

# Recent advances in the pharmacotherapy of osteoarthritis

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## Abstract

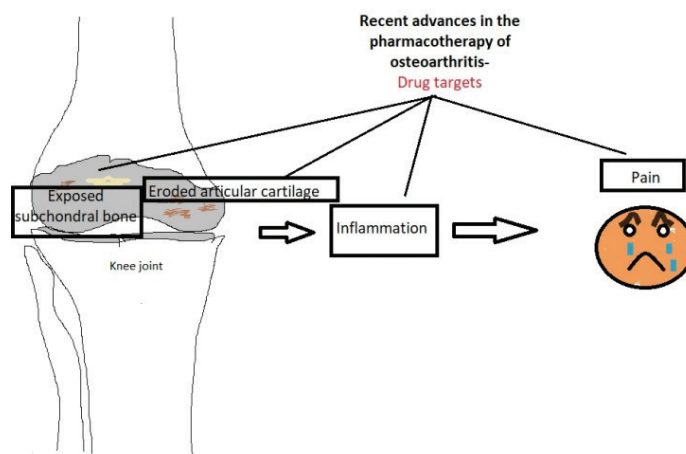
**Introduction:** Osteoarthritis (OA) is a common debilitating disease affecting the geriatric population. Management of osteoarthritis is a challenge for orthopedicians because till date there has been no such drug that can completely cure the disease or at least retard/arrest the disease progression. In addition to the currently available treatment options for OA like NSAIDs, opioids, nutraceuticals (glucosamine sulphate and chondroitin sulphate), many new drugs are being discovered or repurposed for use in osteoarthritis. Most of these recent drugs aim at retarding the disease progression rather than providing just a symptomatic relief.

**Materials and methods:** All relevant articles regarding approved new drugs and pipeline drugs for osteoarthritis published between 2012–2021 were analysed. Those included animal studies as well as clinical trials. Some older articles were also referred to, provided they highlighted any significant data. The obtained data were analysed and compiled.

**Results and discussion:** Broadly the recent drugs for OA can be classified based upon their site of action as (i) drugs targeting articular cartilage, (ii) drugs targeting inflammation, (iii) drugs targeting the subchondral bone, and (iv) drugs for relieving pain. Ranging from in vitro studies to clinical trials, these drugs are in various phases of drug discovery. Early diagnosis of OA and its management with a drug that retards disease progression rather than prescribing just a symptom reliever is very much necessary in the current situation.

**Conclusion:** Need for new drugs for OA is increasing day by day. More number of clinical trials with larger sample sizes alone can satisfy the need of disease modifying drugs for OA. This review provides a deep insight into all the recent advances in the pharmacotherapy of osteoarthritis.

### Graphical abstract:



## Keywords

osteoarthritis, pharmacotherapy, new drugs.

## Introduction

Osteoarthritis (OA) is a degenerative disease of joints. In fact, it is the most common arthritis. It mainly affects the joints that have been continuously stressed upon, such as the hip joint, the knee joint, and small joints of hands and feet. According to the WHO, it is one of the ten most disabling diseases in developed countries. It produces a significant impact on people's physical health as well as mental health. By affecting mental health, it increases the risk of suicidal tendency among affected individuals. It has become one of the leading causes of hospitalization among elderly individuals. Worldwide, 9.6% of men aged over 60 years and 18% of women aged over 60 years are suffering from symptomatic osteoarthritis. In India, the prevalence of osteoarthritis is about 28.7% (Pal et al. 2016). As the proportion of geriatric population as well as proportion of obese individuals continues to increase, the burden of osteoarthritis is increasing every year.

Because of the multifactorial etiology of the disease, there is variation in the clinical presentation as well as variation in treatment response of affected individuals. Because of these factors, it makes it difficult or almost impossible to find an effective cure for OA. Researchers around the world are putting in lots of efforts in discovering new drugs and repurposing the already approved ones so as to find a permanent solution to this problem, the magnitude of which has increased out of proportion in the recent years.

## Risk factors for development of osteoarthritis

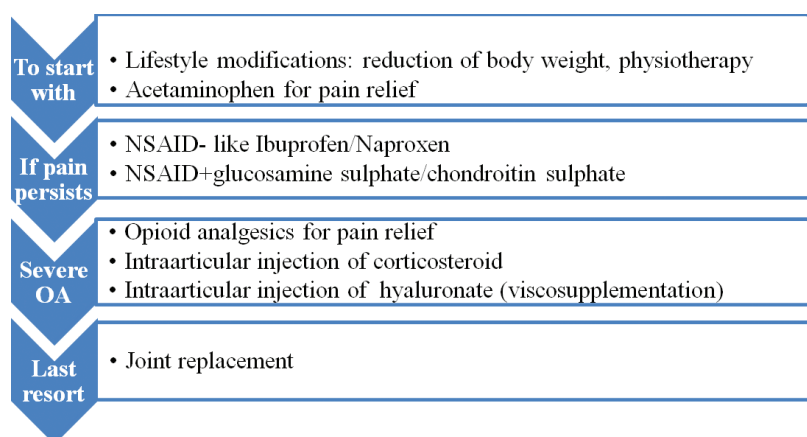
The risk factors for the development of OA include (Bortoluzzi et al. 2018):

- i. Age: The risk of developing OA increases as age advances. The peak incidence of OA is in the age group of 55 to 64 years.
- ii. Gender: The prevalence of OA is greater among women. This can be explained based on the fact that estrogen promotes the formation of proteoglycans by chondrocytes and regulates osteoblastic activity in the subchondral bone. In postmenopausal women, as the estrogen levels decline, the above functions get disrupted placing women at an increased risk of developing OA.
- iii. Obesity: As body weight increases, there is greater stress upon the weight-bearing joints, thus increasing the damage of these joints.
- iv. Genetic factors may also predispose an individual to develop OA.
- v. Excessive manual labour is another important risk factor.

## Etiopathogenesis of osteoarthritis

Osteoarthritis is a wear and tear disease. It may be primary (with no obvious underlying cause) or secondary OA (with a known underlying cause). Secondary OA may be due to any previous trauma to joints, connective tissue disorder, etc. The most commonly affected joints include hip joint, knee joint and the small joints of the hands and feet.

The articular cartilage of a joint consists of extracellular matrix (ECM), which is composed of water, collagen, proteoglycans and chondrocytes. Chondrocytes play a major role in the synthesis of the ECM components whereas proteolytic enzymes degrade them. When there is an imbalance between the synthesis and degradation triggered by trauma or inflammation or any other factor, then it ultimately results in osteoarthritis (Man and Mologhianu 2014).



**Schema 1.** Current treatment options for Osteoarthritis (Sinusas 2012).

## Materials and methods

We made a thorough search of literature to obtain all published information regarding recent advances in the pharmacotherapy of osteoarthritis. All relevant articles regarding new drugs and pipeline drugs published between 2012–2021 were analysed. Some older articles were also referred, provided they highlight any significant data. All obtained data were analysed, compiled and the newer agents were categorized into four groups and discussed in detail.

## Results and discussion

The recent drugs for the management of OA can be broadly classified depending upon their target of action as follows:

- I. Agents targeting articular cartilage
- II. Agents targeting inflammation
- III. Agents targeting subchondral bone
- IV. Agents targeting pain

### Agents targeting articular cartilage

It is a well-known fact that articular cartilage is composed of collagen and cartilage specific proteoglycan (also known as aggrecan). Collagen is degraded by matrix metalloproteinase (MMP) whereas aggrecan is degraded by aggrecanases. So, if these degrading enzymes are inhibited, it is possible to stop progression of OA.

#### *MMP inhibitors*

Out of all matrix metalloproteinases, MMP-13 is specifically found in degenerated cartilage of OA patients (Wang et al. 2004) and absent in normal healthy cartilage. Initially broad spectrum MMPs were tried for OA, which produced adverse effects in the form of joint stiffening and pain (musculoskeletal syndrome) (Wojtowicz-Praga et al. 1998).

#### *Aflapin*

It is an MMP-3 inhibitor. It is obtained from *Boswellia serrata* gum resin. It was found to decrease pain and improve physical function in OA patients (Sengupta et al. 2010).

#### *Pycnogenol*

It is an MMP-3 and MMP-13 inhibitor. It is obtained from maritime pine bark extract. It had been in use already as a herbal medication with anti-inflammatory property. It was found to reduce pain and joint stiffness in OA patients (Belcaro et al. 2008).

#### *ADAMTS inhibitors*

ADAMTS inhibitors inhibit the enzyme aggrecanase. ADAMTS-4 is another name for aggrecanase-1 and ADAMTS-5 is another name for aggrecanase-2. Out of the

two, aggrecanase-2 (ADAMTS-5) is specifically involved in cartilage degradation in OA patients (Larkin et al. 2015).

#### *GSK2394002*

It is a humanized monoclonal antibody that selectively inhibits ADAMTS-5. In vitro, ex vivo and animal studies have shown that GSK2394002 modifies the disease structure and causes alleviation of pain-related behaviour in OA (Larkin et al. 2015).

#### *Growth factors*

Growth factors are known to have anabolic effect on articular cartilage and they also promote cartilage repair.

#### *Sprifermin*

Sprifermin is a recombinant human FGF18 (Fibroblast Growth Factor 18). In preclinical studies, FGF 18 was found to stimulate chondrogenesis (Moore et al. 2005). Phase 1 trial showed that sprifermin not only promotes cartilage thickness, but also reduces cartilage loss in OA (Eckstein et al. 2015).

#### *GEC-TGF-β*

GEC-TGF-β stands for 'Genetically Engineered Chondrocytes expressing TGF-β'. Phase 2 trial with this drug showed that GEC-TGF-β produced more positive responses on IKDC (International Knee Documentation Committee Questionnaire, a knee-specific patient-reported outcome measure) and VAS (Visual Analog Scale for pain) scores (Cherian et al. 2015).

#### *BMP*

Bone Morphogenetic Protein (BMP) belongs to the TGF-β family. It plays an important role in bone cartilage homeostasis. Animal studies have demonstrated that osteochondral defects in rabbit knee can be repaired by BMP-2 delivered via viral vectors (Betz et al. 2017). But human studies lack to demonstrate the efficacy of this agent.

#### *Cathepsin K inhibitors*

Cathepsin K is an enzyme secreted by osteoclast. It is involved in bone and cartilage degradation. Thus inhibiting this enzyme can prevent the degradation process. MIV-711 is a novel *cathepsin K* inhibitor. Phase 2 trial showed that the drug causes significant reduction in disease progression. But it failed to produce a significant pain reduction (Conaghan et al. 2018a).

#### *Wnt/β-catenin signalling pathway inhibitors*

Wnt/β-catenin signalling pathway is involved in the pathogenesis of OA. SM04690, an inhibitor of this pathway, proved its potential as a DMOAD (Disease Modifying Osteoarthritis Drug) in phase 2 trial (Yazici et al. 2018).

#### *VEGF inhibitors*

Elevated levels of VEGF (Vascular Endothelial Growth Factor) are associated with OA progression and inhibition of VEGF and its receptors can prove as a potential treatment for OA (Hamilton et al. 2016).

In rabbit models of OA, intra-articular administration of **bevacizumab** (VEGF inhibitor) reduced degeneration of articular cartilage and also decreased osteophyte formation. Also, the intra-articular route of administration of **bevacizumab** was compared with an intravenous route, and the intra-articular route was found to have greater advantage (Nagai et al. 2014).

### **Diacerein**

**Diacerein** is a semi-synthetic anthraquinone derivative. It inhibits the synthesis of bone resorptive enzymes and reduces osteoclast survival (Boileau et al. 2008). It has anti-inflammatory, anti-catabolic and pro anabolic effects on articular cartilage. It was designated as SYSA-DOA (Symptomatic Slow Acting Drug for Osteoarthritis) (Pavelka et al. 2016). Other SYSA-DOA include chondroitin sulphate, glucosamine sulphate, hyaluronate, etc. The adverse effects of diacerein include soft stools, diarrhoea, skin reactions, etc.

### **NO inhibitors**

**Nitric Oxide** is a pro-inflammatory cytokine. It is a mediator of cartilage destruction in OA. **Cindunistat** (SD-6010) is an oral selective inducible NO synthase inhibitor. It was proposed to reduce joint space narrowing in OA patients; but phase 2 trial to evaluate this effect failed to show positive results (Hellio le Graverand et al. 2013).

### **COX-2 inhibitors**

COX-2 inhibitors have not only analgesic and anti-inflammatory properties, but also protective effects on cartilage. An animal study demonstrated that the COX-2 inhibitor **celecoxib** has beneficial effects in OA (Ou et al. 2012). Another COX-2 inhibitor, **etoricoxib**, was found to reduce pain and improve physical function in knee OA patients in phase 4 trial (Moss et al. 2017).

### **Agents targeting inflammation**

Both local and systemic inflammation plays a pivotal role in the pathogenesis of OA. Thus agents that have been proven to have anti-inflammatory effect have been tried for pharmacotherapy of OA.

### **TNF- $\alpha$ inhibitors**

TNF- $\alpha$  is a pro-inflammatory cytokine released at the site of articular cartilage degradation that further accelerates the damage process. Thus TNF- $\alpha$  inhibitors can slow down this process.

### **Adalimumab**

Among the monoclonal antibodies that inhibit TNF- $\alpha$ , **adalimumab** was the first to be discovered. In a RCT conducted by Wang et al. (2018), it was found that intra-articular injection of **adalimumab** was well-tolerated and more effective in decreasing the VAS pain score and WOMAC-Western Ontario and McMaster Universities Osteoarthritis Index pain score, in comparison to hyaluronic acid (Wang 2018).

### **Infliximab**

Following evidence from preclinical studies that suggested that **infliximab** can slow down cartilage degradation (Zhang et al. 2012), a pilot study was conducted in patients with erosive hand OA (Fioravanti et al. 2009), and it was found that **infliximab** has symptom relieving and disease modifying effects.

### **DLX105**

DLX105 is an antibody against TNF- $\alpha$ . Phase 2a trial with DLX105 was conducted in knee OA patients (ClinicalTrials.gov Identifier: NCT00819572). But the results are yet to be released.

### **IL-1 inhibitors**

IL-1 induces expression of MMP enzyme, thereby promoting inflammation. It also suppresses synthesis of cartilage components like collagen and proteoglycans (Goldring et al. 1988). Thus inhibition of IL-1 can retard OA progression.

### **Canakinumab**

It is a monoclonal antibody that blocks IL-1 receptors. Invitro and preclinical studies were conducted to find the effect of **canakinumab** on human osteoarthritic chondrocytes and it was found that the drug counteracts IL-1 and has chondroprotective action (Cheleschi et al. 2015). Later phase 2 trial was conducted to evaluate safety and efficacy of **canakinumab** in knee OA patients, but results are yet to be released (ClinicalTrials.gov Identifier: NCT01160822).

### **Anakinra**

**Anakinra** is another IL-1 receptor antagonist proven to have positive outcomes in OA patients (Chevalier et al. 2005; Kraus et al. 2012).

### **Gevokizumab**

This drug neutralises IL-1 $\beta$ . Phase 1 trial to evaluate effect of **gevokizumab** in erosive hand OA was conducted, but the results are yet to be released (ClinicalTrials.gov Identifier: NCT01882491).

### **ABT-981**

ABT-981 is an immunoglobulin that neutralises both IL-1 $\alpha$  and IL-1 $\beta$ . Phase I trial demonstrated that the drug significantly reduced ANC (Absolute Neutrophil Count) and serum levels of IL-1 $\alpha$ , IL-1 $\beta$  and C-reactive protein in knee OA patients (Wang et al. 2017b), thus proving its anti-inflammatory and disease modifying effects.

### **Methotrexate**

**Methotrexate** is a well known DMARD (Disease Modifying Antirheumatic Drug). It reduces both local and systemic inflammation. A phase 3 trial named PROMOTE (Pain Reduction with Oral **Methotrexate**) was conducted to evaluate efficacy of **methotrexate** in knee OA patients (Kingsbury et al. 2015), but the results are yet to be released.

## Polyphenols

Among the polyphenols that are being tried for OA management, the popular ones include **EGCG (Epigallocatechin gallate)** found in green tea and **curcumin** found in turmeric. **EGCG** slowed the progression of OA in a post-traumatic OA mouse model, thereby demonstrating its chondroprotective and anti-inflammatory properties (Leong et al. 2014). In another study conducted by Zhang et al (2016) in the post-traumatic OA mouse model, oral **curcumin** reduced OA disease progression and topical **curcumin** application relieved OA-related pain.

## Limonene and Myrcene

Both **limonene** and **myrcene** are terpenes found in essential oils. **Limonene** is found in the peels of citrus fruits. **Myrcene** is a component of cannabis, cardamom, etc. In vitro study with these compounds showed that both **myrcene** and **limonene** prevent inflammatory and catabolic responses in human chondrocytes (Rufino et al. 2015).

## Agents targeting subchondral bone

### Bisphosphonates

Bisphosphonates are the drugs of choice for postmenopausal osteoporosis. It is a matter of controversy whether these drugs can retard progression of OA or not. Studies have demonstrated that the bisphosphonates, **risedronate** (Spector et al. 2005), **clodronate** (Saviola et al. 2017), **alendronate** (Nishii et al. 2013) have beneficial effect in OA patients. However, a recent meta analysis (Vaysbrot et al. 2018) concluded that bisphosphonates neither provide symptomatic relief nor retard disease progression. Further studies are required to find out if these drugs actually have any beneficial effect or not.

### Strontium ranelate

**Strontium ranelate** is already approved for osteoporosis. Phase 3 trial to evaluate the efficacy of this drug in OA revealed that the drug has a structure-modifying effect in knee OA and also provides symptomatic relief (Reginster et al. 2013).

### SERMs (Selective Estrogen Receptor Modulators)

Osteoarthritis is common in postmenopausal women. SERMs are already in use for postmenopausal osteoporosis. Hence SERMs was tried for use in OA as well and it was found that **levormeloxifine** and **raloxifine** have beneficial effects in postmenopausal women with OA and that these drugs are particularly useful in postmenopausal women with osteoporotic OA (Lugo et al. 2014). Osteoporotic OA is associated with reduced bone mineral density and excessive remodeling of subchondral bone.

## Agents targeting pain

Pain is the ultimate problem faced by all OA patients. It severely affects their quality of life and limits their daily

activities. The agents to combat pain in current practice include acetaminophen, NSAIDs and opioids. But because of the adverse effects that occur upon the chronic use of these agents, the need to search for new alternatives has come up.

### Nerve growth factor (NGF) inhibitors

NGF is a neurotrophin whose expression is increased in inflamed tissue (Lane et al. 2010). It causes sensitization of pain receptors, thereby modulating pain perception in OA patients. Thus NGF inhibitors have been tried for pain relief in OA.

### Tanezumab

Tanezumab is an NGF inhibitor. In a recent meta analysis of 10 RCTs (Chen et al. 2017), it was found that tanezumab (in doses of 2.5 mg, 5 mg, and 10 mg) provides greater pain relief and improvement in physical function when compared to placebo. Adverse effects of the drug include peripheral neuropathy, peripheral oedema, etc.

Previously, FDA imposed a partial clinical hold on non-cancer pain-related studies with tanezumab because of serious adverse effects like osteonecrosis reported with the use of tanezumab in some studies. However, this meta-analysis concluded that the occurrence of osteonecrosis is dose dependent and low doses of tanezumab (2.5 mg, 10–25 µg/kg) is well tolerated with acceptable adverse effects only.

### Duloxetine

**Duloxetine** is a selective serotonin norepinephrine reuptake inhibitor used as an antidepressant. **Duloxetine** is approved for the management of fibromyalgia pain. Phase 3 trial with the drug suggested that **duloxetine** is efficacious for the treatment of pain in OA as well (Wang et al. 2017a).

### FX006

Currently intra-articular injection of corticosteroids is widely being used to provide pain relief in chronic OA patients. One such corticosteroid used for intra-articular injection in OA is **triamcinolone acetonide (TA)**. But rapid absorption of this drug into the systemic circulation limits its efficacy as a pain reliever.

FX006 is a novel microsphere-based extended release formulation of **triamcinolone acetonide**. It ensures that **TA** remains confined to the joint space for a longer time and also minimizes systemic exposure (Conaghan et al. 2018b). Phase 3 trial showed that FX006 provides long lasting and clinically meaningful pain reduction in moderate to severe OA.

### Tapentadol

Opioid analgesics are already in use to relieve pain in severe OA. **Tapentadol** is a relatively novel opioid analgesic with dual mechanism of action. It is a mu opioid receptor agonist as well as noradrenaline reuptake inhibitor. It has a better side effect profile when compared to the conventional opioids (Merker et al. 2012). It is associated with

**Table 1.** Summary of recent drugs for OA

SUMMARY		
Target	Drugs	Current status with respect to OA
<b>Articular cartilage</b>	Aflapin	Dietary supplement
	Pycnogenol	Dietary supplement
	GSK2394002	Pre clinical studies – positive outcome
	Sprifermin	Phase 1 trial – positive outcome
	GEC-TGF $\beta$	Phase 2 trial – positive outcome
	BMP	Pre clinical studies – positive outcome
	MIV-711	Phase 2 trial – positive outcome
	SM04690	Phase 2 trial – positive outcome
	Bevacizumab	Animal study – positive outcome
	Diacerein	Dietary supplement
	Cindunistat	Phase 2 trial – failed to show positive outcome
	Celecoxib	Animal study – positive outcome
Etoricoxib	Phase 4 trial – positive outcome	
<b>Inflammation</b>	Adalimumab	Pilot study-positive outcome
	Infliximab	Pilot study-positive outcome
	DLX105	Phase 2a trial – result yet to be published
	Canakinumab	Phase 2 trial – result yet to be published
	Anakinra	Phase 2 trial – positive outcome
	Gevokizumab	Phase 1 trial – result yet to be published
	ABT-981	Phase 1 trial – positive outcome
	Methotrexate	Phase 3 trial – result yet to be published
	Polyphenols(EGCG, curcumin)	Animal studies – positive outcome
	Limonene, Myrcene	In vitro studies-positive outcome
<b>Subchondral bone</b>	Bisphosphonates	Doubtful efficacy
	Strontium ranelate	Phase 3 trial – positive outcome
	SERMs	In vitro and Animal studies – positive outcome. May be particularly useful in osteoporotic OA
<b>Pain</b>	Tanezumab	Phase 3 trial – positive outcome
	Duloxetine	Phase 3 trial – positive outcome
	FX006	Phase 3 trial – positive outcome
	Tapentadol	Phase 3 trial – positive outcome
	Cannabidiol	Animal study – positive outcome

**Note:** GEC-TGF  $\beta$  – Genetically Engineered Chondrocytes expressing TGF- $\beta$ ; BMP – Bone Morphogenic Protein; SERMs – Selective Estrogen Receptor Modulators; EGCG – Epigallocatechin gallate.

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lesser risk of constipation, somnolence and abuse liability. Phase 3 trial showed that **tapentadol** provides more superior pain relief for OA in comparison to oxycodone (Lange et al. 2017).

### **Cannabidiol (CBD)**

A recent animal study investigated the safety and therapeutic potential of CBD for relieving arthritic pain and positive results were obtained. It was found that CBD significantly reduced the production of pro-inflammatory cytokines IL-6 and TNF- $\alpha$  while increasing the levels of anti-inflammatory cytokine, IL-10 (Verrico et al. 2020).

### **Platelet rich plasma**

A recent trial evaluated the efficacy of intra-articular injection of platelet-rich plasma in osteoarthritis, but no satisfactory results were obtained with regard to improvement of knee pain or reduction of cartilage volume loss (Bennell et al. 2021). Novel drug delivery systems, like dendrimers, microspheres and solid lipid nanoparticles that ensure efficient intra-articular drug delivery, are now being investigated (Mao et al. 2021).

## Conclusion

The need for new drugs that alter the disease progression of OA is increasing day by day. All investigational drugs for OA have been summarized in Table 1. Early diagnosis of OA and its management with a drug that retards disease progression rather than prescribing just a symptom reliever is very much necessary in the current situation. More clinical trials with larger sample sizes alone can satisfy the need of disease modifying drugs for OA.

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## Author contributions

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