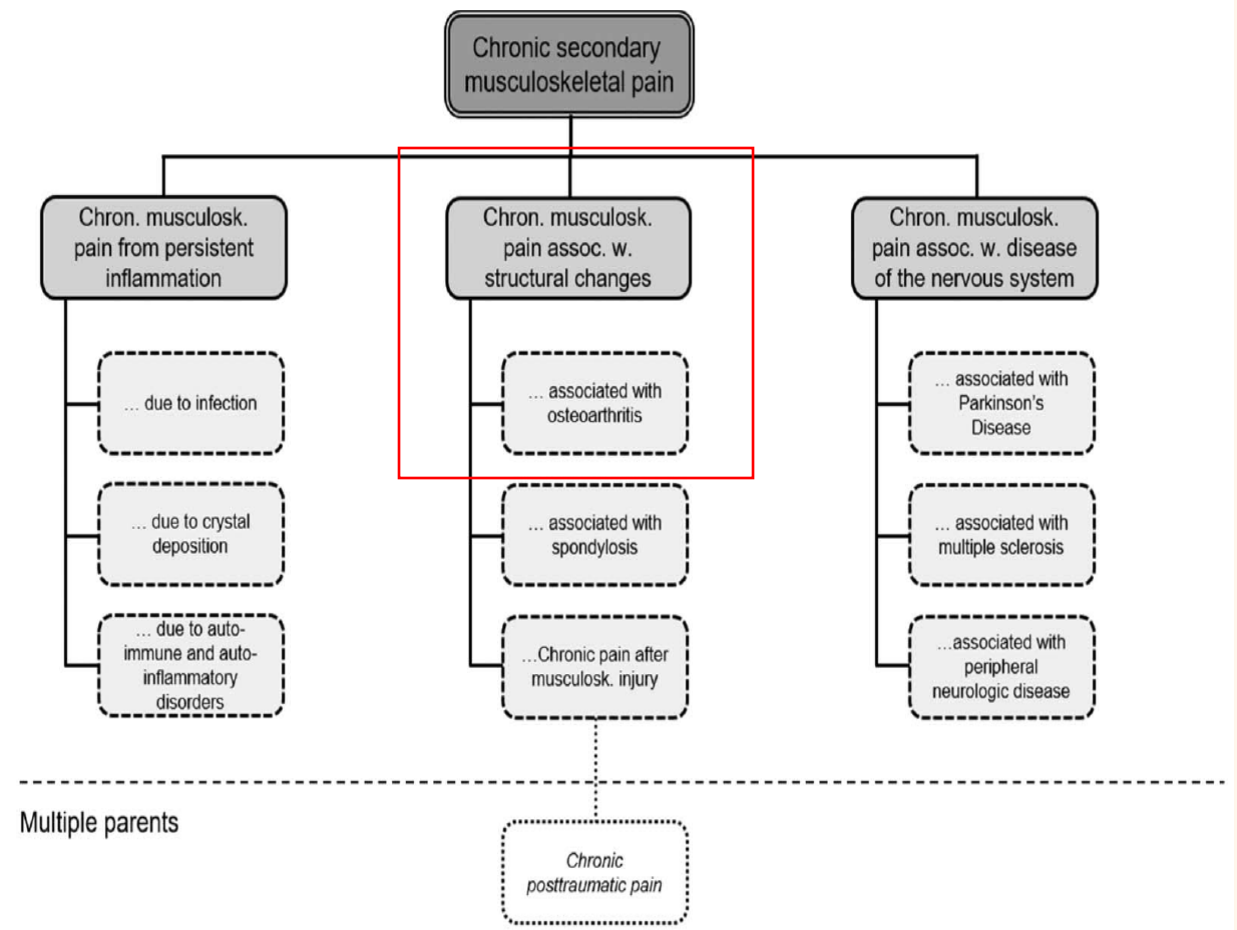
- Dominant and most debilitating OA hallmark (primary reason for visit)
- Pain sensation in OA progression not uniform



N Schäfer et al. Nat Med 2022
Fu, K., et al. Rheumatology 2018
Schmelz, M. et al. Pain 2019
Krupka, E. et al. Osteoarthritis Cartilage 2019

Osteoarthritis: chronic secondary MSK pain – ICD11

- Pain characterized by significant emotional distress and/or functional disability, attributable directly to a known damage process in joint tissues



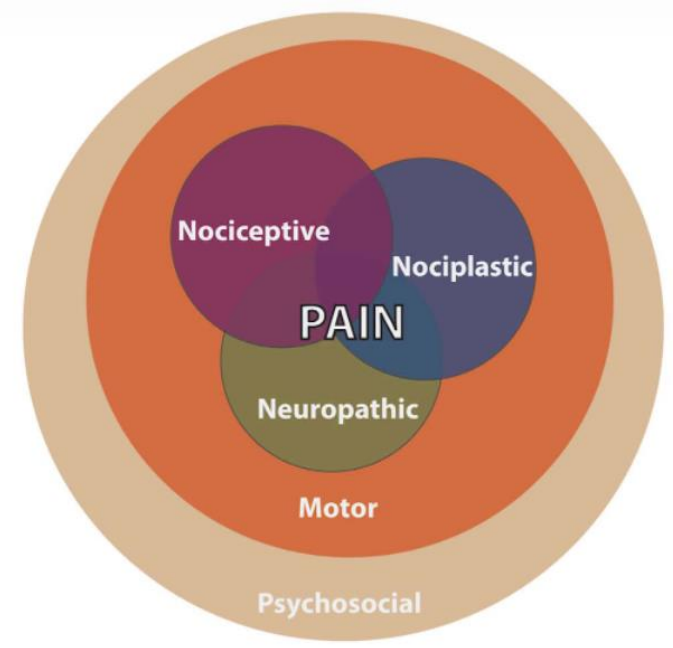
Perrot S et al. Pain 2019
Nicholas M et al. Pain. 2019

Osteoarthritis pain: Biopsychosocial and mechanistic approach

- Available pharmacological and nonpharmacological approaches should be individualized to meet the patient's needs.
- Concurrent use medications that work by different MoA and at different sites might be associated with better analgesia/fewer AE

Nociceptive	Central	Neuropathic	Psychosocial	Motor
•Exercise •Massage •TENS	•Education •Exercise •Massage •Manipulation •TENS	•Exercise	•Education •Exercise •Massage	•Education •Exercise •Manipulation

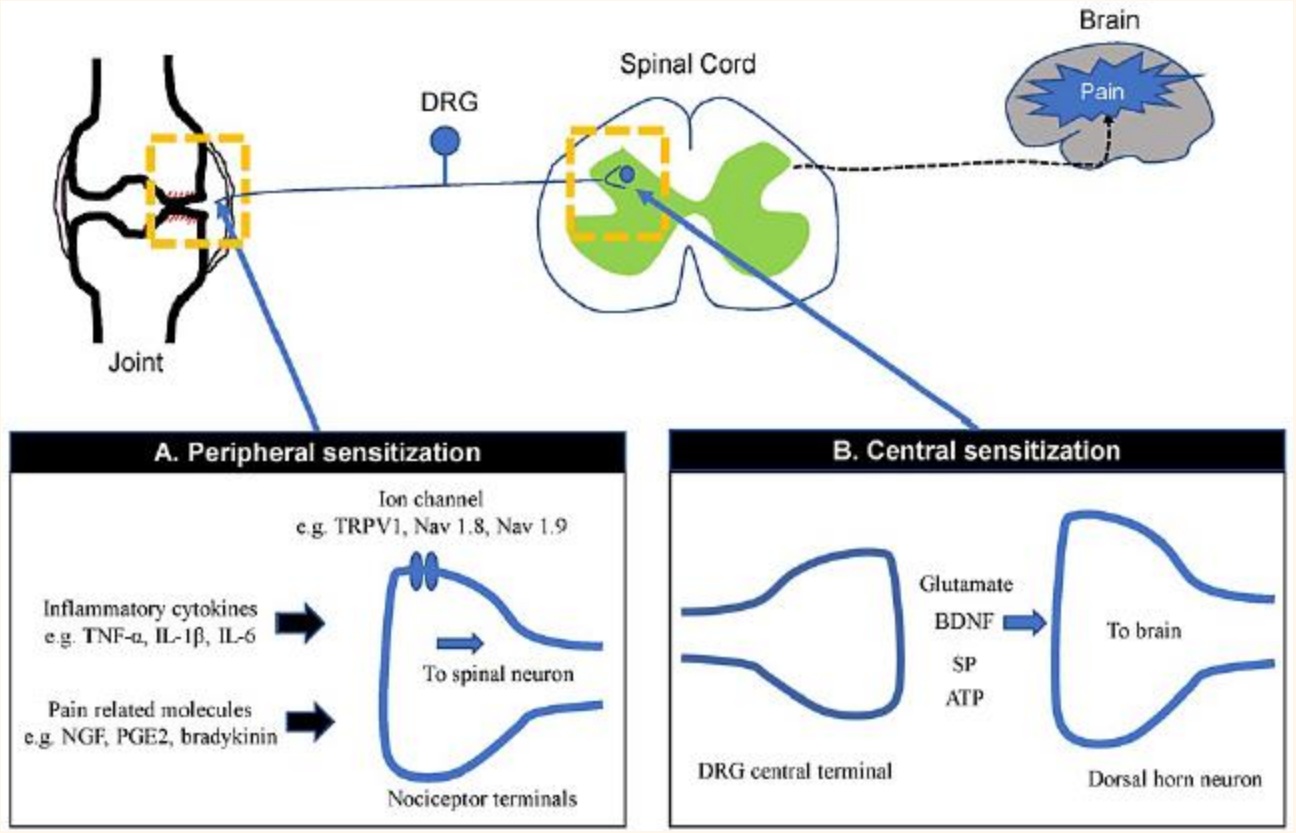
Nociceptive	Central	Neuropathic	Psychosocial	Motor
•Topical analgesic •Nonsteroidal Anti-inflammatory •Opioid •Channel blocker	•Serotonin-noradrenaline reuptake inhibitor •Tricyclic antidepressant	•Gabapentinoid	•Serotonin-noradrenaline reuptake inhibitor •Tricyclic antidepressant	•Muscle relaxant



IASP 2022
SB McMahon et al. Curr Med Res Opin 2021

Osteoarthritis: pain sensitization

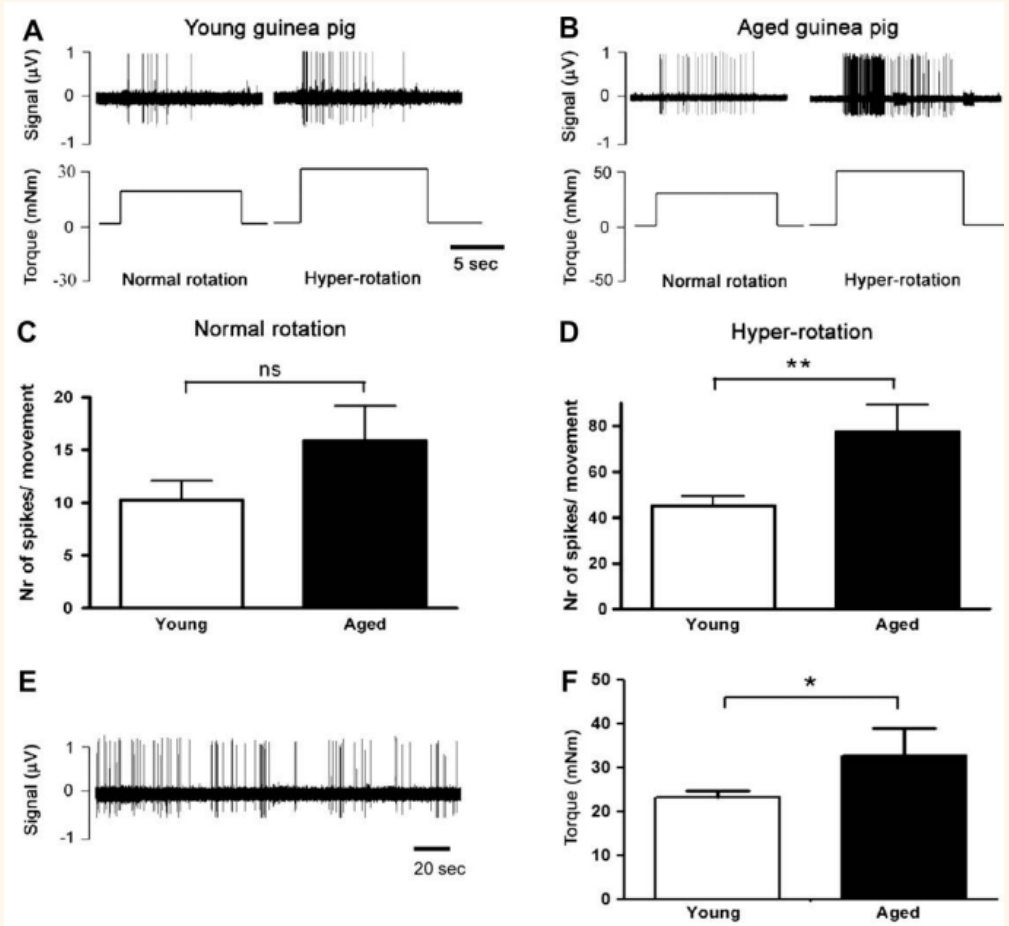
- Pain difficult to explain solely by radiological structural changes
- One reason for this discrepancy is pain sensitization
- Cytokines, NGF, and serotonin targets for OA pain with peripheral/central sensitization



Ohashi Y et al. Cureus 2023

Osteoarthritis: pain sensitization and aging

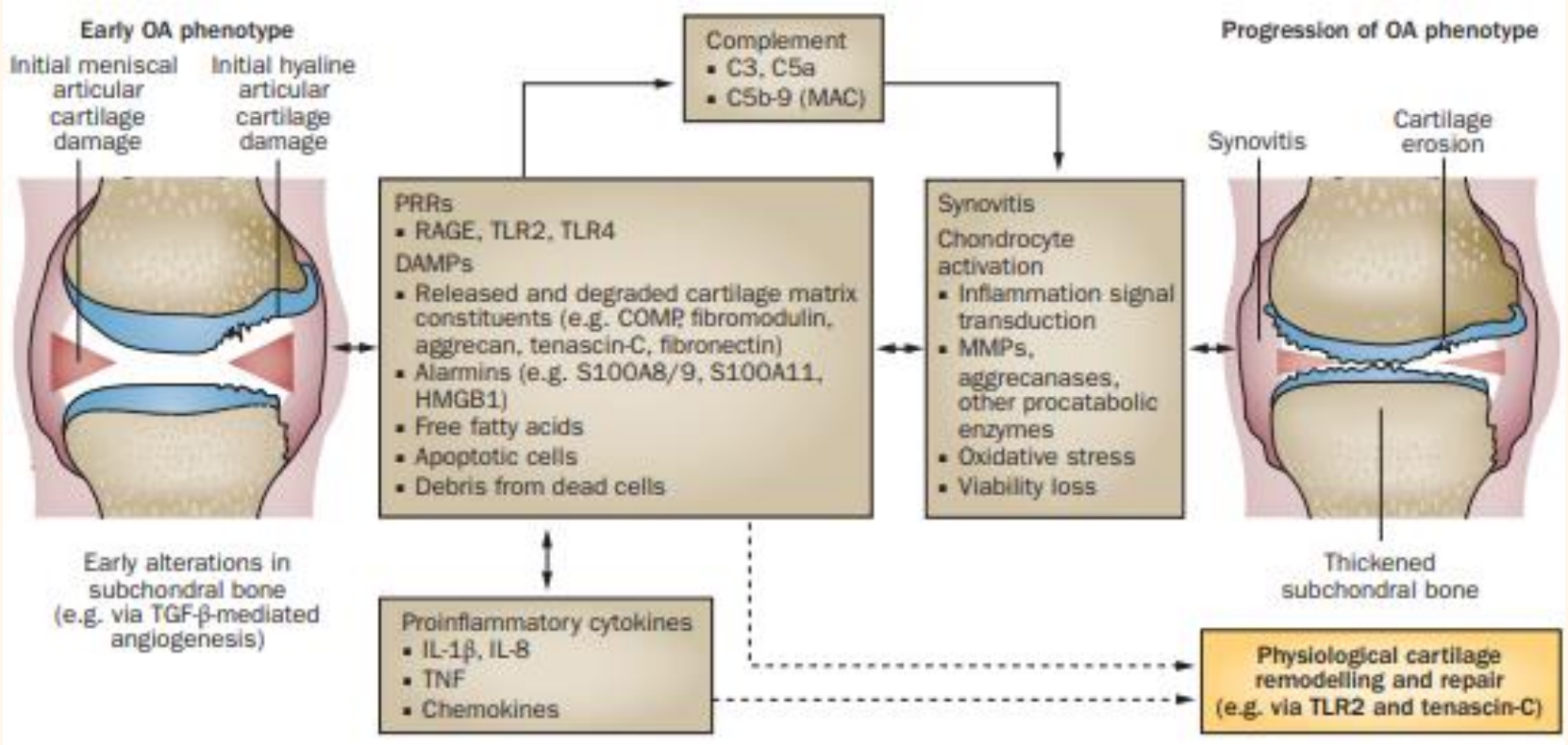
- Joint nociceptors active during cartilage damage or synovitis (hyperexcitability - innocuous or mild irritations)
- Afferent nerve firing rate increased with aging in guinea pig model



McDougall JJ et al. Pain. 2009

Osteoarthritis: pain sensitization and cytokines

- Inflammation-associated molecules (PG, BK, TNF-α, IL-1β, IL-6, DAMPs) ligate to sensory nerve fibers via TRP and sodium channels → lower excitation threshold on high-threshold neurons (joint nociceptors)
- Primarily expressed by synovial macrophages in OA

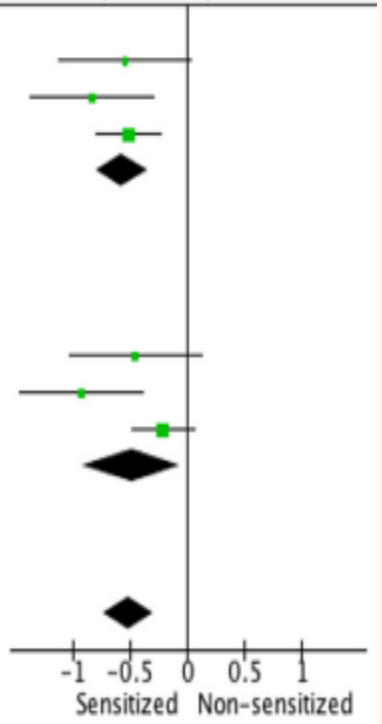


Liu-Bryan, R et al. Nat Rev Rheumatol 2015

Osteoarthritis: pain sensitization and clinical outcomes

- Present in OA, associated with symptom severity, and may affect postoperative pain persistence in TJR

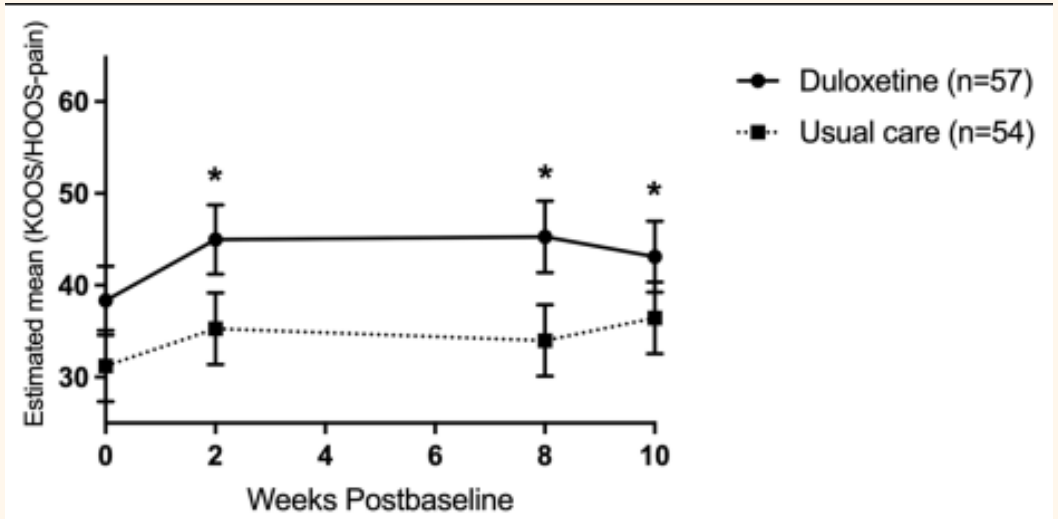
Study or Subgroup	High Symptom Severity Mean	SD	Total	Low Symptom Severity Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Local								
Arendt-Nielsen 2010	405	230	24	551	299	24	10.9%	-0.54 [-1.12, 0.04]
Finan 2013	444.84	185.61	32	616.1	225.13	27	12.2%	-0.83 [-1.36, -0.29]
King 2013	253.1	168.71	96	334.9	153.22	113	26.9%	-0.51 [-0.78, -0.23]
Subtotal (95% CI)			**152**			**164**	**49.9%**	**-0.57 [-0.80, -0.34]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 2 (P = 0.58); $I^2 = 0\%$								
Test for overall effect: Z = 4.94 (P < 0.00001)								
2.1.2 Remote								
Arendt-Nielsen 2010	294	167	24	369	162	24	11.0%	-0.45 [-1.02, 0.13]
Finan 2013	315.59	110.69	32	434.58	144.76	27	12.0%	-0.92 [-1.46, -0.38]
King 2013	218.6	178.46	96	255.3	162.44	113	27.2%	-0.22 [-0.49, 0.06]
Subtotal (95% CI)			**152**			**164**	**50.1%**	**-0.48 [-0.91, -0.06]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.32$, df = 2 (P = 0.07); $I^2 = 62\%$								
Test for overall effect: Z = 2.22 (P = 0.03)								
Total (95% CI)			**304**			**328**	**100.0%**	**-0.51 [-0.73, -0.30]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 7.87$, df = 5 (P = 0.16); $I^2 = 36\%$								
Test for overall effect: Z = 4.66 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 0.12$, df = 1 (P = 0.72), $I^2 = 0\%$								

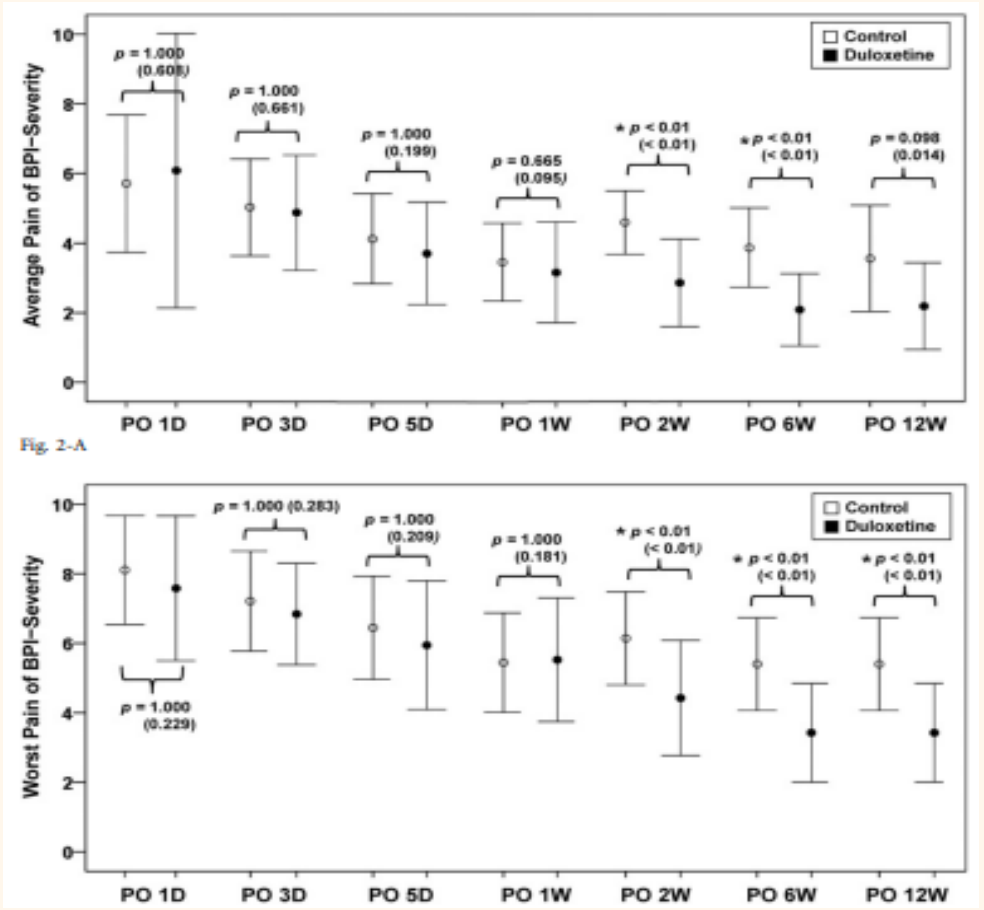


Fingleton C et al. Osteoarthritis Cartilage. 2015
Ohashi Y et al. J Pain Res. 2021

Osteoarthritis therapy: duloxetine

- Adding to usual care for end-stage KOA/HOA with pain sensitization
- Pre-operative seems to improve residual pain in the early post-operative period





Koh IJ et al. J Bone Joint Surg Am. 2019
Blikman T et al. BMC Musculoskelet Disord. 2022

Osteoarthritis therapy: anti-NGF

- Failed due to ADR (fast OA progression), new strategies to inhibit NGF-induced pain concentrate on antagonism of its receptors TrkA and p75NTR, but do not provide prolonged pain reduction

Anti-NGF treatments for pain — two steps forward, one step back?

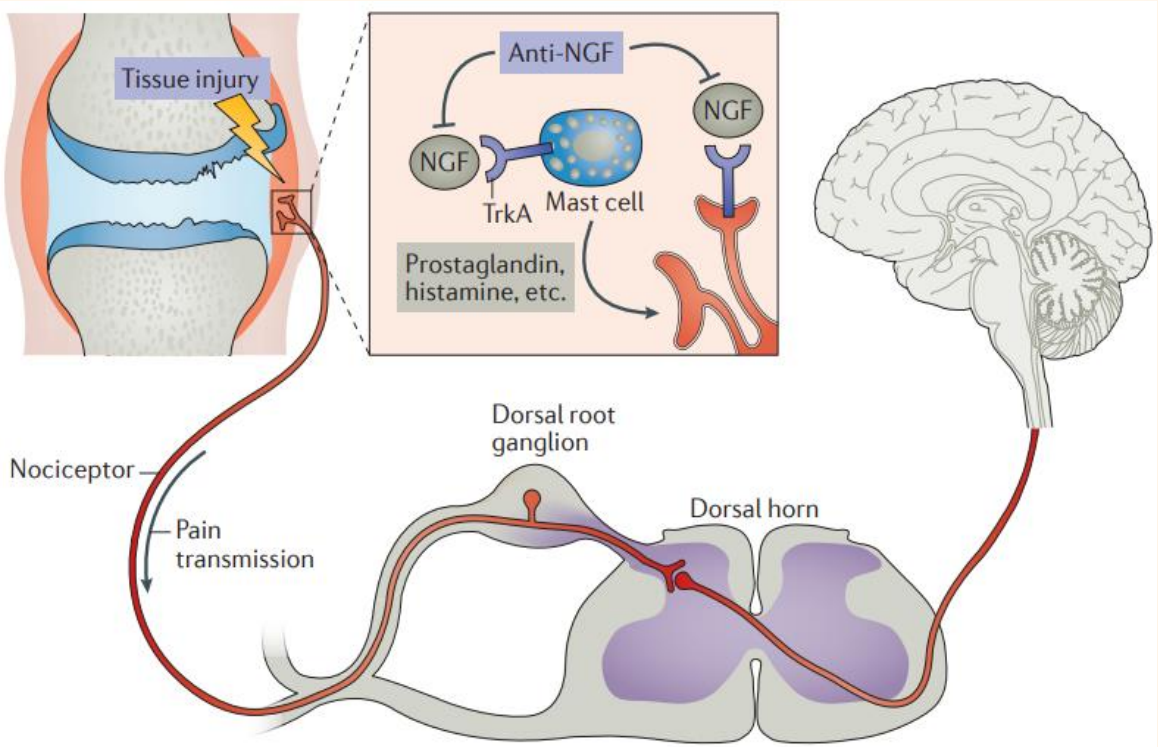
Nancy E. Lane and Maripat Corr

Inhibitors of β-nerve growth factor (NGF) have impressive effects in reducing musculoskeletal pain, but have also been associated with adverse events of unclear aetiology. Several studies in the past year have sought to clarify the relative benefits and risks of anti-NGF treatment.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

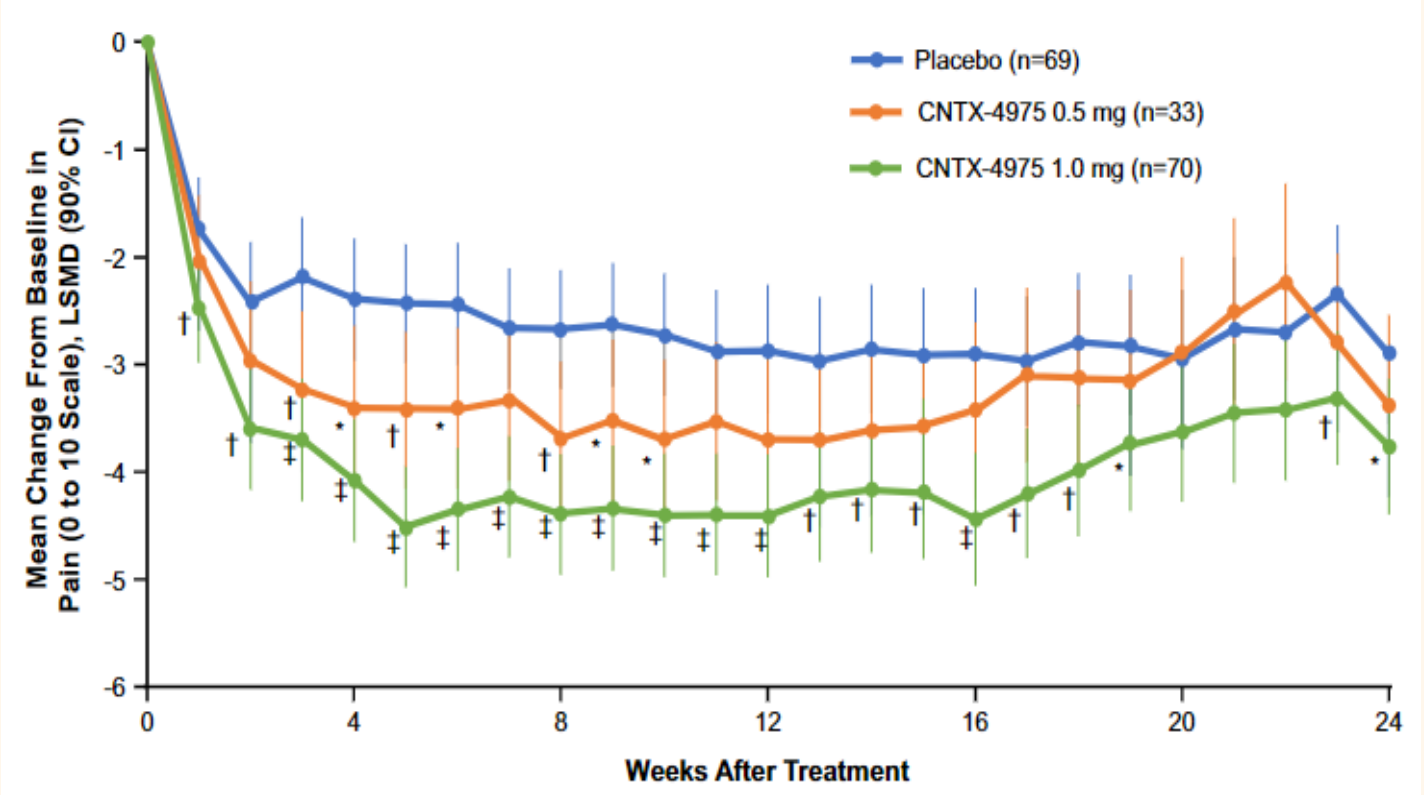
16 September 2021
EMA/CHMP/556162/2021
Committee for Medicinal Products for Human Use (CHMP)

In conclusion, the benefit-risk balance of tanezumab in the treatment of "moderate to severe chronic pain associated with osteoarthritis (OA) of the hip or knee in adult patients for whom treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or any opioid is ineffective, not tolerated or inappropriate" is considered to be negative.



Osteoarthritis therapy: TRPV1-agonists

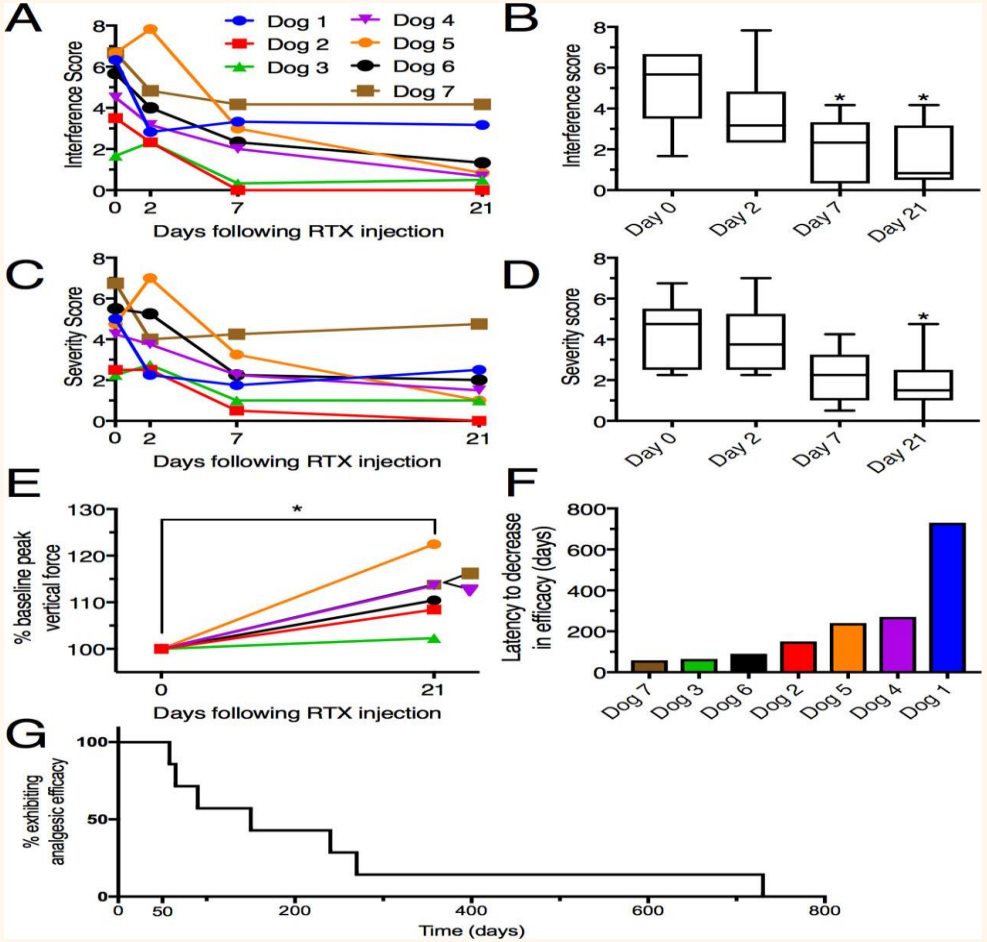
- TRPV1: nonspecific cation channel that opens with exposure to heat, acid; within peripheral nervous system selectively expressed on nociceptors
- After a brief period of activation, capsaicin induces a long-term desensitization (reversible) of nociceptors related to calcium influx into Aδ and C fibers
- Capsaicin injection: tolerated and dose-dependent improvement in KOA pain



Stevens RM et al. Arthritis Rheumatol. 2019

Osteoarthritis therapy: TRPV1-agonists

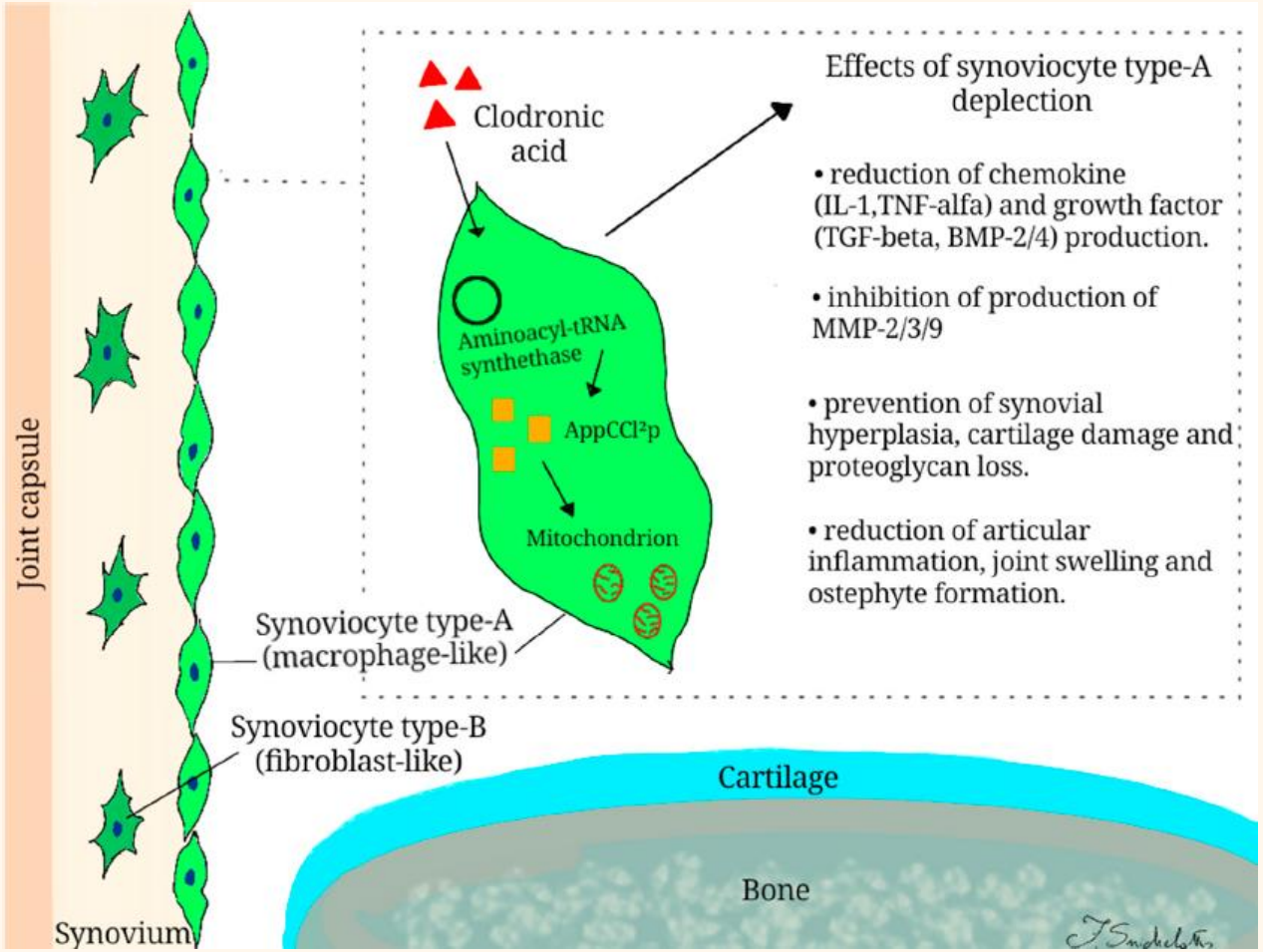
- RTX-GRT7039 (Stable formulation of resiniferatoxin), high-potency ligand at the TRPV1
  - Thousand times "hotter" than capsaicin (16 billion Scoville units vs 16 million), selectively ablates the nerve endings responsible for pain, transient nerve ending ablation can have profound clinical benefits lasting for months
- Phase II trials with RTX-GRT7039 (ex name MTX-071): potential as an effective and well-tolerated treatment option.
- No safety concern at any dose level (up to 1600 ng) after single IA administration of RTX-GRT7039



Iadarola MJ et al. Pain. 2018

Osteoarthritis therapy: clodronate

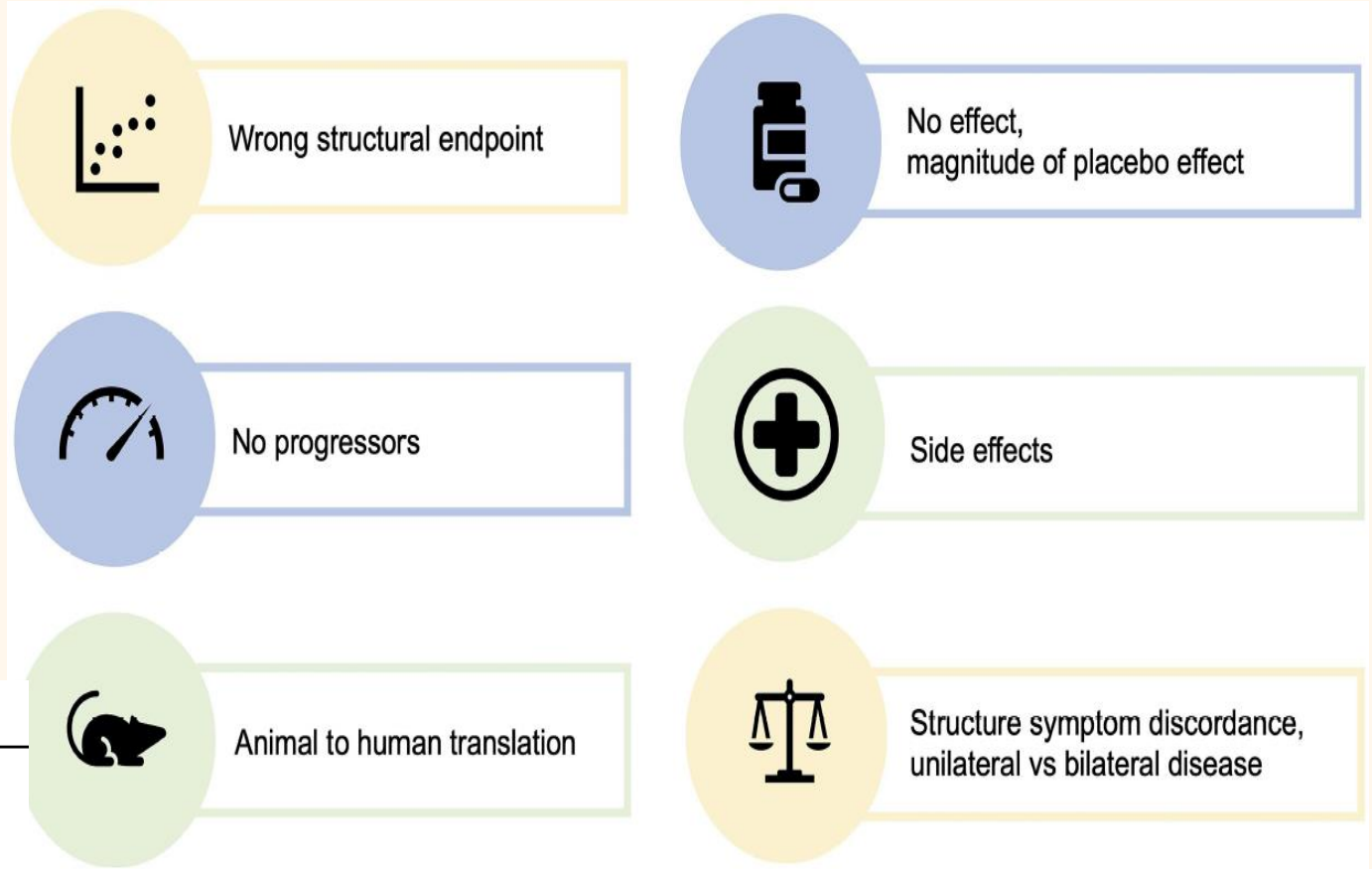
- Seems to be effective for pain relief and functional improvement in KOA



Moretti A et al. Int J Mol Sci 2021

Osteoarthritis therapy: progress and pitfalls

- Few DMOADs made it to clinic
- Pay attention to placebo effects due to injections and US-guided procedures (MCID reached) – lack of efficacy on symptoms in trials
- OA definition: ACR/KL 2-3 (missing early responsive period?)
- Time lag of symptomatic improvement translated from structural improvement >2 y (failure of trials with shorter duration)



Oo, W. M. Et al. Drug Des. Devel. Ther. 2021

Adv Ther (2021) 38:4995–5001
https://doi.org/10.1007/s12325-021-01894-5

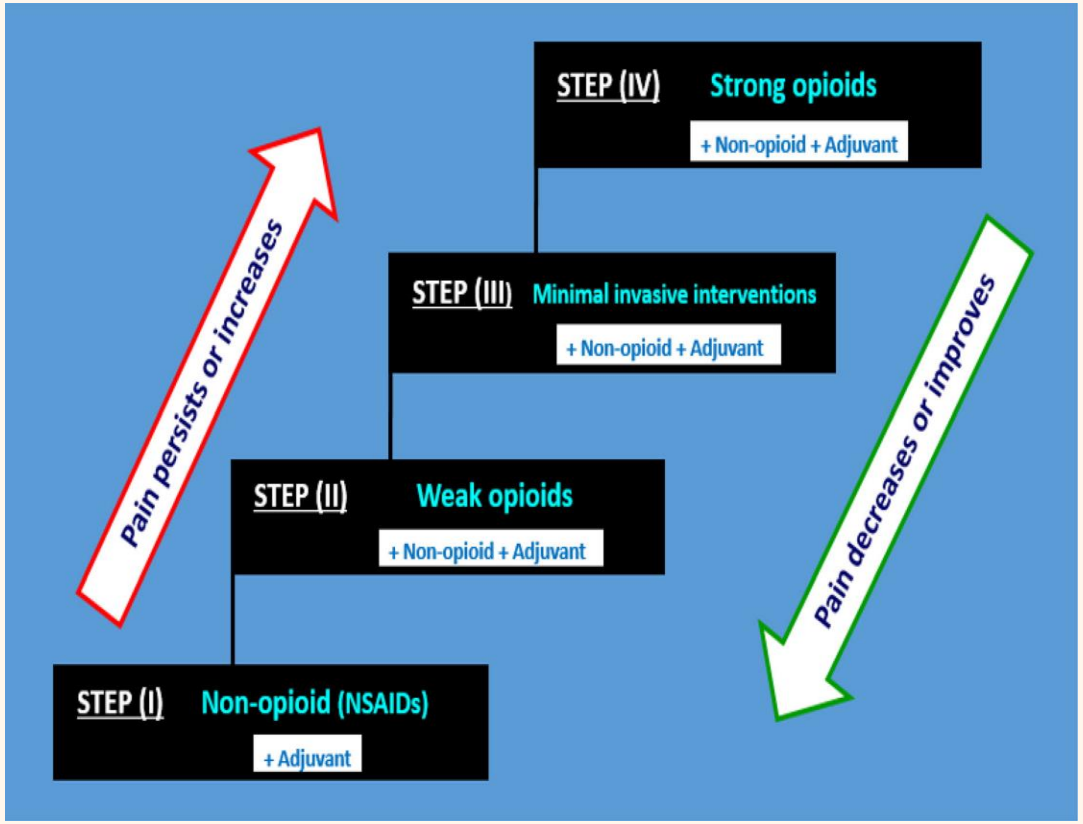
COMMENTARY

Myths and Truths about Placebo Effect in Rehabilitation for Musculoskeletal Pain

Giovanni Iolascon · Antimo Moretti

Osteoarthritis therapy: injections and placebo

Overarching principles
I. IAT are recommended and widely used in the management of joint diseases.
II.The aim of IAT is to improve patient-centred outcomes.
III.Contextual factors are important and contribute to the effect of IAT.
IV.IAT should be offered in the frame of full individualised information and a shared decision-making process.
V. A variety of health professionals perform these procedures routinely.



EULAR 2021
McMahon et al. Curr Med Res Opin 2021
J Yang et al. J Pain Res 2020

Take home messages

- OA is highly heterogeneous
- Effective therapies will need to target clearly defined molecular endotypes, restore mechanical joint function and reduce pain
- A 'one-size-fits-all' approach is unlikely to succeed.
- Identification of reliable biomarkers and advanced imaging, as well as stronger interdisciplinary treatment regimens, will be indispensable
- Immense unmet need for effective and safe targeted interventions to inhibit both pain and disease progression.