

Review Articles

Pharmacotherapy for Osteoarthritis: A Review

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Abstract:

Osteoarthritis (OA) is a leading cause of disability in the elderly. The goal of OA treatment is to control symptoms, prevent disease progression, minimize disability, and improve quality of life. The management can be divided into non pharmacologic interventions, pharmacologic interventions, and surgical options. Pharmacologic interventions can be further subdivided into symptomatic therapy and potential structure- or disease-modifying therapy. There are, at present, no specific pharmacologic therapies that can prevent the progression of joint damage due to OA. Acetaminophen is the first line of therapy, although most of the patient requires NSAIDs. Risk of gastrointestinal (GI) bleeding and cardiovascular risk need to be considered, especially for elderly. With inflammatory components, intra-articular glucocorticoid injection gives short term benefit. Compared with corticosteroid injections, hyaluronan injections have similar clinical effects. But it is more costly. So far research with potential structure- and disease-modifying drugs in osteoarthritis includes tetracyclines, glycosaminoglycan polysulfuric acid, pentosan polysulfate, diacerin, glucosamine and others. Scientists are looking for new therapeutic targets like IL-1 receptor antagonist (IL-1Ra), mitogen-activated protein (MAP) kinases inhibitors, NF-kappaB inhibitors. Gene therapy, Chondrocyte and stem cell transplants showed some promise in animal models.

Keyword: Osteoarthritis, pharmacologic therapy, disease modifying therapy

Introduction:

Osteoarthritis (OA) is accepted as a major public health problem. As estimated by the World Health Organization, it is one of the major causes of impaired function that reduces quality of life worldwide. The magnitude of this problem is likely to rise due to the increasing life expectancy and the increasing rates of obesity among the population¹. The goal of OA treatment is to control symptoms, prevent disease progression, minimize disability, and improve quality of life. Traditional treatment paradigms for OA have conceded the inexorable progression of the disease and concentrated on pain management².

Management of OA includes various techniques and principles including nonpharmacological, pharmacological and surgical. Nonpharmacologic interventions such as weight loss and exercise should be an integral part of the management plan. Currently available pharmacologic interventions are directed at symptomatic relief. Research continues into potential disease-modifying interventions in OA³.

This review will discuss pharmacotherapy of osteoarthritis with available evidences for symptom relieving therapy, disease or structure modifying therapy, nutraceuticals and experimental therapies.

Pharmacotherapy for Osteoarthritis:

Pharmacologic interventions can be further subdivided into symptomatic therapy (Table-I) and potential structure- or disease-modifying therapy (Table-II)³.

Table-I

Symptom-Relieving Pharmacologic Therapies for Osteoarthritis

Topical
Capsaicin
Topical nonsteroidal anti-inflammatory drug (NSAID) preparations
Systemic
Acetaminophen
Nonselective NSAIDs
Cyclooxygenase-2 (COX-2)-specific inhibitors
Tramadol
Narcotic analgesics
Intra-articular
Corticosteroids
Hyaluronic acid derivatives

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Topical analgesics:

Topical NSAIDs and capsaicin may offer alternatives or adjunctive for patients with contraindications to use of systemic agents; or a suboptimal response to conventional therapy.

The long-term efficacy of topical NSAIDs is controversial.⁴ However, a meta-analysis of 4 trials lasting > 4 weeks found that diclofenac and eltenac were effective for long-term pain relief in knee OA.⁵ However, a systematic review of topical NSAIDs in older patients with OA found that while topical application was associated with lower incidence of GI side effects, up to 15% of patients experienced a GI-related side effect.⁶ Further, up to 39.3% reported application site side effects.

Topical capsaicin works by depleting the neuropeptide substance P, and a meta-analysis of 3 trials confirmed that topical capsaicin is more effective than placebo for pain relief in OA.⁷ Capsaicin is commonly associated with a transient local burning sensation and must be used for 3 to 4 weeks to achieve maximal benefit. Despite these limitations, one study reported drop-out rates as low as 2%.⁸ Lidocaine 5% patches may also offer a topical alternative for pain relief in some patients with OA.⁹ In a randomized, open-label trial involving 143 adults with knee OA, pain relief achieved with lidocaine 5% patches was comparable with celecoxib 200 mg daily.¹⁰

Acetaminophen and Nonsteroidal Anti-inflammatory**Drugs:**

Pharmacotherapeutic treatment options for mild-to-moderate pain associated with OA include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). While most data find NSAIDs to be more effective, acetaminophen is considered first-line therapy due to the side effect profile of NSAIDs.^{11, 12}

A Cochrane review involving 5986 patients confirmed that acetaminophen was effective for reduction in overall OA pain and pain on motion¹¹. While this systematic review found that acetaminophen was more effective than placebo in 5 of 7 trials, the degree of overall pain relief was noted to be of questionable clinical significance. This review also found that NSAIDs were superior to acetaminophen in 12 trials. Another meta-analysis that evaluated the safety and efficacy of acetaminophen and NSAIDs found similar results with regard to the efficacy of these agents.¹² Gastrointestinal (GI) side effects were more common in patients taking NSAIDs than in those taking acetaminophen (RR, 1.35; 95% confidence interval [CI]).

NSAIDs have consistently demonstrated efficacy for pain relief in OA;^{13,14} however, a meta-analysis of 23 trials that

included 10 845 patients found that NSAIDs were only slightly more effective than placebo for short-term pain relief in OA of the knee.¹⁵ All NSAIDs, including cyclooxygenase-2 (COX-2)-selective agents, were equally effective for pain relief in OA.^{15, 16}

Gastrointestinal and cardiovascular risks limit long-term use of NSAIDs in many older patients. Caution is recommended when NSAIDs are given to patients with cardiovascular risk factors. While COX-2-selective agents are most often associated with causing cardiovascular events, nonselective agents (eg, diclofenac and indomethacin) have also been implicated in increasing the risk of cardiovascular complications;¹⁷

Narcotic analgesics:

The ACR recommends that opioid analgesics be limited to patients who have failed or cannot tolerate first-line treatment options for OA (eg, acetaminophan, NSAIDs, or tramadol) and continue to experience severe pain.¹⁸ The use of strong opioids for chronic, noncancer pain requires a full evaluation of the risks versus benefits for patients, especially older adults.¹⁹ A meta-analysis of 43 studies (28 of OA) was conducted to evaluate the safety, efficacy, and abuse potential of opioids for chronic, noncancer pain in older adults demonstrated that although opioids were effective in reducing pain, they also had the potential risk of reducing mental capacity in older adults.²⁰

Fentanyl transdermal patches provide continuous medication for 24 hours, but are not to be used in opioid-naïve patients. According to Choquette et al 65% of patients experiencing moderate-to-severe pain due to knee or hip OA experienced an improvement in pain control.²¹

Tramadol:

Tramadol may be considered an alternative option for patients who cannot tolerate NSAIDs for moderate-to-severe pain due to OA or as an adjunctive therapy with NSAIDs²². An extended-release, once-a-day preparation of tramadol showed to relieve pain in OA of the knee and hip²³. Adverse effects are the primary reason for discontinuance of tramadol (up to 33%) when compared with placebo (6.3%)²⁴. The lack of anti-inflammatory properties and tolerability to tramadol may limit its effectiveness in OA²⁵.

Intra-articular glucocorticoid injections:

Although there is no role for systemic corticosteroids in OA, local intra-articular corticoid preparations have a long history in the management of OA. Corticosteroid injections slow macrophage-like cell infiltration of the synovium in OA.²⁶ These agents are useful for acute exacerbations of OA, but long-term pain relief has not been established.^{27, 28}

Another trial attempted to assess the possible disease-modifying effects of corticosteroids by randomizing 68 patients to corticosteroid or saline injections of the knee every 3 months for 2 years. At the study's end, there was no significant difference in rate of joint space narrowing.²⁹

Intra-articular hyaluronate injections:

Hyaluronic acid helps to improve elasticity and viscosity in the joints. Compared with corticosteroid injections, hyaluronan injections have similar clinical effects (mean pain scores, 6.30 ± 1.0 standard deviation [SD] for hyaluronan treatment vs 6.40 ± 1.0 SD for corticosteroid treatment; (P = 0.42). However, they are more costly. One multicenter, randomized, double-blind study evaluated the issue of disease modification with hyaluronic acid but failed to demonstrate a disease-modifying effect for hyaluronan therapy.³⁰

Disease-Modifying Agents:

Previously these agents were called chondroprotective. This was a misnomer, because the goal is to protect the entire joint (not only the cartilage). A workshop of the Osteoarthritis Research Society recommended that the term structure-modifying drugs be used for medications that previously would have been classified as chondroprotective.³¹ These drugs are intended to prevent, retard, stabilize, or even reverse the development of OA. Recently, the term disease-modifying osteoarthritis drug has been used for any such agent (Table-III)³ Unfortunately, to date, no drug has been conclusively proved to be structure or disease modifying in OA.

Table-II

Potential Structure- and Disease-Modifying Drugs in Osteoarthritis

Tetracyclines
Metalloproteinase or collagenase inhibitors
Glucosamine
Diacerein
Growth factor and cytokine manipulation (interleukin-1 receptor antagonist [IL-1Ra], transforming growth factor- β)
Gene therapy (IL-1Ra, IL-1RII)
Chondrocyte and stem cell transplantation

Tetracyclines: Apart from any antimicrobial effect, these are the inhibitors of tissue metalloproteinases, perhaps owing to their ability to chelate calcium and zinc ions.³² Minocycline,

a tetracycline-family antibiotic, has been used in the management of rheumatoid arthritis.³³ Doxycycline, another tetracycline derivative, has been shown to inhibit articular cartilage collagenase activity.^{34,35} A 30-month trial comparing doxycycline with placebo in 431 obese women with OA showed radiological evidence of slowing of the progression of joint space narrowing in 33% of the doxycycline group. Withdrawals were more frequent in the doxycycline group due to adverse effects such as nausea, heartburn, and photosensitivity (23 vs 9).³⁶

Glycosaminoglycan polysulfuric acid (GAGPS): It is a highly sulfated glycosaminoglycan, works by reducing the activity of collagenase, derived from bovine tracheal cartilage.³⁷ In a canine model of OA, GAGPS was administered intra-articularly twice weekly for 4 weeks. Four weeks after completion of the GAGPS treatment, medial femoral condylar lesions had developed to a lesser degree in the treated group than in saline-treated dogs.³⁸ In humans, OA of the knee was studied in a 5-year trial. There was improvement in multiple measured parameters, including less time lost from work.³⁹

Glycosaminoglycan-peptide complex (GP-C): Also known as Rumalon, has been investigated. It has been shown to increase the levels of tissue inhibitor of metalloproteinases (TIMP)⁴⁰. A randomized, placebo-controlled trial selected patients with hip or knee OA to receive 10 courses of injections of placebo or GP-C (2 mL) over 5 years (two courses per year). Each course consisted of 15 injections given twice weekly. GP-C failed to demonstrate a structure- or disease-modifying effect.⁴¹

Pentosan polysulfate: A hemicelluloses, in experimental studies of animal models suggested that it helps preserve cartilage proteoglycan content and retards cartilage degradation.^{42,43} However, a blinded, placebo-controlled study using an oral preparation in a dog model failed to demonstrate either a symptomatic benefit or a structure- or disease-modifying effect.⁴⁴

Diacerein: Diacerein and its active metabolite rhein are anthraquinones related to senna compounds.⁴⁵ They inhibit the synthesis of IL-1 β in human OA synovium in vitro, as well as the expression of IL-1 receptors on chondrocytes.⁴⁶ No effects have been reported on TNF or its receptors. Collagenase production and articular damage have been reduced in animal models.^{47,48, 49}

Nutriceuticals: Two nutritional supplements—glucosamine and chondroitin sulfate—have received significant attention for OA therapy (Table -III).³

Table-III
Nutriceuticals for Osteoarthritis

Glucosamine
Chondroitin sulfate
Ginger extracts
Avocado and soy unsaponifiables
Cat's claw
Shark cartilage
S-adenosyl methionine

Glucosamine and Chondroitin sulfate: Although in the 2005 meta-analysis of glucosamine there was a significant advantage of glucosamine over placebo for pain relief and functional improvement, further analyses indicating no significant difference in trials with adequate concealment (blinding) cast doubt on the efficacy of glucosamine sulfate.⁵⁰ The combination of glucosamine and chondroitin sulfate, does not appear to be significantly more efficacious than placebo for pain relief or functional improvement in patients with OA of the knee. This was illustrated in the GAIT trial in which 1583 patients with painful OA of the knee were randomly assigned to one of three groups: placebo, glucosamine HCL (500 mg three time daily), chondroitin sulfate (400 mg three time daily), glucosamine plus chondroitin sulfate (500 mg + 400 mg three time daily), or celecoxib 200 mg/day.⁵¹

Other nutritional supplements, such as cat's claw and shark cartilage, have become entrenched in regional and international popular cultures. Many people take them, despite limited or no data to support their use. A small, placebo-controlled trial showed improvement of OA pain with activity in those taking cat's claw extracts.⁵² Shark cartilage contains a small amount of chondroitin sulfate.⁵³ S-adenosyl methionine, a methyl group donor and oxygen radical scavenger, is often touted as a remedy for OA, although little evidence of its effectiveness has been published.^{54, 55}

Research with new therapeutic targets:

IL-1 receptor antagonist (IL-1Ra): The potential methods of intervention in OA include growth factor and cytokine manipulation.⁵⁶ Cytokines, such as IL-1 and TNF- α , are produced by the synovium and contribute to inflammation within osteoarthritic joints.⁵⁷ Moreover, there may be deficient expression of naturally occurring anti-inflammatory compounds such as IL-1Ra by the chondrocytes of patients with OA.⁵⁸ In some cases, increased nitric oxide production by OA articular chondrocytes may inhibit IL-1Ra synthesis.⁵⁹ In a dog model of OA, IL-1Ra therapy reduced the expression

of collagenase-1 in cartilage.⁶⁰ The severity of cartilage lesions is also diminished.⁶¹ In a rabbit model of OA, transfer of the IL-1Ra gene to joints prevented OA progression.⁶²

The MAP kinase inhibitors: The mitogen-activated protein (MAP) kinases are intracellular signaling proteins which play a central role in controlling the activity of pathways that regulate production and activity of multiple mediators of joint tissue destruction. The MAP kinase inhibition has the potential to slow disease progression in osteoarthritis and also might reduce pain; however, safety concerns have limited the use of general MAP kinase inhibitors in humans.⁶³

NF-kappaB inhibitors: NF-kappaB transcription factors can be triggered by a host of stress-related stimuli including pro-inflammatory cytokines, excessive mechanical stress and ECM degradation products. Thus the NF-kappaB activating kinases are potential therapeutic OA targets. However, work remains in its infancy to evaluate the effects of efficacious, targeted NF-kappaB inhibitors in animal models of OA disease.⁶⁴

Gene therapy: It has been attempted as well. The control of genes such as TIMP and MMPs would, in theory, provide the opportunity to modulate the patient's disease. As previously noted, gene expression of IL-1Ra has already been tried in rabbits and dogs, as well as in an equine model of OA using an adenovirus vector.⁶⁵

Chondrocyte and stem cell transplants: Chondrocyte and stem cell transplants into articular cartilage defects have been tried as well. Chondrocytes transplanted into human cartilage explants survived up to 45 days in vitro in one trial.⁶⁶ Transfection of chondrocytes with the galactosidase gene has been successful both before and after transplantation.

Conclusions:

Still nonpharmacologic therapy is the corner stone for OA management. Pharmacologic therapies are mainly aimed at symptomatic relief. The future holds promise for drugs that may genuinely modify structure, but these will require careful evaluation so that they may be appropriately positioned in the management of OA.

Conflict Interest : None

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