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Emerging Pharmacotherapies for Osteoarthritis- A Systematic Review on Recent Development

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A B S T R A C T

Objective: The purpose of this study is to assess novel pharmacotherapies for osteoarthritis (OA) that attempt to slow disease progression and improve patient outcomes by targeting fundamental pathophysiological pathways, rather than simply relieving symptoms.

Methods: This review used PRISMA criteria to collect studies. The study included peer-reviewed articles, clinical trials, meta-analyses, and systematic reviews published between 2000 and 2023 on both traditional and innovative treatments for OA. A comprehensive PubMed search yielded publications employing keywords linked to specific OA pharmacotherapies, resulting in 76 eligible studies once exclusion criteria were applied.

Results: Conventional medications for pain management, such as NSAIDs, paracetamol, and corticosteroids, continue to be helpful, but they have severe adverse effects. Novel pharmacotherapies provide promise for disease modulation. Fibroblast growth factor 18 (FGF-18) and Wnt pathway modulators such as lorecivivint show promise in cartilage regeneration and joint health. Matrix extracellular phosphoglycoprotein (MEPE)-derived peptides and matrix metalloproteinase (MMP) inhibitors, notably selective MMP-13 inhibitors, target cartilage breakdown mechanisms and have demonstrated promising preclinical results. RNA-based treatments and aggrecanase inhibitors have also shown promise in decreasing OA progression, however clinical validation is still awaited.

Conclusion: While traditional treatments are important for symptom alleviation, new pharmacotherapies offer exciting opportunities for disease modification in OA. Continued clinical trials are required to ensure efficacy and safety. Integrating these innovative techniques with standard medicines and personalised care has the potential to transform OA therapy and improve long-term patient outcomes.

Keywords: Osteoarthritis, Pharmacotherapy, Disease Modification, Cartilage Regeneration, MMP Inhibitors.

INTRODUCTION

Osteoarthritis (OA) is a prevalent, disabling condition impacting millions worldwide, characterized by joint degeneration. It poses significant health, economic, and societal burdens, exacerbated by aging, obesity, and injuries. Radiographic evaluation, particularly the Kellgren-Lawrence grading system, remains the gold standard for diagnosis and monitoring of OA progression(1)(2).OA is the most common form of arthritis and can be classified into two categories: primary and secondary OA. Primary OA, the more prevalent type, occurs without a predisposing trauma or disease but is associated with risk factors such as age, female gender, obesity, anatomical factors, muscle weakness, and joint injury from occupational or sports activities. Secondary OA, on the other hand, arises from preexisting joint abnormalities or conditions. These predisposing factors include trauma or injury, congenital joint disorders, inflammatory arthritis, avascular necrosis, infectious arthritis, and various metabolic and genetic disorders such as Paget disease, osteopetrosis, osteochondritis dissecans, hemochromatosis, Wilson's disease, hemoglobinopathy, Ehlers-Danlos syndrome, and Marfan syndrome. Clinically, OA presents with joint pain and loss of function but can range from asymptomatic incidental findings to severe, permanently disabling conditions(3)(4).

Osteoarthritis (OA) pathogenesis involves mechanical, inflammatory, and metabolic factors leading to the structural destruction of the synovial joint. It is an active disease resulting from an imbalance between the repair and destruction of joint tissues, not merely a wear-and-tear condition. The disease begins with changes in cartilage composition, leading to its loss of integrity and increased susceptibility to physical forces. Initially, cartilage erosion occurs at the surface, progressing to deep fissures and expansion of the calcified cartilage zone. Hypertrophic chondrocytes attempt repair by increasing synthetic activity but produce matrix degradation products and proinflammatory mediators, disrupting chondrocyte function and stimulating synovial inflammation and proliferation. This process involves proliferating synoviocytes releasing proinflammatory products, causing tissue hypertrophy and increased vascularity.In the subchondral bone, turnover is increased with vascular invasion extending into the cartilage, resulting in bone remodeling and subchondral bone marrow lesions. Osteophytes form at joint margins due to endochondral ossification influenced by inflammatory factors and mechanical overload. OA is considered a heterogeneous syndrome with diverse pathways leading to joint destruction, varying by risk factors such as age, injury, and obesity. Different mechanistic subgroups include increased inflammation, mechanical overload, metabolic alterations, and cell senescence, often overlapping and requiring further validation.(5–7)

There is no known cure for OA, although joint function can be improved, pain can be reduced, and symptoms can be improved. Exercise, weight control, physical therapy, medication, and surgery are recommended by the American Academy of Orthopaedic Surgeons (AAOS) and the Osteoarthritis Research Society International (OARSI). Exercise helps joints and muscles work better, and it is recommended that overweight people lose weight. For people with symptomatic knee OA, assistive equipment such as walkers and canes are helpful. greater clinical validations are needed for complementary therapies like massage, acupuncture, and nutritional supplements. Although they are often used, painkillers and anti-inflammatory drugs may have unfavourable side effects. Reconsideration of surgery, such as arthroscopic irrigation, debridement, drilling, and microfracture, is limited to severe patients that do not improve with conservative measures. While these surgical techniques provide temporary respite, they are not long-term solutions(8–10).

METHODOLOGY

This review includes articles which were systematically collected by performing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The authors assessed all eligible studies independently. A consensus was reached if there were any cases of disagreement between the authors. This study employs a comprehensive review of existing literature, clinical trials, and meta-analyses to evaluate the efficacy and safety of conventional and newer therapies for osteoarthritis (OA). The methodology section outlines the steps taken to gather, analyze, and synthesize data on the treatments for OA, focusing on both established and emerging therapeutic approaches. A thorough literature search was conducted using database PubMed. Keywords and the article count included 6645 articles for "NSAIDs and Osteoarthritis",1062 articles for "acetaminophen and OSTEOARTHRITIS", 1593 articles for "opioids and OSTEOARTHRITIS", 2052 articles for "corticosteroids and OSTEOARTHRITIS", 2760 articles for "new pharmacotherapies for OSTEOARTHRITIS", 64 articles for "FGF-18 and OSTEOARTHRITIS", 67 articles for "Wnt pathway modulator and OSTEOARTHRITIS" 5 articles for "MEPE and OSTEOARTHRITIS",1174 articles for "MMP inhibitors and OSTEOARTHRITIS" and 419 articles for "aggrecanases and OSTEOARTHRITIS".

The study included articles which were Peer-reviewed articles, clinical trials, meta-analyses, and systematic reviews focused on OA treatment, Studies involving human subjects and only the articles written in English language. Articles published between 2000 and 2023 were considered, ensuring a comprehensive understanding of both historical and recent advancements in OA treatment. Exclusion of articles were made for Non-peer-reviewed articles, case reports, editorials, studies focusing solely on animal models without human data and for articles not available in English.

Figure 1 shows the PRISMA flow chart which details the systematic process of identifying and selecting studies for a review on newer therapies for osteoarthritis (OA). Initially, 16,317 records were identified from databases. After removing duplicates (2,543), ineligible records (285), and other irrelevant entries (1,012), 12,477 records remained for screening. Language exclusions removed 4,377 records, leaving 8,100 reports sought for retrieval. Of these, 2,864 reports were not retrieved. Subsequently, 5,236 reports were assessed for eligibility, leading to the exclusion of 1,584 non-relevant studies, 3,280 non-peer-reviewed articles, and 295 reports with unclear methodology or insufficient data. Ultimately, 76 studies were included in the review. This rigorous selection process ensures the inclusion of high-quality and relevant studies.

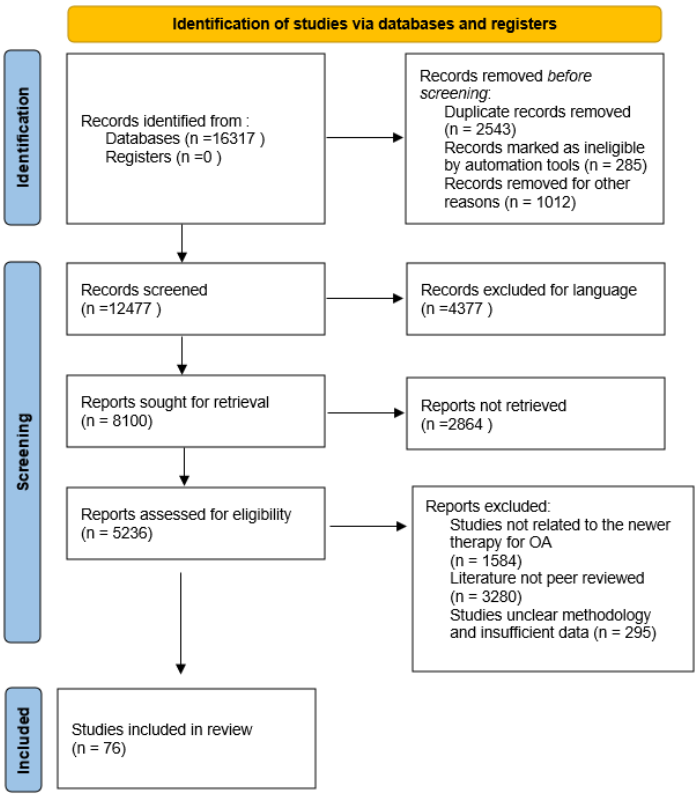

Figure 1Prisma flow chart

RESULTS

Conventional Therapies:

NSAIDs:

NSAIDs, or non-steroidal anti-inflammatory drugs, are frequently used for symptomatic knee and hip OA, particularly when acetaminophen is ineffective. These medications reduce prostaglandin synthesis and have analgesic, antipyretic, and anti-inflammatory properties by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2). Despite their effectiveness in pain relief, demonstrated by meta-analyses showing small to moderate effect sizes (0.23 to 0.35), NSAIDs are limited by significant side effects. About 30% of users experience adverse effects, with gastrointestinal (GI) complications occurring annually in 1-2% of users. Additionally, there is a higher chance of cardiovascular events such as acute myocardial infarction and kidney damage, particularly during the first week of treatment.(10,11)(12–14).

When compared to oral versions, topical NSAIDs—like diclofenac—provide comparable pain relief with fewer side effects. For individuals with knee OA who do not have any comorbidities, the Osteoarthritis Research Society International (OARSI) highly advises topical NSAIDs. Research backs up the effectiveness of topical NSAIDs in pain management with less systemic exposure, lowering the risk of cardiovascular and gastrointestinal issues.(15–17).
Although they were created to lessen GI side effects, selective COX-2 inhibitors have raised questions about safety, leading to the withdrawal of some, like rofecoxib and valdecoxib, due to cardiovascular risks. Consequently, in order to reduce side events, NSAIDs should be administered for the shortest amount of time and at the lowest effective dose, particularly in older adults with OA. The benefit-risk ratio is crucial in determining NSAID use, favoring short-term application to manage OA symptoms effectively while mitigating health risks(9).

Acetaminophen

Many guidelines suggest using acetaminophen, commonly referred to as paracetamol, as the initial line of treatment for mild to moderate osteoarthritis (OA). This over-the-counter analgesic is readily available. It acts by weakly inhibiting cyclooxygenase (COX)-1 and COX-2, essential for prostaglandin synthesis, and by strongly inhibiting COX-3, thereby reducing pain and fever. Despite its common use, its overall effectiveness is modest. Acetaminophen demonstrated statistically significant pain reduction when compared to placebo in seven randomized controlled trials (RCTs); however, it did not significantly enhance outcomes on the Lequesne or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)(18–20).

Acetaminophen is thought to be rather safe, but if taken in excess of authorized dosages, it may damage or fail the liver. The American Academy of Orthopaedic Surgeons (AAOS) advises not exceeding 3,000 mg in order to reduce liver risk,

but the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) guidelines recommend a maximum daily dose of 4,000 mg. Acetaminophen has the potential to cause hepatotoxicity and offers only modest clinical improvements in pain and function for people with osteoarthritis, according to recent meta-analyses. Consequently, OARSI's latest guidelines conditionally recommend against its use, highlighting the importance of adhering to dosage limits and avoiding long-term use to reduce side effects(21–23).

Opioids

Most guidelines advise against long-term opioid use for osteoarthritis due to the high risk of addiction and serious side effects(24). Opioids lessen pain by binding to the mu-opioid receptor and obstructing the central nervous system's pain pathway(25). However, its use is discouraged due to side effects such as constipation, headache, nausea, vomiting, dizziness, and tiredness. Based on a meta-analysis of 18 RCTs, more than 25% of patients in the opioid group discontinued due to adverse effects(26). Opioid tolerance, addiction, unintentional overdose, and even death can result from prolonged opioid usage(27).

It is strongly advised by the Osteoarthritis Research Society International (OARSI) not to take oral or transdermal opioids for OA of the knee due to these risks. Opioids are only used when first-line therapies, such as acetaminophen or NSAIDs, are unsuitable or ineffective. Opioids have a significant risk of addiction and adverse effects, which restricts their utility even though they can lessen pain intensity and have a little positive impact on physical function when compared to placebo. Because of this, opioids should only be used for refractory pain and for the shortest amount of time necessary at the lowest effective dose(24).

Corticosteroids

For moderate-to-severe pain that is not alleviated by first-line treatments, intra-articular (IA) corticosteroid injections, such as methylprednisolone acetate, triamcinolone acetate, betamethasone, triamcinolone hexacetonide, and dexamethasone, are advised. They act rapidly by targeting nuclear steroid receptors, reducing pro-inflammatory proteins, and cytokines. Reported side effects include post-injection pain, flushing, septic arthritis, and rare cases of Tachon Syndrome and osteoporosis in children with 21-hydroxylase deficiency. While the trials were generally of low quality, making the benefits uncertain and warranting further research, a Cochrane review of 27 trials with 1,767 participants indicated benefits in pain reduction and functional improvement over placebo(28–32).

Subjacent Conventional agents

Duloxetine is one of the serotonin-norepinephrine reuptake inhibitors (SNRIs) used to treat chronic musculoskeletal pain, particularly osteoarthritis (OA). For people who don't respond to first treatments like acetaminophen and NSAIDs, duloxetine is conditionally advised. Research shows that it helps with OA pain and physical function, but common adverse effects include fatigue, somnolence, gastrointestinal problems, and sexual dysfunction. To verify its safety and effectiveness, more extensive trials are required(33–35).

A vitamin D deficiency is associated with the onset and progression of OA. While some research demonstrate that vitamin D supplementation can enhance function and lessen discomfort, other studies find no appreciable advantages. Vitamin D was found to reduce pain and function loss but not stiffness or cartilage volume in a meta-analysis of four RCTs. An additional study showed weekly high-dose vitamin D2 improved pain and quality of life, but a two-year NIH-funded RCT found no benefits. Thus, vitamin D's role in OA pain modification remains uncertain, requiring further long-term trials(36–38).

Glucosamine and chondroitin sulfate, components of cartilage, are popular OA supplements. They promote cartilage health and reduce catabolic enzyme activity. Long-term use, especially glucosamine sulfate, which has preventive effects on joint space narrowing, may slow the onset of osteoarthritis. However, because of conflicting data, the American College of Rheumatology does not advise them as first therapies for OA(21,39,40).

Antioxidants are promising for OA treatment by reducing reactive oxygen species (ROS) that harm chondrocytes. Patients with knee OA have higher oxidant and lower antioxidant parameters. Antioxidant supplements, including vitamins A, E, and C, and natural extracts like turmeric, avocado, and boswellia, have shown potential in reducing pain and improving joint function. Despite these benefits, antioxidant supplements are not FDA-approved for OA treatment, and it is crucial to consult healthcare providers before use to avoid side effects and interactions with other medications. To determine the effectiveness and safety of these supplements in the management of OA, more research is required (41–44).

Newer Therapies

Fibroblast growth factor 18

FGF-18, a member of the paracrine FGF-8 subfamily, is a key regulator of cell proliferation, particularly in osteoblasts, chondrocytes, and osteoclasts. It interacts primarily with FGFR-1, -2, and -3. In osteoarthritis (OA), FGF-18 promotes

osteogenic and chondrogenic differentiation, enhancing cartilage repair and bone regeneration. Studies have shown that recombinant FGF-18 (rhFGF-18) stimulates markers like RUNX2, ALP, and COL1A1, activating the ERK1/2 and PI3K pathways, leading to osteogenic differentiation. FGF-18 also boosts the osteoinductive potential of BMP-2 by inhibiting noggin, a BMP antagonist. In animal models, FGF-18 has demonstrated improved bone and cartilage healing, making it a promising therapeutic candidate for OA management(45).

Recombinant human FGF-18, or sprifermin, has demonstrated encouraging outcomes in the treatment of osteoarthritis (OA). It promotes chondrogenesis and cartilage repair by stimulating chondrocyte proliferation and maintaining their phenotype. In vitro studies have demonstrated its ability to upregulate chondrocyte markers(46).

In a five-year phase II clinical investigation, Eckstein et al. have shown that intra-articular injection of Sprifermin can improve knee cartilage regeneration in patients with osteoarthritis (OA). Sprifermin is the first DMOAD candidate drug that can promote the healing of articular cartilage injury. Sprifermin, a recombinant human FGF-18, showed promise as a disease-modifying osteoarthritis medication (DMOAD) in phase 2 trials. Compared to a placebo, intra-articular administration of 100 µg of sprifermin every 6 or 12 months resulted in a significant increase in cartilage thickness in the femorotibial joint over a two-year period. Although there were no appreciable increases in WOMAC scores, the therapy did have a dose-dependent effect on cartilage regeneration, especially in locations with high loads carrying capacity. MRI data supported these findings, indicating enhanced cartilage thickness with sprifermin. The treatment was well-tolerated, with similar rates of adverse events across all groups, and no treatment-related deaths reported(47,48). A phase III clinical trial is now being conducted on sprifermin, and thus far, there have been no complaints of systemic or local safety problems.

Wnt pathway modulator

One area where the Wnt pathway is crucial for tissue homeostasis and regeneration is the regulation of progenitor cell differentiation in the knee joint. It preserves a narrow range of conditions necessary for chondrocyte development and operation. An increased vulnerability to osteoarthritis (OA) results from aberrant Wnt pathway activation, which skews progenitor cell development towards osteoblasts rather than chondrocytes. Lorecivivint (SM04690) inhibits dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and CDC-like kinase 2 (CLK2), which in turn affects Wnt pathway activity and may be used as a disease-modifying osteoarthritis medication (DMOAD). By enhancing chondrocyte health and lowering inflammation, this dual inhibition supports the maintenance of adequate Wntsignaling(49).

With the aim of improving joint health, locrecivivint is a novel small-molecule Wnt signaling pathway inhibitor that increases the formation of new articular cartilage, delays the degeneration of existing cartilage, and reduces joint inflammation. Phase I clinical studies (NCT02095548) suggested that it may be used as a medication to treat osteoarthritis (DMOAD). Significant reductions in pain and function were seen in phase II studies (NCT03122860), with a tendency to preserve medial joint space width (mJSW). Additional Patients treated with 0.07 mg of Lorecivivint at weeks 39 and 52 experienced a statistically significant reduction in pain when compared with placebo, according to phase II trials reported at the 2017 ACR Meeting and the 2018 EULAR Congress(50–52).

Lorecivivint underwent a Phase III clinical trial (NCT05603754) for osteoarthritis, completed by Biosplice Therapeutics in February 2024. Despite the fact that the trial's main goal of reducing pain was not achieved, participants with less severe structural disease showed effectiveness signs. Lorecivivint was deemed safe and well-tolerated. Given these findings, Biosplice plans to target earlier intervention and higher doses in future trials. On April 18, 2024, Biosplice announced plans to seek FDA and other regulatory agencies' approval for Lorecivivint, indicating ongoing efforts to bring the treatment to market(53,54).

Matrix extracellular phosphoglycoprotein (MEPE)

Another promising approach involves targeting mineralization processes in subchondral bone and cartilage. Mineralization is negatively regulated by matrix extracellular phosphoglycoprotein (MEPE), which is mostly expressed in osteocytes and odontoblasts. Two phase II clinical trials (NCT01925261, NCT03125499) have evaluated TPX-100, a 23-amino-acid peptide produced from MEPE, for the treatment of mild to moderate patellofemoral OA. When compared to the placebo, the TPX-100 treated group's KOOS and WOMAC ratings significantly improved. Nevertheless, after a 12-month period, quantitative MRI did not show any discernible structural alterations. There were no significant adverse drug-related events noted. To confirm TPX-100's safety and efficacy and ascertain its therapeutic advantages in the treatment of osteoarthritis, long-term clinical trials are required(55,56).

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases critical in osteoarthritis (OA) due to their role in degrading articular cartilage collagen. More than 20 MMPs, classified by substrates they degrade, contribute to joint destruction by releasing growth factors, inactivating proteinase inhibitors, and modulating inflammatory cytokines.

MMPs are produced by leukocytes, macrophages, endothelial cells, and connective tissue cells, including chondrocytes and synoviocytes*(57,58)*.

MMP-13 inhibitors such as ALS 1-0635 and PF152 show promise in preclinical tests for delaying the advancement of the illness since MMP-13 is particularly important in the pathogenesis of OA. However, in order to confirm their effectiveness in people, clinical trials are required. Intraarticular injections of hyaluronic acid and iron-glutathione complexes have been demonstrated to decrease MMP activity in vitro without impairing chondrocyte viability, making them one treatment option that targets MMP activity*(59)*.

Emerging therapies involve microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), which regulate MMP expression and inflammatory responses. miRNAs such as miRNA-203a, miRNA-103, and miRNA-122, and lncRNAs like SNHG1 and PVT1, have shown potential in preclinical studies to modulate MMP activity and cartilage degradation. The table 2 outlines various developments related to matrix metalloproteinases (MMPs) in the context of osteoarthritis (OA) research and treatment. In preclinical trials, selective MMP-13 inhibitors like PF152 and ALS 1-0635 have shown promise in delaying the progression of disease and minimizing cartilage damage. However, broad-spectrum MMP inhibitors, while inhibiting multiple MMPs, are associated with adverse effects, limiting their clinical use. Intra-articular injections of hyaluronic acid (HA) combined with iron-glutathione complexes have shown promise in preclinical trials by lowering MMP activity and being well-tolerated by chondrocytes. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are being investigated as potential targets for therapy, with some miRNAs being upregulated in OA and influencing MMP expression. Furthermore, in certain populations, gene polymorphisms in MMPs have been linked to an elevated risk and severity of OA. Ghrelin, an anti-inflammatory neuropeptide, shows therapeutic potential despite limitations due to its short half-life. Finally, novel synthetic molecules like 2-(8-methoxy-2-methyl-4-oxoquinolin-1(4H)-yl)-N-(3-methoxyphenyl) acetamide are being explored for their ability to down-regulate MMPs, showing promise in preclinical in vitro studies*(57)*.

While novel MMP inhibitors and RNA-based therapies show promise, they require extensive clinical trials to confirm their safety and effectiveness in managing OA.

Table 1 Development of MMP inhibitors

Development	Description	Findings	Stage
Selective MMP-13 Inhibitors	ALS 1–0635, PF152	Shown to slow disease progression and reduce cartilage damage in preclinical trials.	Preclinical trials
Broad-spectrum MMP Inhibitors	General inhibition of multiple MMPs	Associated with adverse effects like musculoskeletal syndromes, limiting clinical use.	Clinical trials
Intra-articular HA with Iron-Glutathione Complex	HA injections combined with iron-glutathione in synovial fluid	Lowered MMP activity, well-tolerated by chondrocytes, no significant difference in cellular activity.	Preclinical trials
MicroRNAs (miRNAs)	miRNA-203a, miRNA-103, miRNA-122	Upregulated in OA, increase ECM degradation and MMP-13 expression, potential targets for therapy.	Research phase
Long non-coding RNAs (lncRNAs)	lncRNA SNHG1, lncRNA PVT1	SNHG1 decreases MMP expression, PVT1 suppression reduces MMP activity and ECM degradation, potential therapeutic targets.	Research phase
CRPM as OA Biomarker	MMP-generated neoepitope of C-reactive protein	Biomarker of local and systemic inflammation in knee OA, independent of BMI.	Research phase
Gene Polymorphisms	MMP-1 rs1799750 (1G/2G), MMP-13 rs2252070 (-77G > A)	Associated with increased risk and severity of OA in specific populations.	Clinical trials
Ghrelin	Anti-inflammatory neuropeptide	Inhibits chondrocyte apoptosis, downregulates MMP-13, potential therapeutic but has limitations due to short half-life.	Research phase
Novel Synthetic Molecule (3-B2)	2-(8-methoxy-2-methyl-4-oxoquinolin-1(4H)-yl)-N-(3-methoxyphenyl) acetamide	Down-regulates MMP-13 and MMP-3, showed synergistic effect with betamethasone in vitro.	Preclinical (in vitro)

Aggrecanases

Aggrecanases are a type of metalloproteinases that selectively target aggrecan. They are often referred to as disintegrin and metalloproteinases with thrombospondin motifs (ADAMTS).Aggrecanases, in particular ADAMTS-4 and ADAMTS-5, are essential for the cartilage's aggrecan breakdown, which aggravates osteoarthritis (OA). These enzymes generate aggrecan fragments found in OA cartilage and synovial fluid, indicating their involvement in aggrecan catabolism. While ADAMTSs are newly discovered, their biological and pathological roles in cartilage degradation in vivo are not fully understood. Elevated levels of MMPs, also involved in aggrecan breakdown, are found in OA cartilage. Understanding the precise function and regulation of these enzymes could aid in developing targeted therapies to prevent cartilage matrix degradation in OA(60).

Phase 1 clinical trials (NCT00454298 and NCT00427687) involving AGG-523, the first oral aggrecanase inhibitor that specifically targets ADAMTS-4 and ADAMTS-5, were discontinued for undisclosed reasons. Using explant models of cartilage and synovial joint tissue, the anti-ADAMTS-5 nanobody®, M6495, showed cartilage protection in vitro. It is presently being assessed in phase I (NCT03224702) and phase Ib (NCT03583346) clinical trials(61,62).

Nerve growth factor(β-NGF) antibody

Nerve Growth Factor (NGF) plays a significant role in the pathogenesis of osteoarthritis (OA) pain by facilitating peripheral and central sensitization. Elevated levels of NGF are observed in synovial specimens from OA patients, correlating with pain presence. NGF sensitizes nociceptors and promotes neuronal sprouting, contributing to mechanical hyperalgesia and chronic pain. It also induces ectopic nerve sprouting and remodeling, potentially forming nonmalignant neuroma-like formations. Clinical trials of NGF antibodies, such as tanezumab, fulranumab, and fasinumab, have demonstrated efficacy in reducing OA pain by targeting NGF, highlighting its pivotal role in OA pain mechanisms(63).

Therapeutic monoclonal antibodies against nerve growth factor (NGF) show promise in treating osteoarthritis (OA) pain. The most researched anti-NGF antibody is tanezumab, created by Pfizer and Lilly, which has demonstrated notable pain alleviation in clinical trials. Tanezumab was found to considerably reduce pain in a research involving 450 patients with osteoarthritis (OA) when compared to a placebo. However, it was also linked to an increased risk of adverse events, including upper respiratory infections and headaches, as well as instances of OA that progressed quickly, particularly when paired with NSAIDs. Consequently, trials were resumed with restricted NSAID use and tanezumab doses capped at 5 mg(64,65).

Fulranumab and fasinumab are other NGF antibodies in clinical development. Although fulranumab shown effectiveness, Janssen stopped it in 2016. Phase 3 trials for futinumab have demonstrated dose-dependent hazards of rapid development of osteoarthritis. In 2017, the FDA designated tanezumab as Fast Track, accelerating the review process for both OA and persistent low back pain(59).

Tanezumab, an investigational humanized monoclonal antibody targeting β-NGF, has shown significant efficacy in clinical trials for osteoarthritis (OA) pain. Tanezumab considerably decreased knee discomfort and enhanced overall assessments in a sizable randomized experiment as compared to a placebo. Tanezumab was shown to be superior than NSAIDs and opiates in phase III trials, with standardized effect values ranging from 0.22-0.24. At lower doses (≤2.5 mg), tanezumab had equal efficacy with fewer side effects, despite a larger prevalence of adverse events, such as quickly advancing osteonecrosis and OA at higher doses. These findings highlight tanezumab's potential as a novel treatment for moderate to severe osteoarthritis pain; however, on October 26, 2021, Pfizer Inc. and Eli Lilly and Company announced that they were discontinuing their global clinical development program because of regulatory reviews of tanezumab for osteoarthritis conducted by the US Food and Drug Administration and the European Medicines Agency(59,66).

Retinoic Acid-Related Orphan Receptor Alpha's Inverse Agonist (RORα)

Osteoarthritis (OA) is mostly a result of the interaction between ROR and cholesterol metabolism, with the CH25H-CYP7B1-RORα axis showing cartilage-specificity. Cholesterol and its oxysterol metabolites have the ability to activate RORα, a downstream target of the CH25H-CYP7B1 axis. This activation results in the overexpression of MMP3, MMP13, and ADAMTS5, all of which are involved in the breakdown of cartilage in osteoarthritis. Studies show that mice with severe OA are more likely to have double knockouts of INSIG1 and INSIG2, which increase chondrocyte cholesterol production. Furthermore, compared to a regular diet in mice models, a high-cholesterol diet raises serum cholesterol levels and exacerbates OA, according to recent studies. Additionally, the treatment of SR3335, an inverse agonist of RORα, intra-articularly not only inhibits the upregulation of MMP3 and MMP13 caused by cholesterol and its metabolites, but also significantly mitigates cartilage degradation caused by RORα overexpression or medial meniscus surgery. These results imply that new therapeutic approaches for the management of OA may be available by focusing on RORα and cholesterol metabolism(67,68).

Transforming Growth Factor Beta

In osteoarthritis (OA), elevated active TGF-β levels in joint tissues, which are usually not exposed to such high concentrations, drive significant changes. These include the activation of the Smad1/5/8 pathway in chondrocytes, leading to chondrocyte hypertrophy and loss of cartilage protection. In the subchondral bone, high TGF-β levels contribute to accelerated remodeling and osteophyte formation, while also promoting synovial fibrosis and inflammation. The dual role of TGF-β in both promoting inflammation and potentially having anti-inflammatory effects complicates its overall impact on OA progression, indicating a need for context-specific therapeutic strategies(69).

Several studies indicate a correlation between serum TGFβ concentrations and osteoarthritis (OA) severity, though this is not consistently observed. TGFβ1 levels have been associated with OA severity and progression, with higher levels linked to increased Kellgren-Lawrence grades. Greek studies found TGFβ2 and -3 levels significantly higher in OA patients, correlating with disease severity and WOMAC scores. However, some studies, such as those by Nelson et al., did not find significant correlations. Variations in measurement methods, patient populations, and TGFβ's sticking properties may account for inconsistent findings. Elevated TGFβ levels might reflect joint damage rather than being the cause(70).

High levels of active TGF-β1 lead to increased nestin-positive mesenchymal stem cell (MSC) clusters, which contribute to abnormal subchondral bone formation and increased angiogenesis. In mouse models, knockout of the TGF-β type II receptor (TβRII) in nestin-positive MSCs inhibited OA development. Additionally, inhibiting TGF-β1 signaling through the injection of a TGF-β type I receptor inhibitor (SB-505124) or the implantation of an antibody to TGF-β (1D11) in alginate beads into subchondral bone effectively protected against OA degeneration. These findings suggest that targeting TGF-β1 signaling pathways holds promise for OA treatment. The TGF-β inhibitor is considered a potential new target for future drug development in OA therapy. The promising results from animal studies have sparked interest in exploring TGF-β inhibitors in clinical trials, aiming to develop effective treatments that can prevent or slow the progression of OA by targeting its underlying mechanisms. This approach could lead to novel therapeutic strategies that improve the quality of life for patients with OA(71).

Bone Morphogenetic Protein-7 (BMP-7)

The TGF-β superfamily member BMP-7, sometimes referred to as OP-1, has received FDA approval for spinal fusion and bone non-union treatment. It is essential for preserving and rebuilding bone and cartilage as well as for embryogenesis. BMP-7 stimulates the creation of extracellular matrix elements unique to articular cartilage, such as collagen type II and aggrecan, without inducing chondrocyte enlargement or the synthesis of proteins associated to bone. Furthermore, BMP-7 controls the expression of other TGF-β/BMPs and growth factors including IGF-1(14,72,73).

BMP-7 (OP-1) therapy in osteoarthritis (OA) leverages its anabolic effects on cartilage and its ability to regulate key growth factors. BMP-7 enhances the synthesis of cartilage-specific extracellular matrix components, such as collagen type II and aggrecan, without causing chondrocyte hypertrophy or bone-related protein production. It also modulates the expression of growth factors like IGF-1 and TGF-β/BMPs, contributing to cartilage repair and regeneration. In OA, BMP-7 helps counteract cartilage degradation and inflammation, promoting tissue homeostasis and reducing symptoms. Clinical trials have shown BMP-7 can improve pain and joint function, but further research is needed to confirm its efficacy and long-term benefits for OA treatment(74).

Intraarticular injections of BMP-7 at dosages of 0.1 and 0.3 mg decreased WOMAC pain ratings and enhanced the OARSI response rate compared to placebo, whereas a 1 mg dose was associated with injection site discomfort in a Phase I, multi-center, placebo-controlled RCT of BMP-7. Similar to those in the placebo group, the majority of the BMP-7 group's adverse events were mild to severe in nature(75).

Mesenchymal stem cells

The controversy surrounding MSCs in OA treatment, often labeled as 'quack medicine', necessitates clarity through robust evidence. Recent systematic reviews analyzed 18 clinical trials, indicating symptom improvement at 12 and 24 months post-MSC intervention. However, when considering only RCT data, MSC treatment failed to demonstrate superiority. Publication bias and methodological heterogeneity were evident, with adverse events reported in seven trials, predominantly local swelling and transient pain. Structural effects remain inconclusive, suggesting a dose-response relationship and limited efficacy in advanced disease stages. Rigorous, well-powered RCTs are essential for definitive conclusions in MSC therapy for OA(76,77).

DISCUSSION

The study evaluated various therapeutic approaches for managing osteoarthritis (OA), focusing on both conventional and newer therapies. Table 2 shows the mechanism advantages and drawbacks of conventional therapy. Among conventional

treatments, NSAIDs showed effectiveness in pain relief but were limited by significant gastrointestinal, renal, and cardiovascular side effects, highlighting the importance of cautious, short-term use. Acetaminophen, despite being a first-line treatment, demonstrated minimal clinical improvement and potential hepatotoxicity, leading to conditional recommendations against its long-term use. Opioids, while effective in pain reduction, posed high risks of addiction and severe adverse effects, restricting their recommendation to cases unresponsive to other treatments. Corticosteroid injections provided temporary pain relief, but their benefits were uncertain due to the low quality of evidence and potential side effects.

Table 2 Conventional Therapy

Therapy	Mechanism of Action	Advantages	Disadvantages
NSAIDs	Inhibit COX enzymes, reducing inflammation	Effective pain relief	Gastrointestinal, cardiovascular, renal side effects
Acetaminophen	Analgesic, weak anti-inflammatory	Safe in moderate doses, effective for mild pain	Hepatotoxicity at high doses
Opioids	Bind to opioid receptors, reducing pain perception	Strong pain relief for severe pain	Risk of addiction, tolerance, constipation, respiratory depression
Corticosteroids	Anti-inflammatory	Rapid relief of severe inflammation	Joint damage with repeated use, systemic side effects

Table 3 describes about the varies newer therapy regimen available. Newer therapies demonstrated promising results. Fibroblast growth factor 18 (FGF-18), particularly Sprifermin, showed potential in promoting cartilage regeneration and increasing cartilage thickness, although clinical improvements in pain and function were not significant. The Wnt pathway modulator Lorecivivint showed efficacy in reducing pain and improving joint health, with ongoing efforts to optimize its use in early OA stages. Matrix extracellular phosphoglycoprotein (MEPE)-derived peptide TPX-100 improved pain and function in patellofemoral OA but lacked measurable structural changes. Matrix metalloproteinase (MMP) inhibitors, including selective MMP-13 inhibitors and RNA-based therapies, demonstrated preclinical success in slowing cartilage degradation and OA progression, though clinical validation is needed. Aggrecanase inhibitors, such as AGG-523 and anti-ADAMTS-5 nanobody M6495, showed potential in protecting cartilage, though clinical trials were incomplete.

Table 3: Description on newer therapies for OA

Therapy	Mechanism of Action	Advantages	Disadvantages
FGF-18	Promotes cartilage repair	Potential to regenerate cartilage	Still in clinical trials, long-term effects unknown
Lorecivivint (SM04690)	Modulates Wnt pathway to inhibit cartilage degradation	Disease modification potential	Limited clinical data, under investigation
MEPE-derived peptides	Inhibits MEPE to protect cartilage	Promotes cartilage health	Early stage research, efficacy not fully established
MMP inhibitors	Inhibits matrix metalloproteinases to reduce cartilage breakdown	Potential to slow disease progression	Safety and long-term efficacy concerns
Aggrecanase inhibitors	Inhibits enzymes degrading aggrecan in cartilage	Protects cartilage structure	Limited data on long-term benefits and safety

The evolving landscape of osteoarthritis (OA) management points towards a more personalized and targeted therapeutic approach. Future research should focus on enhancing the understanding of OA pathophysiology to develop therapies that not only alleviate symptoms but also halt or reverse disease progression. Integration of genetic, molecular, and imaging biomarkers could facilitate early diagnosis and tailor treatments to individual patient profiles. The development of disease-modifying osteoarthritis drugs (DMOADs) is promising, with therapies like FGF-18, Lorecivivint, and MMP inhibitors showing potential in preclinical and early clinical trials. These innovative treatments could transform OA management by addressing the underlying causes of cartilage degradation.

In summary, while conventional therapies remain essential for symptom management, newer treatments show potential for disease modification and improved outcomes in OA, warranting further clinical trials to validate efficacy and safety. Furthermore, advancements in regenerative medicine, including stem cell therapy and tissue engineering, hold significant promise. Combining these approaches with precision medicine strategies could lead to breakthroughs in cartilage repair and regeneration. Additionally, exploring the role of lifestyle modifications and non-pharmacological interventions, such as exercise and weight management, in conjunction with pharmacological treatments could enhance overall patient outcomes.

Conclusion

The study underscores the limitations and potential of current and emerging OA therapies. Conventional treatments, such as NSAIDs, acetaminophen, opioids, and corticosteroids, remain crucial for symptom management but come with significant risks and side effects. In contrast, newer therapeutic approaches like FGF-18, Wnt pathway modulators, MEPE-derived peptides, MMP inhibitors, and aggrecanase inhibitors offer promising avenues for disease modification and improved patient outcomes. While these innovative treatments are still under investigation, their potential to address the underlying mechanisms of OA and promote cartilage health represents a significant advancement in the field.

The future of OA treatment lies in a multifaceted approach that combines symptom relief with strategies aimed at modifying disease progression. Continued research, clinical trials, and advancements in biotechnology are essential to realize the full potential of these therapies. By integrating traditional and novel treatments, personalized medicine, and lifestyle interventions, we can aspire to achieve better quality of life for OA patients and mitigate the burden of this debilitating disease.

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