Safety of Drugs Used in Osteoarthritis

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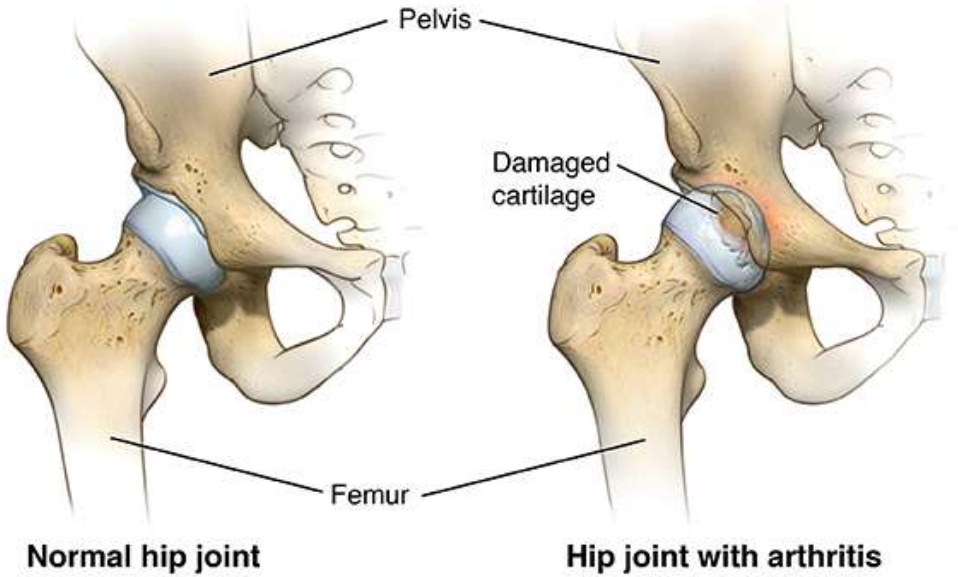
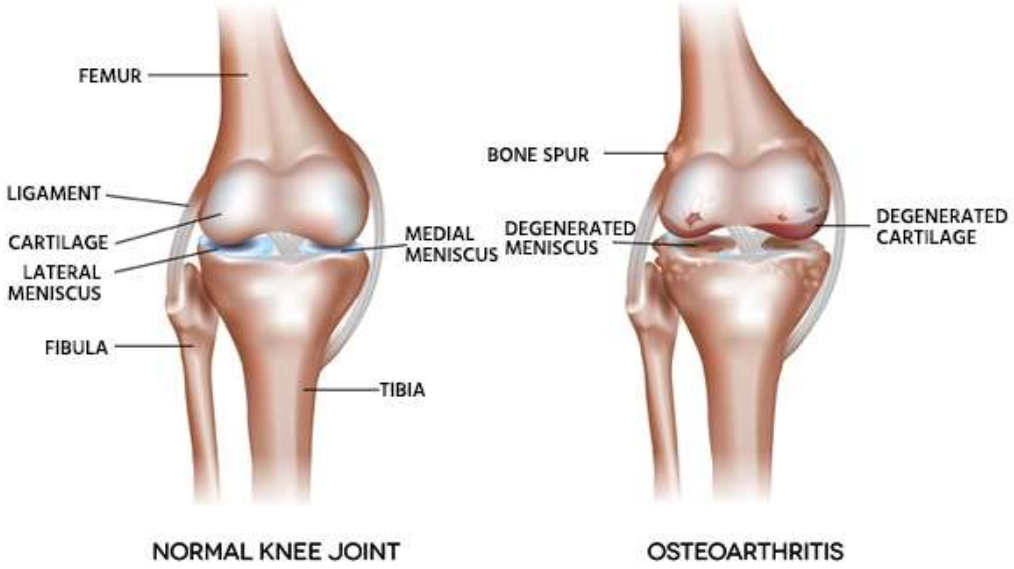
- Osteoarthritis (OA) is the most common **musculoskeletal chronic progressive disorder** of the synovial joints that is often age related and/or trauma induced.

- OA often severely affects patients' **quality of life** and symptoms include pain, stiffness, swelling, tenderness, and loss of joint range of motion.



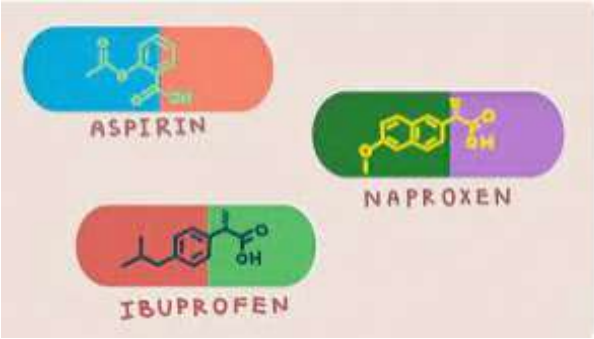


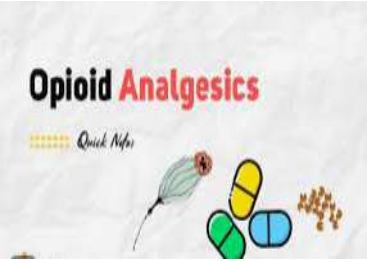
- **The guidelines treatment options ;**

- **Appropriate exercises help strengthen muscles and improve joint function**
- **Weight loss is encouraged to those who are overweight**
- **Assistive devices, such as canes and walkers are recommended for patients with symptomatic knee OA**
- **Current pharmaceutical treatment**
- **Physical therapy,**
- **Surgery**

There is no cure for OA. Existing treatments aim to reduce pain and symptoms, as well as improve joint functional capacity.

Current pharmaceutical treatment for OA is largely restricted to analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs)





Opioid analgesic

- Tramadol
- Morphine
- Hydromorphone
- Pethidine
- Fentanyl
- Codeine
- Methadone
- Oxycodone
- Hydrocodone

Compared to the controls, the oxidant parameters (total peroxide, lipid hydroperoxide, and oxidative stress index) were significantly higher whereas the antioxidant parameters (serum thiol levels, thiol level, prolidase, and catalase activity) were lower in patients with grade II-III knee OA .

Antioxidant supplements to inhibit ROS production. Vitamin supplements **(vitamins A, E, and C), and natural herbs extract (turmeric, avocado, and boswellia)**
Potential side effects and avoid interactions with other OA medications

Benefits of antioxidant supplements for knee osteoarthritis: rationale and reality. Nutr J. (2016) 15:1.

CONVENTIONAL THERAPY

Classification	Name	Indications	Pharmacological mechanisms	Side effects
Traditional medications	Acetaminophen	Relief mild to moderate pain relief	Inhibit COX-3 activity and synthesizing prostaglandin.	Liver damage; liver toxicity; transient liver enzyme elevations and hepatotoxicity
	Non-steroidal anti-inflammatory drugs (NSAIDs)	Relief mild to moderate pain; analgesic and anti-inflammatory	Inhibit cyclooxygenase enzymes and prostaglandin synthesis; inhibit COX-1 and COX-2 activity	Gastrointestinal complications, kidney disease and adverse cardiovascular events
	Opioid analgesics	Pain relief	Inhibit pain pathways in the central nervous system	Nausea, vomiting, headache, constipation, fatigue and drowsiness
	Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Treatment of depression and mood disorder	Inhibit serotonin-norepinephrine reuptake	Fatigue and somnolence; sexual dysfunction; gastrointestinal problems
	Intra-articular injections of corticosteroids	Relief moderate-to-severe pain and inflammation	Down-regulate genetic expression of pro-inflammatory proteins; decrease inflammatory markers and cytokines	Post-injection pain and flushing; septic arthritis; possible rare Tachon syndrome
	Vitamin D supplements	Reduction of WOMAC pain and WOMAC function; reduction of VAS pain	Increase calcium absorption and have effects on cartilage and bone metabolism	No severe safety issues were reported
	Glucosamine and chondroitin sulfate supplements	Management of the symptoms of OA	Inhibit catabolic enzymes activities, and reduce IL-1 β levels in synovial fluids	No severe safety issues were reported
	Antioxidant supplements	Pain relief and function improvement in knee OA	Inhibit reactive oxygen species signal transduction	Large-scale RCTs are needed

Zhang W, Robertson WB, Zhao J, Chen W and Xu J (2019) Emerging Trend in the Pharmacotherapy of Osteoarthritis. Front. Endocrinol. 10:431. doi: 10.3389/fendo.2019.00431

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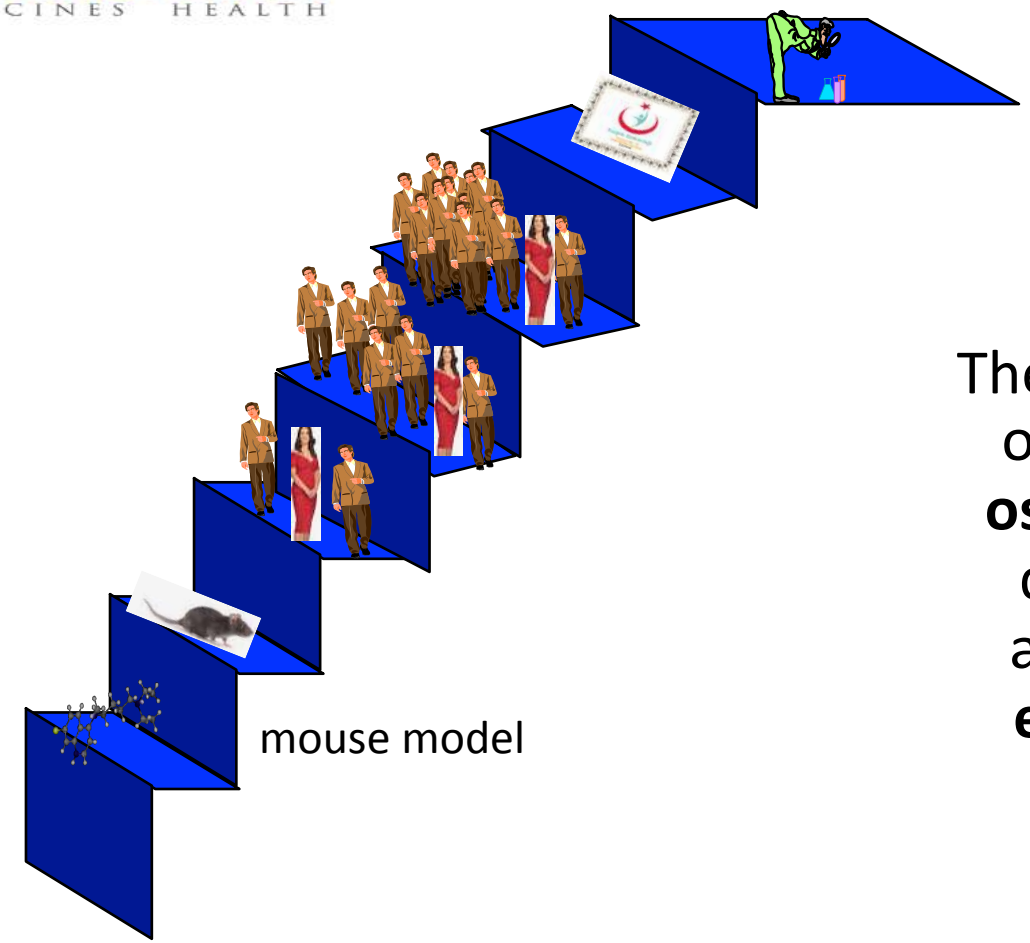
The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs)



The guidelines from the FDA and EMA point out that the effective **disease-modifying osteoarthritis drugs** (DMOADs) should be developed, highlight the importance of addressing the **unmet medical need for effective treatments for osteoarthritis.**

Major emerging drugs

Type of drug	Route of administration	Major findings	Stage of development	Clinical trials. gov identifier
Targeting inflammatory mechanisms				
IL-1 inhibitors				
Anakinra	Intra-articular	Anakinra did not significantly improve symptoms in patients with knee OA.	Phase II (knee OA)	NCT00110916
AMG 108	Subcutaneous/Intra-articular	AMG 108 showed statistically insignificant but numerically greater improvements in pain.	Phase II (knee OA)	NCT00110942
Canakinumab	Intra-articular	The clinical trial was completed, but the results have not been published.	Phase II (knee OA)	NCT01160822
Gevokizumab	Subcutaneous	The clinical trials were completed, but the results have not been published.	Phase II (erosive hand OA)	NCT01683396
			Phase II (erosive hand OA)	NCT01882491
Lutikizumab (ABT-981)	Subcutaneous	Lutikizumab was generally well tolerated in patients with knee OA and elicited an anti-inflammatory response.	Phase I (knee OA)	NCT01668511
		Lutikizumab did not improve pain or imaging outcomes in erosive hand OA compared with placebo.	Phase IIa (erosive hand OA)	NCT02384538
		Lutikizumab was not an effective analgesic/anti-inflammatory therapy in most patients with knee OA associated synovitis.	Phase IIa (knee OA)	NCT02087904 (ILL-USTRATE- K trail)
TNF-α inhibitors				
Etanercept	Subcutaneous	Subcutaneous injection of Etanercept for 24 weeks did not relieve pain effectively in patients with erosive hand OA compared with placebo.	—	NTR1192 (EHOA trail)
Infliximab	Intra-articular	Treatment with Infliximab can reduce the incidence of secondary OA in proximal interphalangeal joints in patients with active RA.	Exploratory observational longitudinal study	—
		Infliximab was safe, and significantly improved pain symptoms	Plot study (erosive hand OA)	—

Cai X, Yuan S, Zeng Y, Wang C, Yu N and Ding C (2021) New Trends in Pharmacological Treatments for Osteoarthritis. Front. Pharmacol. 12:645842. doi: 10.3389/fphar.2021.645842

National Library of Medicine
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ClinicalTrials.gov

Lutikizumab, Subcutaneous, NCT01668511

Results Overview

No Study Results Posted on ClinicalTrials.gov for this Study

Study results have not been submitted. This may be because the study isn't done, the deadline for submitting results has not passed, or this study isn't required to submit results.

Recruitment Status	Actual Primary Completion Date	Actual Study Completion Date
Completed	2013-10	2013-10

https://clinicaltrials.gov/study/NCT01668511?cond=osteoarthritis&intr=Lutikizumab&rank=1&term=NCT01668511

Clinical Trial > Osteoarthritis Cartilage. 2017 Dec;25(12):1952-1961.
doi: 10.1016/j.joca.2017.09.007. Epub 2017 Sep 28.

Safety, tolerability, and pharmacodynamics of an anti-interleukin-1α/β dual variable domain immunoglobulin in patients with osteoarthritis of the knee: a randomized phase 1 study

S X Wang [1], S B Abramson [2], M Attur [3], M A Karsdal [4], R A Preston [5], C J Lozada [6], M P Kosloski [7], F Hong [8], P Jiang [9], M J Saltarelli [10], B A Hendrickson [11], J K Medema [12]

Affiliations + expand

PMID: 28964890 DOI: 10.1016/j.joca.2017.09.007

Free article

Abstract

Objective: To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ABT-981, a human dual variable domain immunoglobulin simultaneously targeting interleukin (IL)-1α and IL-1β, in patients with knee osteoarthritis (OA).

Method: This was a randomized, double-blind, placebo-controlled, single-center study of multiple subcutaneous (SC) injections of ABT-981 in patients with mild-to-moderate OA of the knee (NCT01668511). Three cohorts received ABT-981 (0.3, 1, or 3 mg/kg) or placebo every other week for a total of four SC injections, and one cohort received ABT-981 (3 mg/kg) or placebo every 4 weeks for a total of three SC injections. Assessment of safety and tolerability were the primary objectives. A panel of serum and urine biomarkers of inflammation and joint degradation were evaluated.

Results: A total of 36 patients were randomized (ABT-981, n = 28; placebo, n = 8); 31 (86%) completed the study. Adverse event (AE) rates were comparable between ABT-981 and placebo (54% vs 63%). The most common AE reported with ABT-981 vs placebo was injection site erythema (14% vs 0%). ABT-981 significantly reduced absolute neutrophil count and serum concentrations of IL-1α/IL-1β, high-sensitivity C-reactive protein, and matrix metalloproteinase (MMP)-derived type 1 collagen. Serum concentrations of MMP-derived type 3 collagen and MMP-degraded C-reactive protein demonstrated decreasing trends with ABT-981. Antidrug antibodies were found in 37% of patients but were not associated with the incidence or severity of AEs.

Major emerging drugs

Adalimumab	Subcutaneous	Adalimumab was not superior to placebo in relieving pain in patients with erosive hand OA.	Phase III (erosive hand OA)	NCT00597623
		Adalimumab did not affect synovitis or BMLs in patients with hand OA with MRI-detected synovitis.	—	ACTRN12612000791831 (HUMOR trial)
		Adalimumab significantly slowed the progression of joint aggressive lesions in a subpopulation with palpable tissue swelling of the interphalangeal joints.	—	EudraCT 2006–000925–71
DMARDs				
HCQ	Oral	HCQ did not relieve symptoms or delay structural damage.	—	ISRCTN91859104 (HERO trial)
MTX	Oral	MTX significantly reduced pain and improved synovitis in patients with symptomatic knee OA.	—	NCT01927484
		MTX added to usual care demonstrated significant reduction in knee OA pain at 6 months, and significant improvements in WOMAC stiffness and function. No effect on synovitis	Phase III (knee OA)	ISRCTN77854383 (PROMOTE trial)
		The clinical trial is ongoing	—	NCT03815448
Removing SnCs				
UBX0101	Intra-articular	The clinical trials were completed, but the results have not been published.	Phase I (knee OA) Phase I (knee OA) Phase II (knee OA)	NCT03513016 NCT04229225 NCT04129944
Curcuma longa extract	Oral	Curcuma longa extract was more effective than placebo for knee pain but did not affect knee effusion–synovitis or cartilage composition.	Phase II (knee OA)	ACTRN12618000080224
		The clinical trial is ongoing	Phase III (hip or knee pain)	NCT04500210

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Major emerging drugs

Targeting Cartilage Metabolism				
Wnt pathway inhibitors				
Lorecivivint (SM04690)	Intra-articular	Lorecivivint 0.07 mg was superior to the placebo in improving pain and function, and increased the JSW in patients with knee OA.	Phase I (knee OA)	NCT02095548
		Lorecivivint had no significant effects in knee OA patients, but significantly relieved pain, improved joint function, and increased JSW in a subgroup of patients (patients with unilateral symptomatic knee OA and unilateral symptomatic knee OA without extensive pain).	Phase IIa (knee OA)	NCT02536833
		The clinical trial is ongoing	Phase III (knee OA)	NCT03928184
Cathepsin-K inhibitors				
MIV-711	Oral	MIV-711 was not more effective than placebo for pain, but it significantly reduced bone and cartilage progression with a reassuring safety profile.	Phase IIa (knee OA)	NCT02705625

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Major emerging drugs

MMP/ADAMTS inhibitors				
AGG-523	Oral	The clinical trials were completed, but the results have not been published	Phase I (knee OA) Phase I (knee OA)	NCT00454298 NCT00427687
M6495	Subcutaneous	The clinical trial was completed, but the results have not been published.	Phase Ib (knee OA)	NCT03583346
Growth factors				
Sprifermin (rhFGF18)	Intra-articular	Sprifermin appeared safe and well-tolerated, and it showed a statistically significant dose-dependent effect in reducing the loss of total and lateral femorotibial cartilage thickness and loss of lateral radiographic JSW.	Phase I (knee OA)	NCT01033994
		Sprifermin had a limited effect on pain improvement, but had a statistically significant effect in reducing the loss of total femorotibial cartilage thickness.	Phase II (knee OA)	NCT01919164 (FO-RWARD trial)
GEC-TGF-β1	Intra-articular	GEC-TGF-β1 significantly improved pain function and physical ability.	Phase II (knee OA) Phase II (knee OA)	NCT01221441 NCT01671072
		GEC-TGF-β1 had beneficial effects on pain and functional improvement in patients with OA, but had limited effects on structural improvement.	Phase III (knee OA)	NCT02072070
Activating AMPK pathway				
Metformin	Oral	Metformin may have a beneficial effect on long-term knee joint outcomes in those with knee OA and obesity.	Prospective cohort study (knee OA)	—

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Major emerging drugs

Targeting the Subchondral Bone				
Bisphosphonate				
Zoledronic Acid	Intra-articular	Zoledronic acid did not significantly reduce cartilage volume loss, relieve pain, or improve BMLs.	Phase III (Knee OA)	ACTRN12613000039785
Calcitonin				
Salmon calcitonin	Oral	Salmon calcitonin did not improve pain symptoms and JSW in patients with symptomatic knee OA.	Phase III (Knee OA)	NCT00486434 NCT00704847
Strontium Ranelate	Oral	Strontium Ranelate significantly inhibited the narrowing of the medial femoral joint space, relieved pain, and improved physical function in patients with moderate to severe knee OA.	Phase III (Knee OA)	ISRCTN41323372 (SEKOIA trial
Teriparatide	Subcutaneous	The clinical trial is ongoing.	Phase II (knee OA)	NCT03072147
Vitamin D	Oral	Vitamin D supplementation, compared with placebo, did not result in significant differences in change in MRI-measured tibial cartilage volume or WOMAC knee pain score over 2 years, but might have beneficial effects on physical function, foot pain, depressive symptoms and effusion-synovitis.	Phase III (Knee OA)	NCT01176344
Investigational Drugs to relieve pain				
NGF inhibitors				
Tanezumab	Subcutaneous	Tanezumab was significantly better than the placebo in improving pain and physical function, and PGA-OA.	Phase III (hip or knee OA)	NCT02697773
		Tanezumab statistically significantly improved pain, physical function and PGA-OA in patients with moderate to severe OA who had not responded to or could not tolerate standard-of-care analgesics	Phase III (hip or knee OA)	NCT02709486
Fasinumab	Subcutaneous	Fasinumab significantly improved pain and function in patients with OA, even in those who obtained little benefit from previous analgesics	Phase IIb/III (hip or knee OA)	NCT02447276
		The clinical trials are ongoing	Phase III (hip or knee OA)	NCT02683239 NCT03285646 NCT03161093 NCT03304379

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Major emerging drugs

Triamcinolone acetonide sustained-release agent				
Zilretta (FX006)	Intra-articular	Zilretta significantly reduced ADP-intensity compared with saline-solution placebo. Zilretta significantly improved pain, stiffness, physical function, and the quality of life compared with both placebo and TAcs	Phase III (knee OA)	NCT02357459

corticosteroid

No medical procedure can restore the frayed cartilaginous tissue to its former state

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Lack of reporting of adverse effect (AE) data and inconsistencies in the data reported.

A consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases Working Group published specific, clear, practical, and standardized guidance on the reporting of AE data

"Most drugs are in clinical phases for five to seven years
Only one or two compounds in 10,000 tested actually make it through to being licensed treatments.

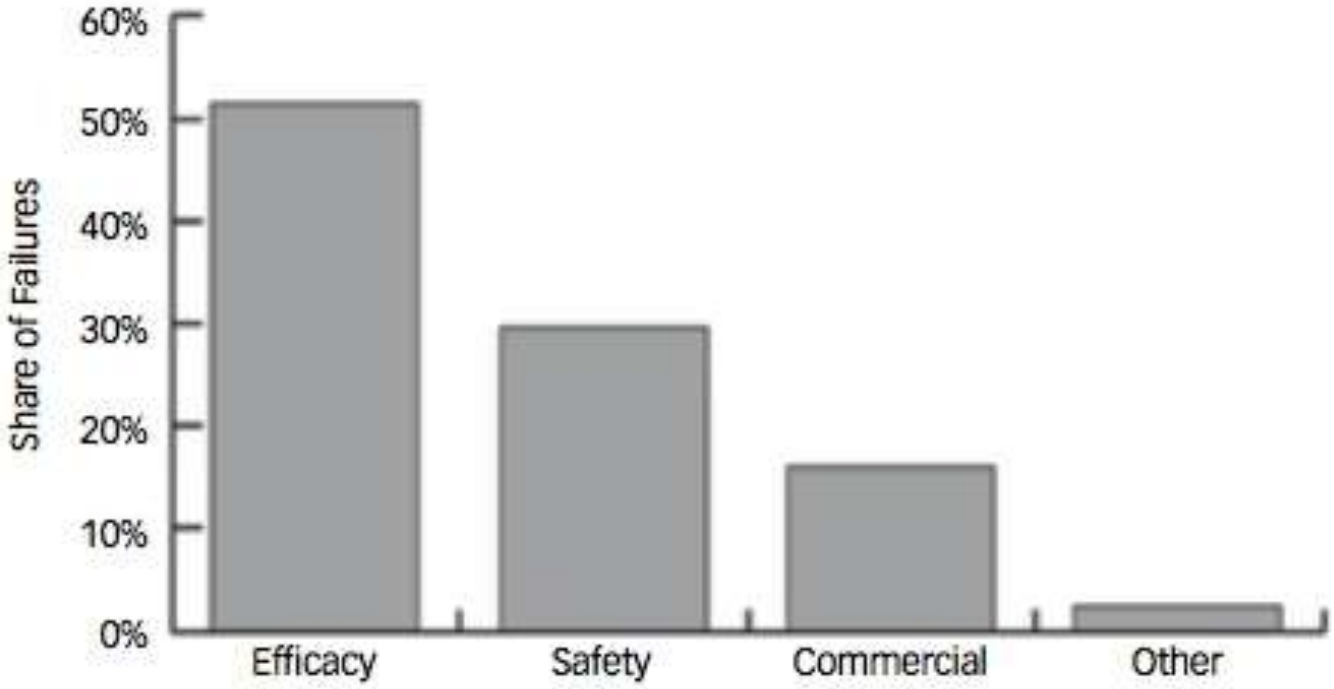
Phase III Failures: Lack of Efficacy

THERAPEUTIC AREA	NUMBER OF TRIALS	PATIENTS ENROLLED	AGENTS/COMBINATIONS TESTED
CARDIOVASCULAR *Indications studied: acute coronary syndrome, acute heart failure, atherosclerotic disease, cardiovascular cell damage*	6	**58,759**	darapladib, evacetrapib, losmapimod, otamixaban, serelaxin
ENDOCRINE/METABOLIC *Indication studied: diabetes*	4	**38,066**	aclerastide, aleglitazar, basal insulin peglispro[a], saxagliptin
ONCOLOGY *Indications studied: breast cancer, castrate-resistant prostate cancer, colorectal cancer, leukemia, non-small cell lung cancer, lymphoma, ovarian cancer, uveal melanoma*	18	**19,856**	alisertib, cabozantinib, dacomitinib, enzastaurin, etirinotecan pegol, ganetespib + docetaxel, iniparib, lapatinib + trastuzumab, MAGE-A3, motesanib, onartuzumab, ramucirumab, selumetinib + dacarbazine, trebananib + paclitaxel, True Human™ antibodies[b], vintafolide, vosaroxin + cytarabine
PULMONARY *Indication studied: chronic obstructive pulmonary disease*	1	**16,485**	fluticasone furoate + vilanterol
CENTRAL NERVOUS SYSTEM *Indications studied: Alzheimer's disease, depression, schizophrenia*	5	**9,140**	bitopertin, edivoxetine, pomaglumetad methionil, solaneumab
AUTOIMMUNE *Indications studied: ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus*	4	**3,378**	apremilast, tabalumab, vercirnon
TOTALS	**38**	**145,684**	**34 AGENTS/COMBINATIONS**

[a]Program terminated due to focus on other drugs in portfolio and to assess effects on liver fat.
[b]Phase III trial terminated due to insufficient number of per-protocol patients available for primary endpoint analysis and protocol violations

Applied Clinical Trials, Applied Clinical Trials-08-01-2016, Volume 25, Issue 8

Reasons for Failures



Source: Tufts Center for the Study of Drug Development (CSDD)

Figure 1. The reasons attributed to Phase III clinical trial failures by percentage.

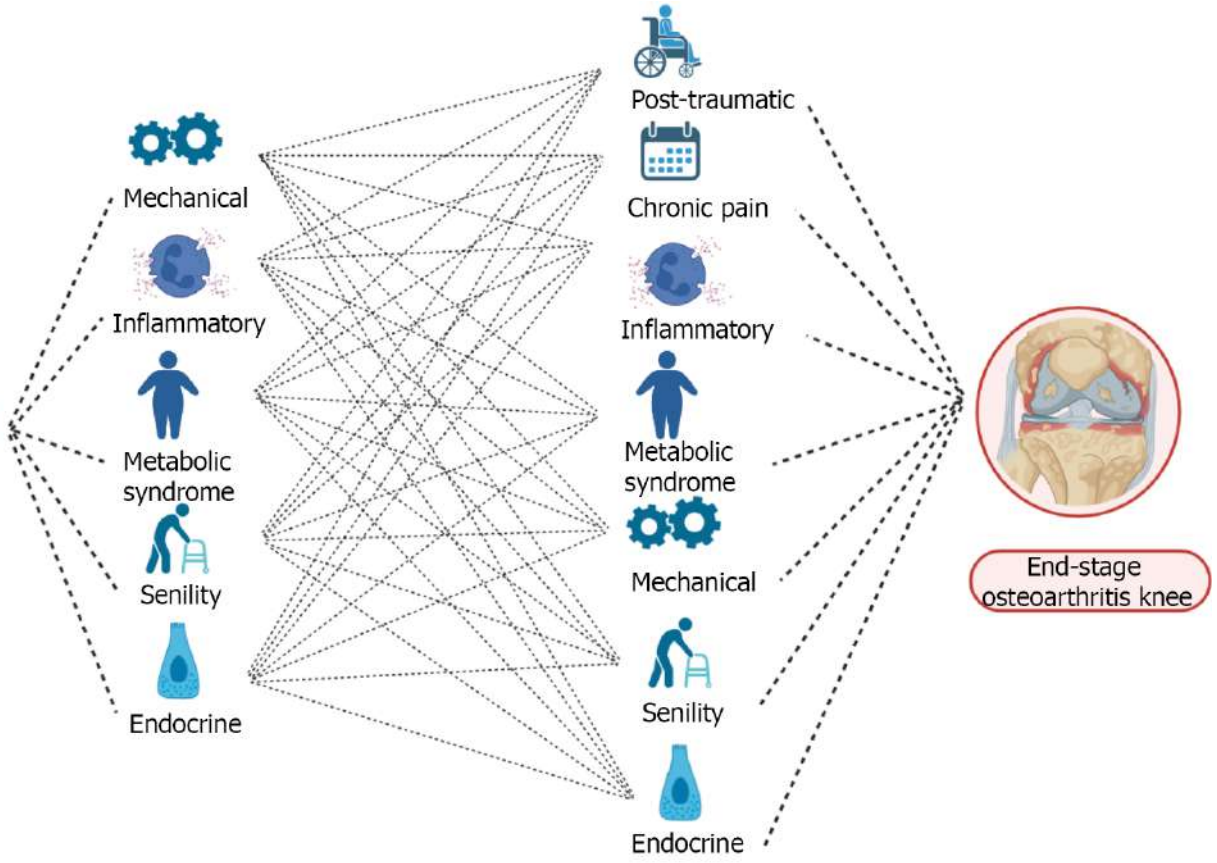
Applied Clinical Trials, Applied Clinical Trials-08-01-2016, Volume 25, Issue 8

synovial inflammatory phenotype,

- osteoporotic phenotype,
- articular cartilage degradation phenotype,
- metabolic phenotype

There are few clinical trials to stratify patients based on these phenotype-guided approaches yet.

Various OA phenotypes and endotypes is the barrier



Drugs & Aging (2019) 36 (Suppl 1):S145–S159
https://doi.org/10.1007/s40266-019-00667-8

LEADING ARTICLE

Recommendations for the Reporting of Harms in Manuscripts on Clinical Trials Assessing Osteoarthritis Drugs: A Consensus Statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

Germain Honvo[1,2] · Raveendhara R. Bannuru[3] · Olivier Bruyère[1,2] · Francois Rannou[4] · Gabriel Herrero-Beaumont[5] · Daniel Uebelhart[6] · Cyrus Cooper[2,7,8] · Nigel Arden[8,9] · Philip G. Conaghan[10] · Jean-Yves Reginster[1,2,11] · Thierry Thomas[12] · Tim McAlindon[13]

Abstract

Background There is strong evidence of under-reporting of harms in manuscripts on r
compared with the volume of raw data retrieved from these trials. Many guidelines hav
they have failed to address some important issues that would allow for standardization a
harms reporting in manuscripts remains suboptimal.

Objective The European Society for Clinical and Economic Aspects of Osteoporosis,
Diseases (ESCEO) aimed to deliver accurate recommendations for better reporting of
on anti-osteoarthritis (OA) drugs. These could help to better inform clinicians on harms
researchers conducting meta-analyses.

Methods Using the outcomes of several systematic reviews on the safety of anti-OA drug
harms have been reported in OA RCT manuscripts to date. Next, we drafted some recom
Delphi process that involved a panel of clinicians and clinical researchers to build an exp
from the ESCEO for the reporting of harms in future manuscripts on RCTs assessing ar

Results These recommendations emphasize that all treatment-emergent adverse events
account for harms reporting, with no frequency threshold, and describe how specific AEs
a list of the most relevant organ systems to be considered according to each class of drug for
section of a manuscript. Irrespective of the drug, the ESCEO recommends that total, seve
due to AEs should always be reported; guidance on the reporting of specific events pert
The ESCEO also recommends the reporting of information on drug effect on biological p

Conclusions These recommendations may contribute to improve transparency in the fie
Pharmaceutical companies developing drugs for OA, and researchers conducting clinic
with them when reporting harms-related results in manuscripts on RCTs. The ESCEO als
ESCEO recommendations in their instructions to authors for the publication of manuscri

OA phenotyping would be helpful to therapy selection and expedite the development of investigational tailored drugs directly toward variable courses of OA.

Honvo, G., Bannuru, R. R., Bruyère, O., Rannou, F., Herrero-Beaumont, G., Uebelhart, D., ... & McAlindon, T. (2019). Recommendations for the reporting of harms in manuscripts on clinical trials assessing osteoarthritis drugs: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Drugs & aging*, *36*, 145-159.

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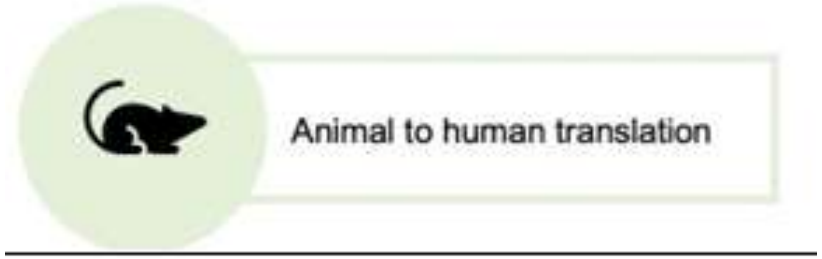
Investigations of OA susceptibility genes using genome-wide association studies (GWAS) have revealed several **gene loci** with potential for disease modification. Some of these genes, such as **GDF-5**, have been validated in animal models.

GDF5 growth differentiation factor 5 ,located in Chromosome 20
Mutations in this gene are associated with susceptibility to osteoarthritis.

Gene ID: 8200, updated on 23-Nov-2023
GDF5 in **Genome Data Viewer**



Thank you…

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