



# New Developments in Clinical Trials for Osteoarthritis: Are We Closer to Improving Pain Management and Disease Modification?

## Editor's Pick

My editor's pick for this issue is an insightful review article in which the authors discuss the future of therapeutic agents in osteoarthritis, targeting inflammation, pain, and cartilage regeneration. Though there are currently no effective disease-modifying anti-rheumatic drugs licensed for the treatment of osteoarthritis, which affects 10 million people in the UK, Sofat and colleagues concluded that the present Phase II and III trials show promising results for the future.

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## Abstract

Osteoarthritis (OA) is a chronic condition that can lead to pain, disability, and loss of function. There are currently few pharmacological treatments, and none are disease modifying. It is important to identify new treatments to reduce associated morbidity, as well as high costs to the individual and society. OA pathogenesis involves the cartilage, synovium, and bone, with many mediators in the immune system implicated in this process. These provide several targets for pharmacotherapy that can be divided into treatments that target pain or disease-modifying drugs that aim to maintain the joint. Previous OA trials conducted have failed to either meet efficacy or safety measures. Notably, anti-nerve growth factor drugs that were superior to placebo had several adverse events that subsequently limited their usage. The aim of this paper is to highlight the current treatments under investigation that are in Phase II and III of development.

This review searched trials that have been registered on [clinicaltrials.gov](https://clinicaltrials.gov) with the term “osteoarthritis” and a primary completion date of 2021 or after that are in Phase II and III. This identified 252 studies, 52 of which were included in the review after screening and eligibility checks, that were then categorised as either targeting pain and inflammatory pathways or disease-modifying osteoarthritis drugs. Two further papers were included as they present two distinct therapies for hand OA. The results showed numerous avenues in development, with promising results, and provides hope to reduce the global burden of morbidity. It is important that these treatments are affordable for this chronic condition.

## Key Points

1. Osteoarthritis (OA) is a common arthritic condition, affecting 10 million people in the UK alone. There are currently no effective disease-modifying anti-rheumatic drugs licensed for the treatment of OA.
2. This study was a narrative review of clinical trials identified from clinical trials databases to identify Phase II and III studies with a primary completion on or after December 2021. The authors identified 52 studies categorised as either targeting pain modulation /inflammatory pathways or disease-modifying OA drugs that were reviewed in this article.
3. There is a strong pipeline of drug discovery with Phase II and III trials of new therapeutic agents in OA that are targeting several pathways including inflammation, pain, and cartilage regeneration.

## INTRODUCTION

Osteoarthritis (OA) is the most common arthritis worldwide, causing pain, disability, and loss of function due to chronic joint disease.<sup>1</sup> The most affected joint is the knee, followed by the hand and hip.<sup>1</sup> Knee OA makes up 85% of the clinical burden of disease.<sup>2</sup> There is a higher prevalence of radiologically evidenced OA compared to symptomatic OA.<sup>2</sup> Significant costs are associated with the disease, including direct costs such as medication and surgery, but also indirect costs due to early retirement and loss of work.<sup>2</sup> There remains a huge unmet need to develop new treatments for OA. This narrative review will discuss the pathogenesis of OA, current management, and clinical trials exploring new treatment avenues.

### Pathogenesis

OA is an active disease in which there is an imbalance of repair and destruction of the whole joint.<sup>2</sup> It involves all structures, including hyaline articular cartilage, subchondral bone, capsule, synovium, and periarticular muscles.<sup>2</sup> It is theorised there are numerous subtypes, such as neuropathic, inflammatory, and metabolic, which allow for different treatment targets.<sup>3</sup>

In the early stages of damaged cartilage repair, increased chondrocyte activity is apparent. By-products of this increased activity include matrix degradation compounds and pro-inflammatory mediators, which lead to dysregulation of chondrocyte function. These by-products affect the adjacent synovium leading to tissue hypertrophy and increased vascularity.<sup>4</sup> There is a predominance of macrophages in the synovitis seen in OA, reflecting a more focused innate immune response compared to rheumatoid arthritis.<sup>5</sup> The effects on subchondral bone lead to increased bone turnover and subsequent vascular proliferation invades the cartilage. The development of subchondral bone marrow lesions (BML) is observed.<sup>2</sup> BMLs can be best visualised on T2-weighted, fat-saturated MRIs as hyperdense diffuse lesions. There is a consensus now that the presence and frequency of BMLs correlate with pain.<sup>6</sup> The abnormal loading leads to damage and remodelling, evidenced on histological analysis by subchondral bone trabecular thickening, cysts, angiogenesis, and new nerve formation.<sup>7</sup>

Degradation of cartilage is caused by IL-1 $\beta$ , which binds to synoviocytes, leading to the production of matrix metalloproteinases,

cyclooxygenase-2, prostaglandin E2, and nitric oxide. This accelerates degradation via nuclear factor kappa-B and MAPK signalling pathways. Cartilage destruction is further enhanced by IL-1 $\beta$  triggering downstream gene expression of proteolytic enzymes including the disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), also known as aggrecanases. TNF- $\alpha$  also plays a role in coordinating an inflammatory response and release of matrix metalloproteinases. Hence, there are many pro-inflammatory cytokines involved in OA pathogenesis that could be potential targets for novel treatments.

### Current Treatment Therapies

There is good consensus on management strategies from stakeholders.<sup>8,9</sup> First-line treatment is non-pharmacological. This includes education, exercise, weight loss, and walking aids. Encouragement of self-management is important; patient outcomes improve if interventions around non-pharmacological measures are used.<sup>10</sup> Key messages to communicate to people with OA are about treatment approaches, the disease pathophysiology, and imaging.<sup>11</sup> One important message is the importance of a personalised exercise plan, best delivered by a therapist, as they can consider the complexities of a patient's situation. Two systematic reviews found exercise reduces pain, improves physical function, and improves quality of life.<sup>12,13</sup> Another systematic review found no radiographic progression of disease or increase in pain in elderly patients who undertake low-impact exercise.<sup>14</sup>

Topical nonsteroidal anti-inflammatory drugs (NSAID) are recommended. A systematic review of 43 studies found NSAIDs superior to a placebo, with a 0.3 effect size for relieving pain and 0.35 for improving function. In the study and general population, no serious gastrointestinal and renal side effects were reported.<sup>15</sup>

Paracetamol is no longer seen as first-line after it was found to be only minimally effective when compared to placebo, while still having an adverse effect profile.<sup>16</sup> While paracetamol can be useful in clinical practice, it should be used carefully to

avoid unwanted side-effects. Oral NSAIDs are effective in managing pain; however, they have significant cardiovascular and renal side effects that need to be noted in certain patient groups. Due to these side effects, NSAIDs should be started after medical advice and for limited time periods. Guidelines suggest using concurrent proton-pump inhibitors or cyclooxygenase-2 inhibitors in appropriate patients without co-existing conditions.<sup>17</sup>

Duloxetine has been found to be efficacious in the treatment of OA.<sup>18</sup> Centrally acting analgesics, such as nortriptyline, were compared to a placebo in a randomised control trial (RCT) in New Zealand, where it was found to have no benefit at 14 weeks for reducing pain.<sup>19</sup>

Intra-articular steroids are used for short term pain relief and as an adjunct therapy. However, regular injections are not recommended as it is associated with a greater loss of cartilage volume when compared to placebo, which was shown in a 2-year study using triamcinolone.<sup>20</sup> Current guidelines do not favour the repeated use of corticosteroid injections for OA.

### Recent Failed Treatment Targets

Many theoretical treatments have been tried and tested, with a failure to translate into clinical efficacy from animal models.<sup>21</sup> A meta-analysis by Singh et al.,<sup>22</sup> looked at nine studies that used colchicine in RCTs for hand and knee OA and found there was no significant improvement in pain or function.

Nerve growth factor (NGF) is implicated in pain modulation in OA.<sup>23</sup> NGF enhances neurotropic and nociceptive pathways by interacting with its receptor, tropomyosin receptor kinase A (TrkA), modulating the pain pathway. Due to its role in the mediation of pain, pain therapies using monoclonal antibodies have been developed (e.g. tanezumab, fulranumab, and fasinumab). Tanezumab was tested in a Phase III trial and was shown as superior compared to a placebo.<sup>23</sup> The safety profile of NGF agents has been questioned, as a dose-dependent side effect is the development of rapidly progressive osteoarthritis (RPOA).<sup>24,25</sup> This

has been related to the co-prescription of NSAIDs.<sup>24,25</sup> One possible hypothesis for this side effect is that reduction in pain leads to increased weight bearing, causing increased tissue damage to the joint. Concerns over RPOA have led to NGF-neutralising antibodies' use being limited to those with palliative diagnoses.<sup>26</sup>

TrkA inhibitors are also being investigated due to their role in the same pathway. Despite promising pre-clinical trials, a Phase II trial using an oral TrkA inhibitor failed to meet its primary endpoint of an improvement of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.<sup>27</sup> A proof-of-concept study found an intra-articular injection of a TrkA inhibitor to be effective in significantly reducing WOMAC scores at 4 weeks; however, at 12 weeks the difference was no longer statistically significant. Comparably, intra-articular steroid injections demonstrated joint pain reduction for a maximum of usually 3 weeks.<sup>28</sup> Although, 67.3% of those who received the treatment had injection joint inflammatory reactions.

The paper proposes that in the clinical setting this could be masked or ameliorated by co-prescription of other analgesic medication.<sup>28</sup> Unlike NGF inhibitors, no damage to the joints or evidence of RPOA was noted at the end of the trial.<sup>28</sup>

Since there are currently no disease-modifying drugs available to treat OA, there has been a large growth in clinical trials investigating novel therapeutics for OA, which will be discussed further in this review.

## METHODS

The authors conducted an electronic search of clinicaltrials.gov to identify clinical trials. It was chosen as the most comprehensive database for clinical trials. This was a structured search, limited to trials in Phase II and III and with a completion date on or after December 2021 to keep the review current. Initially, studies that were not regarding osteoarthritis and its treatment were excluded. A focus was put on pharmacological trials, and trials that were

addressing gene therapy/mesenchymal stem cells were removed as there was a limited word count and this could be covered in a future larger review. The exclusion criteria also included existing therapies, as they are well understood. The authors sought to describe the compounds' mechanism of action and target receptors. Where possible they discussed the merits of the trials, the foundation on which the trial was chosen (previous Phase I data).

The search term "osteoarthritis" was used and all Phase II and III trials with a primary completion on or after December 2021 were included. They identified 252 studies in total. Trials that were terminated, withdrawn, or whose status was unknown were excluded. Trials that were beyond the scope of this review were gene therapy, mesenchymal stem cells, and surgery trials, which were excluded. They also excluded trials of non-pharmacological management of OA. The 52 remaining studies are discussed in this study. Important trials that were published during this review but not available on clinicaltrials.gov are also discussed (Figure 1).

## RESULTS

The search yielded 52 studies, which were categorised as either targeting pain modulation/inflammatory pathways or disease-modifying osteoarthritis drugs. They are summarised in Table 1 with their mechanism of action and drug names.<sup>29-80</sup>

### Treatments Targeting Pain and Inflammation

There are nociceptive pain receptors in the synovium and joint capsule but not in the cartilage. Pain sensitisation is indicated in OA joints, showing evidence of plasticity, as in normal ageing joints the number of nociceptive receptors should decrease. Pain pressure thresholds are decreased in people with OA, indicating central sensitisation.<sup>81-83</sup>

Botulinum Toxin Type A has a role in pain modulation. A systematic review in 2019 showed that at 4 and 8 weeks there are benefits compared to placebo in Visual Analogue Scale (VAS) and WOMAC.<sup>84</sup> A

**Table 1: Summary of potential therapies under investigation with a completion date in 2021 or later.**

Agent(s)	Target	Effect	Clinicaltrials.gov Identifier
Adalimumab	Anti-TNF	Anti-inflammatory	NCT02471118 <sup>29</sup>
Amobarbital	Reduction of reactive oxygen species	Less cartilage destruction	NCT04589611 <sup>30</sup>
Bisphosphonates	Osteoclast inhibition	Articular preservation	NCT04303026 <sup>31</sup> NCT06263517 <sup>32</sup>
Botulinum toxin A	Neuromuscular junction	Pain modulation	NCT02832713 <sup>33</sup>
Canakinumab	Monoclonal antibody against IL-1 $\beta$	Anti-inflammatory	NCT04814368 <sup>34</sup>
Cannabinoid	Targets CB1 found in the CNS	Pain modulation	NCT04992624 <sup>35</sup> NCT03693833 <sup>36</sup> NCT05020028 <sup>37</sup> NCT06234631 <sup>38</sup>
Clitazol	PDE 3	Prevents cartilage destruction	NCT04789837 <sup>39</sup>
CNTX-6970	CCR2 receptor antagonist	Pain reduction	NCT05025787 <sup>40</sup>
DFV890	Oral NLRP3 inhibitor	Anti-inflammatory	NCT04886258 <sup>41</sup>
Growth Hormone	Stimulates insulin like growth factor-1	Chondrocyte regeneration	NCT06354023 <sup>42</sup>
GSK-3858279	Anti-CC17, prevents chemotaxis of monocytes	Less cartilage reduction	NCT05838742 <sup>43</sup>
Iguratimod	Small molecule NF- $\kappa$ $\beta$ inhibitor	Reduced inflammatory response	NCT05216757 <sup>44</sup>
LEVI-04	NGF and other neutrophins	Pain modulation	NCT05618782 <sup>45</sup>
LNA043	ANGPTL3 protein mimetic	Chondrocyte stimulation	NCT03275064 <sup>46</sup> NCT04864392 <sup>47</sup>
Lorecivivint	WNT signalling modulation	Chondrocyte stimulation	NCT04520607 <sup>48</sup> NCT03928184 <sup>49</sup> NCT05603754 <sup>50</sup> NCT04385303 <sup>51</sup>
LY3016859	Monoclonal antibody that binds to epiregulin and TNF- $\alpha$	Improved pain profile	NCT04456686 <sup>52</sup> NCT05986292 <sup>53</sup>
LY3526318	TRPA1 antagonist	Pain modulation	NCT05080660 <sup>54</sup> NCT05986292 <sup>53</sup>
LY3556050	Somatostatin receptor subtype 4	Pain modulation	NCT04627038 <sup>55</sup> NCT05986292 <sup>53</sup>
LY3857210	P2XY receptor inhibitor	Reduced inflammatory response	NCT05630196 <sup>56</sup> NCT05986292 <sup>53</sup>
MEDI7352	Targets TNF- $\alpha$ and NGF	Pain modulation	NCT04675034 <sup>57</sup>
Metformin	AMP-activated protein kinase	Pain modulation and chondrocyte regeneration	NCT04767841 <sup>58</sup> NCT05638893 <sup>59</sup> NCT06126029 <sup>60</sup> NCT06231758 <sup>61</sup>
MM-II	Joint lubrication	Pain reduction	NCT04506463 <sup>62</sup>
Oxytocin	Endogenous hormone targeting parasympathetic function	Chondrogenesis	NCT03878589 <sup>63</sup> NCT04431206 <sup>64</sup>

Pentosan Polysulfate Sodium	Anticoagulant heparin analogue	Chondrogenesis	NCT04809376 <sup>65</sup>
Plasma Rich Platelets	Several targets	Regeneration and reduced inflammatory response	NCT05737173 <sup>66</sup> NCT03889925 <sup>67</sup> NCT05824806 <sup>68</sup> NCT05160441 <sup>69</sup> NCT05742763 <sup>70</sup> NCT05657496 <sup>71</sup> NCT04333160 <sup>72</sup> NCT06329492 <sup>73</sup>
Semiglutide	GLP1 mimic	Reduced inflammatory response	NCT05064735 <sup>74</sup>
Teriparatide	PTH receptor	Chondrocyte regeneration	NCT03072147 <sup>75</sup>
Resiniferatoxin	TRPV1 agonist	Pain modulation	NCT05248386 <sup>76</sup> NCT05449132 <sup>77</sup> NCT05377489 <sup>78</sup> NCT04885972 <sup>79</sup>
QUC398	ADAMTS5 inhibitor	Chondrocyte preservation	NCT05462990 <sup>80</sup>

ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; AMP: adenosine monophosphate; ANGPTL3: angiopoietin-like 3; CCR2: chemokine receptor 2; CNS: central nervous system; GLP1: glucagon-like peptide 1; NF- $\kappa$ B: nuclear factor kappa-B; NLRP3: pyrin domain-containing protein 3; PDE: phosphodiesterase; PTH: parathyroid hormone; TRPA1: transient receptor potential cation channel, subfamily A, member 1; TRPV1: transient receptor potential vanilloid subtype.

current trial is looking to check for superiority over hyaluronic acid.<sup>33</sup>

Transient receptor potential vanilloid subtype 1 antagonists and modulators have been seen as a potential target of therapy. Capsaicin can induce pain desensitisation of peripheral nociceptors after an initial transient increase in pain. Low pH and heat can also activate the channel. Previously several trials were terminated due to adverse effects associated with hypothermia and impaired noxious heat sensation.<sup>85</sup> There are current trials with Resiniferatoxin in progress (see [Table 1](#)).

Similarly, transient receptor potential cation channel, subfamily A, member 1 is involved in pain sensitisation, triggered by temperature and noxious stimuli. A recent study testing of the drug LY3526318 in patients with osteoarthritis did not find a statistically significant difference from placebo.<sup>54</sup>

LEVI-04 is a fusion protein in which the Gc portion of human immunoglobulin is fused with the neurotrophin receptor, currently in OA trials.<sup>86</sup>

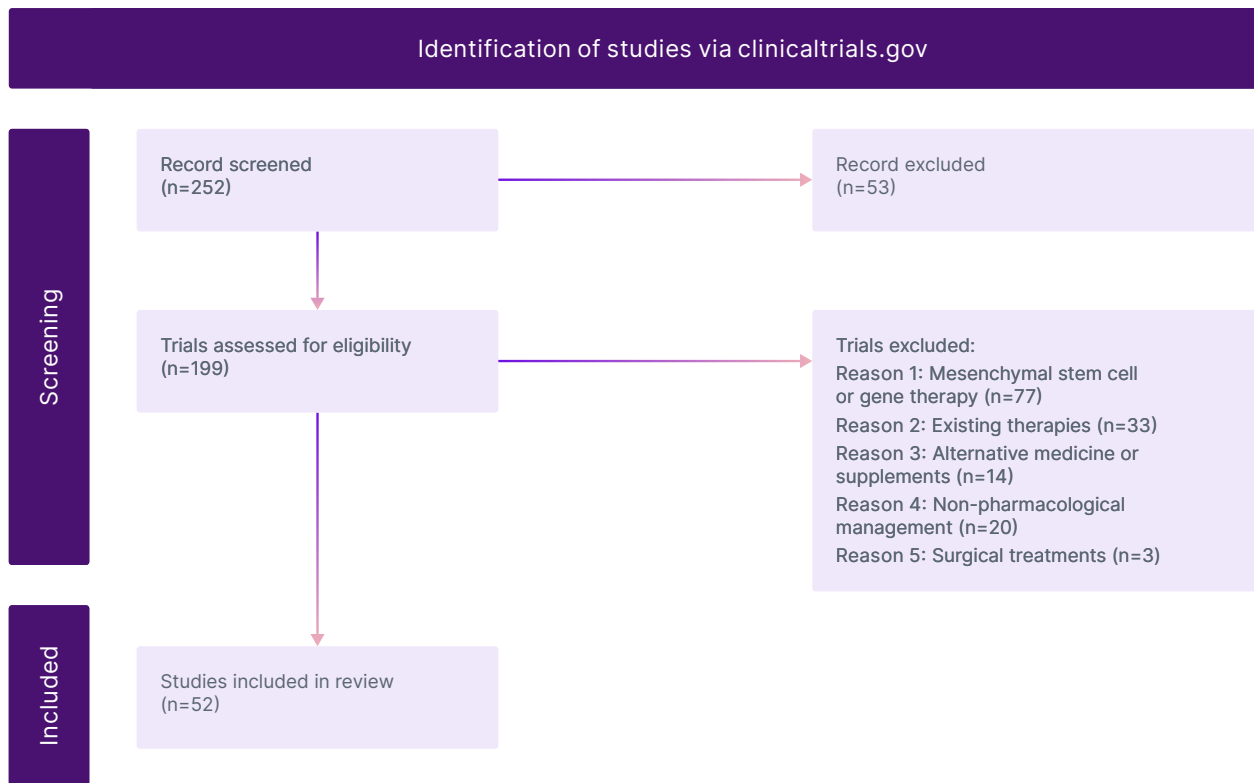
It works by binding to the excess neurotrophins, unlike the anti-NGF that blocks all NGF; therefore, it is hoped that it will not produce the same side effects.

In OA pathogenesis, there is an increase of reactive oxygen species from mitochondria due to cartilage destruction. This has proven a good target for preventing post-traumatic OA in mouse models. Amobarbital blocks mitochondrial ETC member complex I and is now being investigated as an intra-articular injection in humans.<sup>30,96</sup>

There are two current trials looking at using angiopoietin-like 3 signalling pathways that work by promoting chondrogenesis.<sup>46,47</sup> This following a successful Phase I trial showed it preserves and regenerates cartilage *in vivo* in OA models and it met its primary safety endpoint.<sup>97</sup>

Chemokine ligand CCL17 is a T cell chemokine. Elevated levels in OA are associated with elevated pain pressure thresholds.<sup>98</sup> As well T cell interactions, it is known to affect granulocyte-macrophage colony-stimulating factor. Animal studies have shown a lack of OA pain in CCL17

**Figure 1: Modified prisma flow diagram.**



gene-deficient mice.<sup>99</sup> The role of CCL17 in OA is not fully understood. After successful Phase I trials with anti-CCL17, there is a current Phase II trial underway to find the optimum dose for pain management.<sup>99</sup>

An IL-1 inhibitor, canakinumab, a monoclonal antibody, is in Phase II trial.<sup>34</sup> Despite being found in small amounts in synovial fluid, posthoc analysis of the CANTOS trial showed a reduction in joint replacements of those patients on canakinumab.<sup>100</sup> There was no difference in WOMAC pain scores of VAS in a Phase II trial of intra-articular canakinumab.<sup>101</sup> However, a current Phase II trial is testing LNA043 and canakinumab. LNA043 is a modified version of angiopoietin-like 3, which is discussed above.

Macrophages play a role in chronic inflammation, with chemokine receptor 2 playing a major role in the migration and recruitment of monocytes into tissues.<sup>102</sup> To target this inflammatory signalling process a small molecule antagonist, CNTX-6970, is in

a Phase II trial.<sup>60</sup> Animal models have shown a reduction in pain.<sup>102,103</sup>

The NOD-Like receptor family, pyrin domain-containing protein 3 (NLRP3) inflammasome pathway leads to the reduction of pro-inflammatory cytokines, such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , that result in joint destruction and pain.<sup>104</sup> Targeting this with an oral small molecule called DPV890 that binds and locks the pyrin domain-containing protein 3 inflammasome. It has been tested for various other conditions, including COVID-19, and there is a current Phase II clinical trial in patients with knee OA.<sup>41,104</sup>

Human growth hormone intra-articular injections stimulate the proliferation of chondrocytes and Type 2 collagen.<sup>105</sup> A Phase II trial is testing growth hormone injection and will assess response to pain and cartilage regeneration.<sup>42</sup>

MEDI7352 is a monoclonal antibody which targets TNF- $\alpha$  and NGF, reducing the inflammatory cascade. It continues to

be studied in a Phase II trial despite the halting of anti-NGF trials, which target similar pathways.<sup>57</sup>

A novel drug named MM-II, a suspension of empty large multilamellar liposomes composed of dimyristoylphosphatidylcholine and dipalmitoylphosphatidylcholine, is given as an intra-articular injection and works by providing lubrication in the joint. The results of a recent Phase IIb trial did not show a persistent statistically significant result in the reduction of WOMAC pain assessment; however, there were nominally differences in pain scores of 1 mL and 3 mL preparations and it was well tolerated.<sup>106</sup>

Oxytocin is an endogenous hormone that plays a role in bone metabolism via osteoblastogenesis and chondrogenesis. Low levels of oxytocin have been shown in patient with osteoarthritis compared to those without in an *in vitro* study; there are two ongoing clinical trials to understand this process.<sup>63,64,107</sup>

Semaglutide has revolutionised Type 2 diabetes and weight loss management. It decreases blood glucose, promotes satiety, and reduces hunger by mimicking glucagon-like peptide 1. A current trial, STEP-9, will compare Semaglutide against a placebo and measure their WOMAC pain scores and weight.<sup>74,108</sup>

Another avenue of pain relief is targeting somatostatin receptor 4, which is involved in pain pathways and not involved in the endocrine actions of somatostatin. Immune cells and neurons are directly inhibited.<sup>109</sup> This novel target is being investigated in a Phase II trial.<sup>55</sup>

Teriparatide is a synthetic form of parathyroid hormone with 34 active amino acids and is used in the treatment of osteoporosis for its role in calcium homeostasis. It has a potential role in chondrocyte regeneration, which is not well understood. Furthermore, it leads to denervation in subchondral bone, reducing pain.<sup>110</sup> There is a current Phase II trial comparing it to placebo.<sup>75</sup>

## Disease-Modifying Treatments

A meta-analysis found that bisphosphonates, a class of drugs known to inhibit osteoclast action, showed limited efficacy for pain relief in OA.<sup>111</sup> However, there are two current trials looking at intravenous zoledronate or intra-articular clodronate.<sup>31,32</sup>

WNT signalling is part of cellular homeostasis, it determines osteoblast and chondrocyte lineage specification. Lorecivint is an intra-articular agent that is a potential disease-modifying osteoarthritis drug.<sup>112</sup> It modulates the WNT signalling pathway by inhibiting intranuclear kinases CDC like kinase 2 and dual specificity tyrosine phosphorylation kinase 1A. In pre-clinical trials, this was effective in reducing inflammation, enhancing chondrogenesis and chondrocyte function.<sup>113</sup> A recent Phase IIa, however, did not meet its primary endpoint of improvement in the WOMAC subscale for pain at Week 13.<sup>112</sup> An ongoing Phase III trial has shown continued safety of the medication and an improved WOMAC pain and function scores at 12 months; despite this, at 18 months post-injection there is a loss of this effect.<sup>114</sup>

Phosphodiesterase inhibitors stop nitric oxide-mediated chondrocyte damage.<sup>115</sup> Clitazol, normally used for the treatment of peripheral vascular disease, is a selective Type 3 phosphodiesterase, stopping the breakdown of cyclic adenosine monophosphate (AMP) and shown to prevent cartilage destruction in rats and human cartilage samples.<sup>115,116</sup> There is a current proof-of-concept trial comparing this against conventional therapy in Egypt.<sup>117</sup>

An endpoint in OA is bone sclerosis as subchondral bone undergoes changes. Cathepsin K is primarily expressed in osteoclasts, chondrocytes, and synoviocytes, which is a cysteine protease that is involved in bone resorption.<sup>118,119</sup> In mice with no cathepsin K, there is a high bone mass and lack of bone resorption. MIV-711 was identified as showing beneficial effects in OA and is a selective inhibitor.<sup>119</sup> A recent RCT showed cathepsin K inhibitor had no effect on improved pain scores, but significantly reduced bone and cartilage progression.<sup>120</sup>



A potential target is ADAMTS-5 as it breaks down aggrecan. After successful Phase I trials, a Phase II trial of GLPG1972 did not meet the primary endpoint of a substantial change in the cartilage thickness compared to placebo.<sup>121</sup> However, there are other trials currently underway with a different inhibitor, M6495, has already shown it can work *ex vivo* with bovine and human tissue, preserving cartilage.<sup>122</sup> It had a successful Phase I trial showing its safety in humans, and there is now scope for further research in this area.<sup>123</sup> There is a Phase II trial of QUC398 an intra-articular injection, targeting ADAMTS-5, which in mouse studies showed when targeted there is a reduction in pain and cartilage degeneration.<sup>79,124</sup>

A previous study of an ADAMTS-5 inhibitor failed at the Phase II stage.<sup>125</sup>

TPX-100 is a synthetic fragment of extracellular matrix phosphoglycoprotein, which is downregulated in OA. In animal studies, it causes articular cartilage proliferation. A Phase II clinical trial of intra-articular injection of TPX-100 found it reduced pain at 4 weeks but did not reach significance in improving patellar cartilage structure.<sup>126</sup> It was well tolerated and there was a reduction in analgesic use. Post-hoc analysis, looking at those with moderate-to-severe bilateral tibiofemoral OA, revealed there was slower femoral bone shape change at 6 and 12 months.<sup>127</sup>

Plasma rich platelets (PRP) are an autologous blood product with a rich amount of growth factors, which has anti-inflammatory properties and reduces pain.<sup>128-130</sup> IL-1 $\beta$ , TNF- $\alpha$ , and fibroblast growth factor are some of the catabolic cytokines that are inhibited. A systematic review comparing PRP to hyaluronic acid found it didn't improve function but reduced pain.<sup>131</sup> The review had issues with heterogeneity in and between studies.<sup>131</sup> There are variations in how PRP is produced between different studies, which could account for the differences seen in efficacy outcomes.<sup>128,131</sup> Possible variations included the amount of blood drawn, centrifuge speeds, and time. Issues with blinding in studies meant there was a possibility of a strong placebo effect.<sup>131,132</sup> It is currently not recommended in guidelines.<sup>8,9,128</sup>

Iguratimod is a small molecule that protects the joint through immunomodulation. It inhibits NF- $\kappa$ B activation, which prevents the release of inflammatory cytokines. It is used in Japan, and a current trial are looking into its effectiveness in hand OA.<sup>44</sup>

There are several clinical trials investigating metformin (Table 1). Its main action is mediated via the 5' AMP-activated protein kinase. It leads to cartilage preservation, immunomodulation, and reduction in pain. Previous human trials were of lower quality and high risk of bias.<sup>133</sup>

### Important Emerging Therapies Beyond This Search

A randomised, double-blind, placebo-controlled trial in hand OA in participants with evidence of MRI-evident synovitis showed methotrexate 20 mg once weekly had positive results. There was a moderate effect size of 0.45 at 6 months, and no effect was seen until 3 months in keeping with drug-effect in inflammatory arthritis.<sup>134</sup> Future research could identify whether this effect persists beyond 6 months. Denosumab is anti-resorptive medication used in osteoporosis, it works by targeting RANK ligand and stopping it from activating RANK receptor found on osteoclasts. A recent Phase IIa trial of denosumab in participants with erosive hand OA showed it prevented progression of the disease.<sup>135</sup> However, a previous study of denosumab use in knee OA showed it was not useful in symptoms or structure, although the studies had different endpoints, with the latter focusing on BMLs as a marker of progression.<sup>136</sup>

## CONCLUSION

Various approaches are currently in progress to address the gap in effective therapies for OA. These range from cartilage regeneration to suppression of localised inflammation that activates inflammatory pathways inducing tissue breakdown. Since the primary symptom of OA is pain, many studies are focusing on the modulation of pain. Any treatments which are developed will need to be safe, efficacious, and cost-effective in managing this chronic condition. The enormous prevalence and chronicity mean

treatments need to be inexpensive to not burden health systems. This could focus on pain modulation and structural modification

in OA that are distinct treatment targets and how research into therapeutics needs to address both aspects.

## References

- Long H et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the global burden of disease study 2019. *Arthritis Rheumatol.* 2022;74(7):1172-83.
- Hunter D J, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393(10182):1745-59.
- Yuan C et al. Classification of four distinct osteoarthritis subtypes with a knee joint tissue transcriptome atlas. *Bone Res.* 2020;8(1):38.
- Loeser R F et al. Articular chondrocytes express the receptor for advanced glycation end products: potential role in osteoarthritis. *Arthritis Rheumatol.* 2005;52(8):2376-85.
- Wood M J et al. Macrophage proliferation distinguishes 2 subgroups of knee osteoarthritis patients. *JCI Insight.* 2019;4(2):e125325.
- Sofat N, Kuttapitiya A. Future directions for the management of pain in osteoarthritis. *Int J Clin Rheumatol.* 2014;9(2):197-276.
- Koushesh S et al. The osteoarthritis bone score (OABS): a new histological scoring system for the characterisation of bone marrow lesions in osteoarthritis. *Osteoarthr Cartil.* 2022;30(5):746-55.
- Kloppenborg M et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis.* 2019;78(1):16.
- Kolasinski S L et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol.* 2020;72(2):220-33.
- Wang S Y et al. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. *Ann Intern Med.* 2012;157(9):632-44.
- French S D et al. What do people with knee or hip osteoarthritis need to know? an international consensus list of essential statements for osteoarthritis. *Arthritis Care Res.* 2015;67(6):809-16.
- Juhl C et al. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol.* 2014;66(3):622-36.
- Fransen M et al. Exercise for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews.* 2015. Available at: <https://doi.wiley.com/10.1002/14651858.CD004376.pub3>. Last accessed: 16 March 2023.
- Quicke J G et al. Is long-term physical activity safe for older adults with knee pain?: a systematic review. *Osteoarthr Cartil.* 2015;23(9):1445-56.
- Zeng C et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. *Br J Sports Med.* 2018;52(10):642.
- Negrini F, Negrini S. Is paracetamol better than placebo for knee and hip osteoarthritis? a cochrane review summary with commentary. *Int J Rheum Dis.* 2020;23(4):595-6.
- Bannuru R R et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil.* 2019;27(11):1578-89.
- Osani M C, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis. *Korean J Intern Med.* 2019;34(5):966.
- Hudson B et al. Nortriptyline for pain in knee osteoarthritis: a double-blind randomised controlled trial in New Zealand general practice. *Br J Gen Pract.* 2021;71(708):e538.
- McAlindon T E et al. Effect of Intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA.* 2017;317(19):1967-75.
- Malfait A M, Little C B. On the predictive utility of animal models of osteoarthritis. *Arthritis Res Ther.* 2015;17(1):1-14.
- Singh A et al. Efficacy and safety of colchicine for the treatment of osteoarthritis: a systematic review and meta-analysis of intervention trials. *Clin Rheumatol.* 2023;42(3):889-902.
- Berenbaum F et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. *Ann Rheum Dis.* 2020;79(6):800-10.
- Hochberg M C et al. When is osteonecrosis not osteonecrosis?: adjudication of reported serious adverse joint events in the tanezumab clinical development program. *Arthritis Rheumatol.* 2016;68(2):382-91.
- Teichtahl A J, Cicuttini F M. Editorial: pain relief in osteoarthritis: the potential for a perfect storm. *Arthritis Rheumatol.* 2016;68(2):270-3.
- Zhao D et al. Does anti-nerve growth factor monoclonal antibody treatment have the potential to replace nonsteroidal anti-inflammatory drugs and opioids in treating hip or knee osteoarthritis? A systematic review of randomized controlled trials. *EFORT Open Rev.* 2022;7(7):470-80.
- Watt F E et al. Tropomyosin-related kinase A (TrkA) inhibition for the treatment of painful knee osteoarthritis: results from a randomized controlled phase 2a trial. *Osteoarthr Cartil.* 2019;27(11):1590-8.
- Krupka E et al. Efficacy and safety of intra-articular injection of tropomyosin receptor kinase A inhibitor in painful knee osteoarthritis: a randomized, double-blind and placebo-controlled study. *Osteoarthr Cartil.* 2019;27(11):1599-607.
- CARE ARTHRITIS LTD. Osteoarthritis of the Knee, Inflammation, and the Effect of Adalimumab (OKINADA). NCT02471118. <https://clinicaltrials.gov/show/NCT02471118>.
- J L Marsh, University of Iowa. Translating Metabolic Responses to Mechanical Insult Into Early Interventions to Prevent PTOA. NCT04589611. <https://clinicaltrials.gov/show/NCT04589611>.
- Morten Halkjær Iversen, Martina Hansen's Hospital. The Effect of Zoledronic Acid on Patients With Osteoarthritis of the Hip. NCT04303026. <https://clinicaltrials.gov/show/NCT04303026>.
- SPA Società Prodotti Antibiotici S.p.A. Clinical Trial to Assess Efficacy, Tolerability of Rising Doses of Clodronate in Painful Knee Osteoarthritis Patients. NCT06263517. <https://clinicaltrials.gov/show/NCT06263517>
- University Hospital, Strasbourg, France. Trial Comparing Botulin Toxin Versus Hyaluronic Acid by Intra-articular Injection for the Treatment of Painful Knee Osteoarthritis (GOTOX). NCT02832713. <https://clinicaltrials.gov/show/NCT02832713>.
- Novartis Pharmaceuticals. A Safety and Efficacy Study of Anti-inflammatory (Canakinumab) and Cartilage Stimulating (LNA043) Drugs Injected Into the Knee Joint of Participants With Knee Osteoarthritis (OA). NCT04814368.

- <https://clinicaltrials.gov/show/NCT04814368>.
35. Steven E Harte, PhD, University of Michigan. Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee. NCT04992624. <https://clinicaltrials.gov/show/NCT04992624>
  36. Jonathan Vela, Aalborg University Hospital. CBD Treatment in Hand Osteoarthritis and Psoriatic Arthritis (NordCAN). NCT03693833. <https://clinicaltrials.gov/show/NCT03693833>
  37. NYU Langone Health. Cannabidiol (CBD) in Pain Reduction for Knee Osteoarthritis. NCT05020028. <https://clinicaltrials.gov/show/NCT05020028>
  38. Chad Brummett, University of Michigan. Cannabidiol for Postoperative Opioid Reduction in Primary Total Knee Arthroplasty (CORK). NCT06234631. <https://clinicaltrials.gov/show/NCT06234631>
  39. Mahmoud Samy Abdallah, Sadat City University. The Phosphodiesterase 3 Inhibitor Cilostazol as an Adjunct to Conventional Therapy in Patients With Osteoarthritis. NCT04789837. <https://clinicaltrials.gov/show/NCT04789837>
  40. Maurizio Fava, MD, Massachusetts General Hospital. A Study to Evaluate the Safety and Efficacy of CNTX-6970 in Subjects With Knee Osteoarthritis Pain. NCT05025787. <https://clinicaltrials.gov/show/NCT05025787>
  41. Novartis Pharmaceuticals. Study of Efficacy, Safety and Tolerability of DFV890 in Patients With Knee Osteoarthritis. NCT04886258. <https://clinicaltrials.gov/show/NCT04886258>
  42. John Sledge, BioShift Life Sciences. Human Growth Hormone Injections in the Knee Joint to Treat Osteoarthritis. NCT06354023. <https://clinicaltrials.gov/show/NCT06354023>
  43. GlaxoSmithKline. A Dose-Finding Study to Evaluate the Efficacy and Safety of GSK3858279 in Adults With Knee Osteoarthritis Pain (MARS-17). NCT05838742. <https://clinicaltrials.gov/show/NCT05838742>
  44. Peking University People's Hospital. Efficacy and Safety of Igruratimod in Patients With Hand Osteoarthritis (ESIGO). NCT05216757. <https://clinicaltrials.gov/show/NCT05216757>
  45. Levicept. Clinical Trial to Evaluate the Efficacy and Safety of LEVI-04 in Patients With Osteoarthritis of the Knee. NCT05618782. <https://clinicaltrials.gov/show/NCT05618782>
  46. Novartis Pharmaceuticals. Study of Safety, Tolerability, Preliminary Efficacy of Intra-articular LNA043 Injections in Patients With Articular Cartilage Lesions and Knee Osteoarthritis. NCT03275064. <https://clinicaltrials.gov/show/NCT03275064>
  47. Novartis Pharmaceuticals. Study of Efficacy, Safety, and Tolerability of LNA043 in Patients With Knee Osteoarthritis (ONWARDS). NCT04864392. <https://clinicaltrials.gov/show/NCT04864392>
  48. Biosplice Therapeutics, Inc. A Long-Term Safety and Efficacy Study of Lorecivivint in Subjects With Osteoarthritis of the Knee. NCT04520607. <https://clinicaltrials.gov/show/NCT04520607>
  49. Biosplice Therapeutics, Inc. A Study Utilizing Patient-Reported and Radiographic Outcomes and Evaluating the Safety and Efficacy of Lorecivivint (SM04690) for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis (STRIDES-X-ray). NCT03928184. <https://clinicaltrials.gov/show/NCT03928184>
  50. Biosplice Therapeutics, Inc. A Study Utilizing Patient-Reported Outcomes to Evaluate the Safety and Efficacy of Lorecivivint (SM04690) for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis (STRIDES). NCT05603754. <https://clinicaltrials.gov/show/NCT05603754>
  51. Biosplice Therapeutics, Inc. A Study Utilizing Patient-Reported Outcomes to Evaluate the Safety and Efficacy of Lorecivivint (SM04690) for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis (STRIDES-1). NCT04385303. <https://clinicaltrials.gov/show/NCT04385303>
  52. Eli Lilly and Company. Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Osteoarthritis. NCT04456686. <https://clinicaltrials.gov/show/NCT04456686>
  53. Eli Lilly and Company. A Master Protocol Study (LY900028) of Multiple Intervention-Specific-Appendices (ISAs) in Participants With Chronic Pain (CPMP). NCT05986292. <https://clinicaltrials.gov/show/NCT05986292>
  54. Eli Lilly and Company. Chronic Pain Master Protocol (CPMP): A Study of LY3526318 in Participants With Osteoarthritis. NCT05080660. <https://clinicaltrials.gov/show/NCT05080660>
  55. Eli Lilly and Company. Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Osteoarthritis. NCT04627038. <https://clinicaltrials.gov/show/NCT04627038>
  56. Eli Lilly and Company. A Chronic Pain Master Protocol (CPMP): A Study of LY3857210 in Participants With Chronic Low Back Pain. NCT05630196. <https://clinicaltrials.gov/show/NCT05630196>
  57. AstraZeneca. A Study of the Efficacy and Safety of MEDI7352 in Subjects With Painful Osteoarthritis of the Knee (BESPOKE). NCT04675034. <https://clinicaltrials.gov/show/NCT04675034>
  58. Mahmoud Samy Abdallah, Sadat City University. The AMPK Modulator Metformin as a Novel Adjunct to Conventional Therapy in Patients With Knee Osteoarthritis. NCT04767841. <https://clinicaltrials.gov/show/NCT04767841>
  59. Amany Abd Elaal Mohamed Aiad, Tanta University. Metformin as Adjuvant Therapy in Obese Knee Osteoarthritis Patients. NCT05638893. <https://clinicaltrials.gov/show/NCT05638893>
  60. Delowar Hossain, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Effect of Metformin as Add-on Therapy to Ibuprofen on Disease Activity in Knee Osteoarthritis Patients. NCT06126029. <https://clinicaltrials.gov/show/NCT06126029>
  61. Mostafa Bahaa, Tanta University. Metformin Safety and Efficacy in Osteoarthritis. NCT06231758. <https://clinicaltrials.gov/show/NCT06231758>
  62. Sun Pharmaceutical Industries Limited. Efficacy and Safety of MM-II for Treatment of Knee Pain in Subjects With Symptomatic Knee Osteoarthritis. NCT04506463. <https://clinicaltrials.gov/show/NCT04506463>
  63. University of Florida. Understanding Cognition, Oxytocin & Pain in Elders (UCOPE). NCT03878589. <https://clinicaltrials.gov/show/NCT03878589>
  64. Wake Forest University Health Sciences. Generate a Pharmacodynamic Model of Oxytocin for Peripheral Analgesic Effects. NCT04431206. <https://clinicaltrials.gov/show/NCT04431206>
  65. Paradigm Biopharmaceuticals USA (INC). Treatment Effects of Subcutaneous Injections of Pentosan Polysulfate Sodium vs Placebo in Participants With Knee OA Pain. NCT04809376. <https://clinicaltrials.gov/show/NCT04809376>
  66. Queen Savang Vadhana Memorial Hospital, Thailand. Intraarticular Leukocyte-rich and Leukocyte-poor PRP for Osteoarthritis of the Knee (PRP). NCT05737173. <https://clinicaltrials.gov/show/NCT05737173>
  67. Andrews Research & Education Foundation. Effect of Different Injection Regimens of Autologous Conditioned Plasma for Knee Osteoarthritis. NCT03889925. <https://clinicaltrials.gov/show/NCT03889925>
  68. Eduardo Branco de Sousa, Instituto Nacional de Traumatologia e Ortopedia. Knee Osteoarthritis Treatment With Platelet-rich Plasma. NCT05824806. <https://clinicaltrials.gov/show/NCT05824806>
  69. Kelly Kilcoyne, MD, Walter Reed National Military Medical Center. Comparing Platelet Rich Plasma and Corticosteroid for Military & Civilian Patients With Glenohumeral Osteoarthritis (PRP). NCT05160441. <https://clinicaltrials.gov/show/NCT05160441>
  70. QC Kinetix LLC. Platelet-Rich Plasma

- and the Effects of NSAIDs on Pain and Functional Scores in Knee Osteoarthritis (PRPNSAIDsKOA). NCT05742763. <https://clinicaltrials.gov/show/NCT05742763>
71. James A. Keeney, University of Missouri-Columbia. Biological Response to Platelet-rich Plasma and Corticosteroid Injections. NCT05657496. <https://clinicaltrials.gov/show/NCT05657496>.
  72. Bone Therapeutics S.A. Phase III Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Symptomatic Knee Osteoarthritis (JTA-KOA2). NCT04333160. <https://clinicaltrials.gov/show/NCT04333160>.
  73. Brennan J. Boettcher, Mayo Clinic. Autologous Alpha-2 Macroglobulin Rich Plasma, Safety and Efficacy in Symptomatic Moderate Knee Osteoarthritis (A2MRP). NCT06329492. <https://clinicaltrials.gov/show/NCT06329492>.
  74. Novo Nordisk A/S. Research Study Looking at How Well Semaglutide Works in People Suffering From Obesity and Knee Osteoarthritis. NCT05064735. <https://clinicaltrials.gov/show/NCT05064735>.
  75. Christopher Ritchlin, University of Rochester. Teriparatide as a Chondroregenerative Therapy in OA. NCT03072147. <https://clinicaltrials.gov/show/NCT03072147>.
  76. Grünenthal GmbH. Efficacy and Safety of RTX-GRT7039 in Adult Subjects With Knee Osteoarthritis. NCT05248386. <https://clinicaltrials.gov/show/NCT05248386>.
  77. Grünenthal GmbH. Comparison of a Single RTX-GRT7039 and Placebo Intra-articular Injection for Pain Associated With Osteoarthritis of the Knee. NCT05449132. <https://clinicaltrials.gov/show/NCT05449132>.
  78. Grünenthal GmbH. Open-label Trial to Check the Safety and Tolerability of RTX-GRT7039 Injections for Pain Associated With Osteoarthritis of the Knee. NCT05377489. <https://clinicaltrials.gov/show/NCT05377489>.
  79. Sorrento Therapeutics, Inc. Study to Evaluate Intra-articular Resiniferatoxin to Treat Moderate to Severe Pain From Knee Osteoarthritis. NCT04885972. <https://clinicaltrials.gov/show/NCT04885972>.
  80. Novartis Pharmaceuticals. A Proof-of-concept Study to Examine QUC398 in Participants With Knee OA. NCT05462990. <https://clinicaltrials.gov/show/NCT05462990>.
  81. Phillips K, Clauw D J. Central pain mechanisms in rheumatic diseases: future directions. *Arthritis Rheumatol.* 2013;65(2):291.
  82. Suokas A K et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthr Cartil.* 2012;20(10):1075-85.
  83. Fingleton C et al. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthr Cartil.* 2015;23(7):1043-56.
  84. Zhai S et al. The efficacy and safety of Botulinum Toxin Type A in painful knee osteoarthritis: a systematic review and meta-analysis. *J Int Med Res.* 2019;48(4):0300060519895868.
  85. Brown W et al. Safety, pharmacokinetics, and pharmacodynamics study in healthy subjects of oral NEO6860, a modality selective transient receptor potential vanilloid subtype 1 antagonist. *J Pain.* 2017;18(6):726-38.
  86. Levicept. Clinical Trial to Evaluate the Efficacy and Safety of LEVI-04 in Patients With Osteoarthritis of the Knee. NCT05618782. <https://clinicaltrials.gov/show/NCT05618782>.
  87. Kersten C et al. Epidermal growth factor receptor – inhibition (EGFR-I) in the treatment of neuropathic pain. *Br J Anaesth.* 2015;115(5):761-7.
  88. Yang A et al. Medical cannabis in hand surgery: a review of the current evidence. *J Hand Surg Am.* 2023;48(3):292-300.
  89. Verrico C D et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain.* 2020;161(9):2191.
  90. Sophocleous A et al. The type 2 cannabinoid receptor regulates susceptibility to osteoarthritis in mice. *Osteoarthr Cartil.* 2015;23(9):1586-94.
  91. Solanki P et al. Repurposing pentosan polysulfate sodium as hyaluronic acid linked polyion complex nanoparticles for the management of osteoarthritis: a potential approach. *Med Hypotheses.* 2021;157:110713.
  92. Ghosh P et al. Effects of pentosan polysulfate in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled pilot study. *Curr Ther Pes Clin Exp.* 2005;66(6):552-71.
  93. Liu X et al. The effect of pentosan polysulfate sodium for improving dyslipidaemia and knee pain in people with knee osteoarthritis: A pilot study. *Osteoarthr Cartil.* 2023;5(2):100343.
  94. Eli Lilly and Company. A Chronic Pain Master Protocol (CPMP): A Study of LY3857210 in Participants With Chronic Low Back Pain. NCT05630196. <https://clinicaltrials.gov/show/NCT05630196>.
  95. Mehta N et al. Purinergic receptor P2X7: A novel target for anti-inflammatory therapy. *Bioorg Med Chem.* 2014;22(1):54-88.
  96. Quarterman J C et al. HPLC-uv method validation for amobarbital and pharmaceutical stability evaluation when dispersed in a hyaluronic acid hydrogel: a new concept for post-traumatic osteoarthritis prevention. *J Pharm Sci.* 2022;111(5):1379-90.
  97. Gerwin N et al. Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial. *Nat Med.* 2022;28(12):2633-45.
  98. Lupancu T J et al. CCL17/TARC in autoimmunity and inflammation-not just a T-cell chemokine. *Immunol Cell Biol.* 2023;101(7):600-9.
  99. Nijjar J S et al. OP0075 efficacy, safety, pharmacokinetics and immunogenicity of repeated dosing of gsk3858279 in patients with knee osteoarthritis: a phase i, randomized, double-blind, placebo-controlled study. *Ann Rheum Dis.* 2023;82(Suppl 1):51.
  100. M R P et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *NEJM.* 2017;377(12):1119-31.
  101. Conaghan P et al. Intra-articular canakinumab (anti-interleukin-1 $\beta$ ) for treatment of symptomatic knee osteoarthritis: a randomized, double-blind, placebo and naproxen-controlled phase ii study. Abstract 0728. *ACR Convergence*, 5-9 November, 2021.
  102. Jin L et al. CCR2 monocytes as therapeutic targets for acute disc herniation and radiculopathy in mouse models. *Osteoarthr Cartil.* 2024;32(1):52-65.
  103. Longobardi L et al. Role of the C-C chemokine receptor-2 in a murine model of injury-induced osteoarthritis. *Osteoarthr Cartil.* 2017;25(6):914-25.
  104. Duan M et al. Medicinal chemistry strategies targeting NLRP3 inflammasome pathway: A recent update from 2019 to mid-2023. *Eur J Med Chem.* 2023;260:115750.
  105. Li Z, Li Y. Effect of growth hormone releasing hormone on chondrocytes of osteoarthritis. *Korean J Intern Med.* 2019;37(1):222-9.
  106. Schnitzer T J et al. Intra-articular mm-ii, a novel suspension of large empty multilamellar liposomes, in painful knee osteoarthritis: a 26 week phase 2b placebo-controlled double blind randomized trial. *Osteoarthr Cartil.* 2023;31(5):688-9.
  107. Roux C H et al. Oxytocin Controls Chondrogenesis and Correlates with Osteoarthritis. *Int J Mol Sci.* 2020;21(11):3966.
  108. Bergmann N C et al. Semaglutide for the treatment of overweight and

- obesity: a review. *Diabetes Obes Metab.* 2023;25(1):18-35.
109. Szőke É et al. Small molecule somatostatin receptor subtype 4 (sst4) agonists are novel anti-inflammatory and analgesic drug candidates. *Neuropharmacology.* 2020;178:108198.
110. Sun Q et al. Parathyroid hormone attenuates osteoarthritis pain by remodeling subchondral bone in mice. *Elife.* 2021;10:e66532.
111. Davis A J et al. Are bisphosphonates effective in the treatment of osteoarthritis pain? a meta-analysis and systematic review. *PLoS One.* 2013;8(9):e72714.
112. Yazici Y et al. Lorecivivint, a novel intra-articular cdc-like kinase 2 and dual-specificity tyrosine phosphorylation-regulated kinase 1a inhibitor and Wnt pathway modulator for the treatment of knee osteoarthritis: a phase ii randomized trial. *Arthritis Rheumatol.* 2020;72(10):1694-706.
113. Deshmukh V et al. Modulation of the Wnt pathway through inhibition of CLK2 and DYRK1A by lorecivivint as a novel, potentially disease-modifying approach for knee osteoarthritis treatment. *Osteoarthr Cartil.* 2019;27(9):1347-60.
114. Simsek I et al. POS0278 a multicenter, observational, extension study evaluating the safety, tolerability, and efficacy of a single lorecivivint injection in knee OA subjects. *Ann Rheum Dis.* 2021;80(Suppl 1):363.
115. Lee S W et al. Cilostazol protects rat chondrocytes against nitric oxide-induced apoptosis in vitro and prevents cartilage destruction in a rat model of osteoarthritis. *Arthritis Rheumatol.* 2008;58(3):790-800.
116. Wang W et al. Cilostazol prevents the degradation of collagen Type II in human chondrocytes. *Biochem Biophys Res Commun.* 2014;451(3):352-5.
117. Mahmoud Samy Abdallah, Sadat City University. The Phosphodiesterase 3 Inhibitor Cilostazol as an Adjunct to Conventional Therapy in Patients With Osteoarthritis. NCT04789837. <https://clinicaltrials.gov/show/NCT04789837>.
118. Ginnetti A T et al. Lead optimization of cathepsin K inhibitors for the treatment of Osteoarthritis. *Bioorg Med Chem Lett.* 2022;74:128927.
119. Lindström E et al. Nonclinical and clinical pharmacological characterization of the potent and selective cathepsin K inhibitor MIV-711. *J Transl Med.* 2018;16(1):125.
120. Conaghan P G et al. Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis. *Ann Intern Med.* 2019;172(2):86-95.
121. Schnitzer T J et al. Efficacy and safety of s201086/GLPG1972, an ADAMTS-5 inhibitor, in patients with knee osteoarthritis: roccella, a 52-week, randomized, double-blind, dose-ranging phase 2 study. *Osteoarthr Cartil.* 2021;29:S264.
122. Siebuhr A et al. The Anti-ADAMTS-5 Nanobody®, M6495, protects against cartilage breakdown in cartilage and synovial joint tissue explant models. *Osteoarthr Cartil.* 2018;26:S187.
123. Guehring H et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending doses of the anti-ADAMTS-5 nanobody (R), M6495, in healthy male subjects: a phase I, placebo-controlled, first-in-human study. Abstract 2175. ACR/ARP Annual Meeting, 8-12 November, 2019.
124. Brebion F et al. Discovery of GLPG1972/S201086, a Potent, Selective, and Orally Bioavailable ADAMTS-5 Inhibitor for the Treatment of Osteoarthritis. *J Med Chem.* 2021;64(6):2937-52.
125. Latourte A, Richette P. Inhibition of ADAMTS-5: the right target for osteoarthritis? *Osteoarthr Cartil.* 2022;30(2):175-7.
126. McGuire D et al. TPX-100 leads to marked, sustained improvements in subjects with knee osteoarthritis: pre-clinical rationale and results of a controlled clinical trial. *Osteoarthr Cartil.* 2018;26:S243.
127. McGuire D et al. Study TPX-100-5: intra-articular TPX-100 significantly delays pathological bone shape change and stabilizes cartilage in moderate to severe bilateral knee OA. *Arthritis Res Ther.* 2021;23:1-9.
128. Costa L A V et al. How does platelet-rich plasma compare clinically to other therapies in the treatment of knee osteoarthritis? a systematic review and meta-analysis. *Am J Sports Med.* 2022;51(4):1074-86.
129. Peng Y N et al. Intra-articular leukocyte-rich platelet-rich plasma versus intra-articular hyaluronic acid in the treatment of knee osteoarthritis: A Meta-Analysis of 14 Randomized Controlled Trials. *Pharmaceuticals.* 2022;15(8):974.
130. Akeda K et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. *Osteoarthr Cartil.* 2006;14(12):1272-80.
131. Hohmann E et al. Is platelet-rich plasma effective for the treatment of knee osteoarthritis? A systematic review and meta-analysis of level 1 and 2 randomized controlled trials. *Eur J Orthop Surg Traumatol.* 2020;30(6):955-67.
132. Saltzman B M et al. The therapeutic effect of intra-articular normal saline injections for knee osteoarthritis: a meta-analysis of evidence level 1 studies. *Am J Sports Med.* 2017;45(11):2647-53.
133. Lim Y Z et al. Metformin as a potential disease-modifying drug in osteoarthritis: a systematic review of pre-clinical and human studies. *Osteoarthr Cartil.* 2022;30(11):1434-42.
134. Wang Y et al. Methotrexate to treat hand osteoarthritis with synovitis (METHODS): an Australian, multisite, parallel-group, double-blind, randomised, placebo-controlled trial. *Lancet.* 2023;402(10414):1764-72.
135. Wittoek R et al. RANKL blockade for erosive hand osteoarthritis: a randomized placebo-controlled phase 2a trial. *Nat Med.* 2024;30(3):829-36.
136. O'Neill T et al. Effect of denosumab on knee pain and bone marrow lesions in symptomatic knee osteoarthritis. Abstract 1982. ACR Convergence, 14 November, 2023.

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