Acta Scientific Pharmacology

Volume 1 Issue 3 March 2020

Review Article

Optimizing Pharmacological Treatment of Osteoarthritis

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Received: February 13, 2020

Published: February 18, 2020

Abstract

Osteoarthritis (OA) is a significant health burden with work disability, and large societal costs which may be comparable. It constitutes a growing public health problem with mounting proportion of elderly population. Effective and evidence-based preventive and treatment strategies for OA are important as they may reduce both the individual burden of OA, and the economic burden to the society. Optimal management of patients with OA hip or knee requires a combination of non-pharmacological and pharmacological modalities of therapy. Pharmacological modalities of treatment include acetaminophen, cyclooxygenase-2 (COX-2) non-selective and selective oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs and capsaicin, intra-articular injections of corticosteroids and hyaluronates, glucosamine and/or chondroitin sulphate for symptom relief; glucosamine sulphate, chondroitin sulphate and diacerein for possible structure-modifying effects and the use of opioid analgesics for the treatment of refractory pain. Topical NSAIDs and capsaicins as alternatives or adjunctive to oral analgesics are safe and well-tolerated. These creams are popular amongst knee OA patients. Topical use of NSAID has known side effects: local burning sensation and dry skin. Recent awareness on role of nutritional supplements (nutraceuticals) is based on presumption that they may have a specific effect on disease pathophysiology. Though mechanism of actions and efficacy continue to be; they can be used as disease-modifying agents. Physicians may have a significant effect on the quality of life of patients with OA by providing education, collaborating with other specialties, knowing the available resources, and incorporating appropriate pharmacological therapies into treatment regimens.

Keywords: Osteoarthritis; Disability; NSAIDs

Introduction

Osteoarthritis (OA) is probably not a single disease but the final end result of various disorders leading to joint failure. It is characterized by degeneration of the articular cartilage and subchondral bone, morphological alterations of the synovial membrane and joint capsule often leading to pain, joint stiffness, and disability. It commonly affects hands, feet, spine, and large weight-bearing joints, such as the hips and knees [1]. Thus it is a chronic degenerative disorder of multifactorial etiology. Softening, ulceration, and focal disintegration of the articular cartilage and synovial inflammation is evident in late stage. Patients experience pain, particularly after prolonged activity and weight-bearing; whereas stiffness is experienced after inactivity. It is classified as primary OA if a cause is not known and is mostly age related. It can present as localized, generalized, or as erosive OA. Secondary osteoarthritis originates from other disease or condition [1,2]. Posttraumatic OA develops after joint injury. Injury may be in the form of fracture, cartilage damage, acute ligament sprain, or chronic ligamentous instability (or a combination of these) [3].

Disease burden

Osteoarthritis is a leading cause of disability whose prevalence and incidence continue to increase. It ranks globally among the 50 most common sequelae of diseases and injuries, affecting over 250 million people or 4% of the world's population. Approximately 27 million adults in the US above 25 years of age have a clinical diagnosis of OA of any joint. The incidence of hand, hip and knee OA increases with age, and women have higher rates than men, especially after the age of 50 years. The prevalence of radiographic hand OA varies greatly and has been reported to range from 27% to over 80% [4]. Data from the Framingham cohort demonstrated a prevalence of 13.2 percent in men and 26.2 percent in women aged 70 or more years with at least one hand joint with symptomatic osteoarthritis [5].

Of the global disease burden for OA, knee OA constitutes 83% [6]. It is more common in women, with female-to-male ratios varying between 1.5:1 and 4:1. Prevalence rates for knee OA, based on population studies in the US, are comparable to those in Europe.

These studies report that severe radiographic changes affect 1% of people aged 25-34 and this figure increases to nearly 50% in those 75 years and above. Among participants aged over 45 years in the Framingham Study, the prevalence of radiographic knee OA was 19.2% and, in those over 80 years, the figure rose to 43.7% [7].

Hip OA is less common then either hand or knee OA. The mean prevalence of primary radiographic hip OA in studies from Asia and Africa is 1.4% and 2.8% respectively. These levels are much lower than those seen in Europe and North America, where the mean prevalence is 10.1% and 7.2% respectively [8].

Idiopathic ankle OA accounts for 1% of the global population. Knee OA is 10 times more likely to be diagnosed than ankle OA [9]. In ankle OA, prior joint trauma is the most common cause, with posttraumatic OA accounting for between 20% and 78% of all cases of ankle OA [10].

By 2050, India's 60 and older population is expected to encompass 323 million people, a number greater than the total US population in 2012. The high share of aging population proportionately increases economic impact of OA [2]. This prevalence and burden is so little published that not a single pan-India study is available. Data on epidemiology, policies, use of public health services and long-term treatment outcomes from the subcontinent are not available [11]. Based on studies conducted in Maharashtra and Amritsar; the prevalence of OA in India is reported to be 17.0%–60.6% [12]. Inspite of these numbers, we are short of community-based health centers, health programs, and access to occupational therapists to manage OA patients.

The problem of OA is physical, psychological and socioeconomic which can be associated with significant disability, such as a reduction in mobility and activities of daily living. Psychological sequelae include distress, devalued self-worth, and loneliness. Moreover in the view of the high prevalence, OA results into heavy economic burden.

Pharmacological treatment

Optimal management of patients with OA hip or knee requires a combination of non-pharmacological and pharmacological modalities of therapy. Recommendations cover pharmacological modalities of treatment including acetaminophen, cyclooxygenase-2 (COX-2) non-selective and selective oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs and capsaicin, intra-articular injections of corticosteroids and hyaluronates, glucosamine and/or chondroitin sulphate for symptom relief; glucosamine sulphate, chondroitin sulphate and diacerein for possible structure-modifying effects and the use of opioid analgesics for the treatment of refractory pain. Recommendations on the use of 12 non-pharmacological modalities are: education and self-management, regular telephone contact, referral to a physical therapist, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation and acupuncture. The osteoarthritis research Society International (OARSI) guidelines are the excellent reference for non-surgical management of KOA [13-15].

Acetaminophen

Paracetamol is first choice in the treatment of mild to moderate OA [16]. It has better safety profile but relatively lesser efficacy in comparison to traditional NSAIDs. The use of paracetamol at the lowest effective dose for the shortest possible period of time is advocated [16]. Increase in paracetamol dose escalates cardiovascular (fatal/nonfatal myocardial infarction, stroke, heart failure), gastrointestinal (upper and lower), and renal adverse events. Co-administration with traditional NSAIDs in elderly patients add to the risk of gastrointestinal bleeding compared to either agent alone [17]. Even with modest efficacy, studies have revealed that paracetamol is less efficacious and more harmful than known earlier [16,18].

Non-steroidal anti-inflammatory drugs

Though chemically heterogeneous; NSAIDs share certain therapeutic actions and adverse effects. They inhibit prostaglandin biosynthesis, the first step of all inflammatory disorders. Cyclooxygenase enzymes, (Cox-I) and (Cox-II) act on arachidonic acid (AA). Unstable intermediated PGG2 and PGH2 lead to production of thromboxane A2 (TXA2) and a variety of prostaglandins. Cox-I is a primary constitutive isoform found in most normal cells and tissues. However, Cox-II production is induced by cytokines and inflammatory mediators that accompany inflammation. It is constitutively expressed in certain areas of kidney and brain and endothelial cells by laminar shear forces [19].

Cox-II inhibitor or nonselective NSAID with misoprostol or a proton pump inhibitor should be prescribed for patients with increased risk of GI adverse effects. After prescribing lowest possible effective dose of NSAIDs, renal function should be monitored over extended periods. The choice is multifactorial but potential benefits and risks and comorbidities of each patient matter. The risk of adverse events increases greatly beyond 70 years, where judicious use of low-dose opiates may be a safer option.

Non-specific cyclooxygenase inhibitors

Both Cox-I and Cox-II are inhibited with little selectivity to slow down prostaglandin synthesis (Table 1). e.g. Ibuprofen, Diclofenac, Meloxicam, Aspirin, etc.

Type of NSAID	Examples	Mechanism of action	Side effects
Non-specific Cox inhibitors	Ibuprofen, Diclofenac, Meloxicam, Aspirin	Inhibit Cox I and Cox II	GIT, CVS, bleeding, renal
Selective Cox II inhibitors	Celecoxib, Refexocib, Valdecoxib	Inhibits Cox II	CVS, stroke

Table 1: Summary of NSAIDs used for knee OA.

Selective Cox-II inhibitors

The selective Cox-II inhibitors are highly selective for Cox-2 enzyme e.g. Celecoxib, Rofecoxib, and Valdecoxib. They are effective and have superior side effect profile than other NSAIDs in treating pain due to osteoarthritis [19]. Rofecoxib and valdecoxib NSAIDs have been withdrawn from the market because of increase in the rate of vascular events such as non-fatal myocardial infarction (MI) or heart attack, non-fatal stroke, and death from a vascular event such as MI or stroke. The regulatory authorities have imposed a boxed warning on the label of celecoxib. Traditional NSAIDs were also found to have cardiovascular risks, leading to similar boxed warnings [20]. Selective Cox-II inhibitors has good quality patient-oriented evidence however, gastrointestinal, renal, and cardiovascular systems side effects offset its place in OA therapy [21].

Opiates

Opiates are the drugs derived from opium; either natural products (morphine, codeine) or many semi-synthetic derivatives. The analgesic effect is executed via their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn. Pain control circuits that descend from the midbrain via the rostral ventromedial medullary tract to the spinal cord dorsal horn are deactivated [22].

All three types; short acting, long acting and partial agonist (Table 4) are effective in pain relief. Inspite of level 3 evidence in their support, the pain relief is limited. Long-term use is coupled with frequent and sometimes severe side effects [19]. Narcotic analgesics should be second choice after failure or intolerance to NSAIDs and Paracetamol; reserving option of strong opioid analgesics only for extreme pain [22].

Tolerance and some degree of physical dependence are attained with daily administration. Though extent of physical dependence will depend on the particular drug, the frequency of administration, and the quality administered. Opioids are cautioned in elderly OA cases due to—their adverse effects include somnolence, constipation, and nausea. So with chronic condition like OA, other efficient and available measures (non-pharmacological therapies) should be opted first. In absence of long-term studies on opiates in OA, surgical treatment should be considered [22].

Type of opioid	Examples	Mechanism of action	Side effects
Short acting	Hydrocodone, Oxycodone, Codeine	Inhibit ascending transmission of nerve impulses	Respiratory depression, addictionConstipation
Long acting	Morphine, Methadone, Fentanyl	Same	Same
Partial agonists	Tramadol, Nalbuphine, Buprenorphine	Same	Same

Table 2: Opioid painkillers used for knee OA.

Other non-opioid oral analgesics

Category of drug	Examples	Mechanism of action	Side effects
Acetaminophen	Paracetamol	Block nerve impulse transmission	Hepatotoxicity
Tricyclic antidepressants	Antidepressants, Amitriptyline, Fluoxetine	Block nerve impulse transmission	Sedation, weight gain
Diacerin	Oral diacerin	Short acting interleukin inhibitor, slows down break down of cartilage	Diarrhea
Nutraceuticals	Glucosamine	Improves cartilage regeneration, inhibits inflammation, analgesic effect	Diarrhea and constipation, nausea
Chondroitin	Chondroitin	Improves cartilage regeneration, anti-inflammatory, analgesic	Diarrhea and constipation, nausea
Collagen hydrolysates	Collagen hydrolysates	Stimulates collagen synthesis	Hair loss, visual problems, anemia
Ovacado soya bean unsaponified	Ovacado soya bean unsaponified	Anti-inflammatory	None
Botanicals –	Green tea, Curcumin	Reduction of nitric oxide and prostaglandin E2	Rare

Table 3: Details of other analgesics used for knee OA.

Intraarticular injections and other forms of parental treatment

Intra-articular corticosteroid's efficacy is time-honored in joints with or without signs of inflammation. It is widely used for knee OA and to a lesser extent for hip OA, which usually requires radiological guidance. Their use in hand OA is limited to the thumb base. Another option is intra-articular hyaluronate therapy. It has delayed onset but comparatively prolonged duration of benefit. Amidst the controversy about its effectiveness and cost, FDA has approved hyaluronic acid derivative injections only for use in the knee [22].

Intraarticular injections should be set aside for cases not responding to simpler analgesics or stages 2 to 3 OA (Table 4).

Drug name	Examples	Mechanism of action	Side effects
Corticosteroids	Methyl prednisolone, Dexamethasone sodium phosphate	Inhibits inflammation, analgesic effect	Skin discoloration, allergic reactions, facial flushing
Hyaluronic acid derivatives	Sodium hyluronate	Inhibits inflammation, cartilage regeneration, analgesic effect, restores HA levels in joints	Agony, swelling hypersensitivity
Autologous blood products	Platelet rich plasma (PRP)	Growth induction, cartilage regeneration, anti-inflammatory effect	None
Whole blood	Unknown	Transfusion reactions	
Stem cell therapy	Unknown	Transfusion reactions	
Other forms of parental treatment			
Prolotherapy	Various formulations containing 15 - 23% dextrose	Collagen strengthening, induction of inflammation of weak soft tissues, analgesic effect	None
Anti-nerve growth factor	Tanezumab, IV, IM, Oral	Blocks interaction of nerve growth factor with its receptors	Headache, paraesthesia, upper respiratory tract infections

Table 4: Intraarticular injections and other forms of parental treatment for knee OA.

Corticosteroids

Various steroid-based injectable formulations in use are Triamcinolone acetonide, Methylprednisolone acetate, Dexamethasone Sodium Phosphate. Their mechanism of action is via reduction in prostaglandins, bradykinin, and histamine and altering pain reception. Efficacy is consistent, with good quality patient-oriented evidence (level A). Significant short-term benefit is followed by tissue atrophy, joint destruction, or cartilage degeneration on repeated use. Oral steroids are not an option for OA because of their modest benefit and high rate of adverse effects [22].

Hyaluronic acid derivatives

They restore normal intraarticular level of HA in OA joints and have either antinociceptive or anti-inflammatory effects. Formulations of various densities and compositions of HA are available. Peak effectiveness is seen 5 - 13 weeks after treatment. Inferior to steroids in short-term duration, but they have improved benefit over longer term results. On comparison with corticosteroids in painful KOA, HA was more effective in pain reduction lasting up to 13 weeks [23].

Platelet-rich plasma (PRP)

The PRP is an autologous concentration of human platelets in a small pool of plasma. Specific growth factors actively secreted by platelets act as therapeutic proteins for cartilage and mesenchymal tissue repair. This innovative and promising tool may heal degenerative lesions of articular cartilage and OA [22].

PRP is efficacious in reducing symptoms among patients with OA. At 12 months follow-up, WOMAC pain score and bodily pain improvement particularly in Kellgren stages 1 and 2. However, HA is superior to steroids and NSAIDs in treatment of OA [22]. Intraarticular injection of PRP revealed improvement in ROM, reduction in pain and WOMAC scores of both groups were equivalent. Comparison of WOMAC scores at second and third evaluation steps shows that in the long run PRP is a better treatment option than physical therapy [22]. A single dose of White blood cell -filtered Platelet-rich plasma (PRP) in concentrations of 10 times the normal amount can alleviate symptoms in early knee OA. However the results deteriorate after 6 months [24,25].

Stem cell therapy

In stem cell therapy, mesenchymal cells (MCS) and platelet-rich plasma are harvested from the patient himself and MSC are separated by centrifugation and other purification steps. MCS delivered to synovial fluid can differentiate into chondrocytes. Stem cells support the self-healing of OA affected knee joint cartilage. Stem cell effectiveness over other therapies has not been supported with sufficient amount of clinical data. Concern about the issues of dosing, timing of intervention, type of MSC, mode, and route of delivery of MSC in clinical studies is still there [26].

The treatment algorithm for knee OS is depicted in the figure 1 [27].

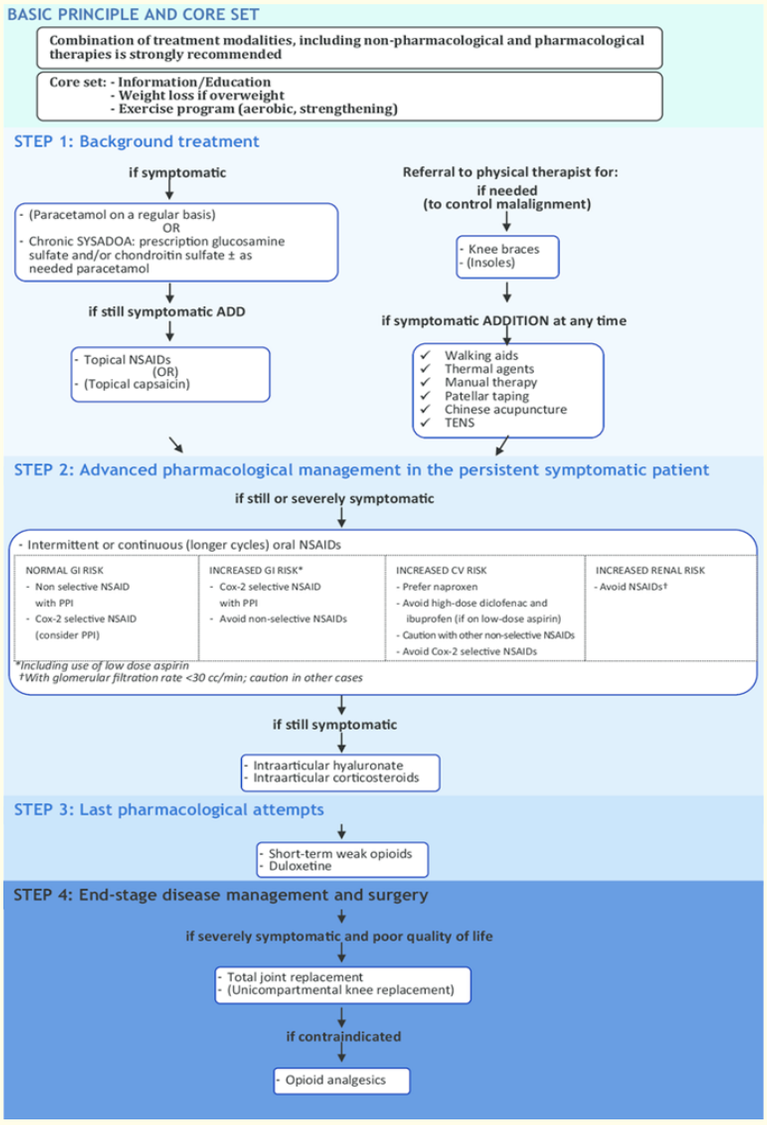

Figure 1: Knee osteoarthritis treatment algorithm [27]. COX-2, cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SYSADOA, Symptomatic Slow Acting Drugs in Osteoarthritis.

Non-intraarticular parental forms of treatment

Prolotherapy or proliferation therapy

A non-surgical treatment of injecting an irritant solution can stimulate body's natural healing mechanisms to repair injured musculoskeletal tissue. Healing mechanism stimulate growth factors (platelet derived GF, ILGF, transforming growth factor β), and that improves expression of type I and III collagens. The synovial tissue exposed to glucose increases HA production. Various formulations containing 15 - 25%. Dextrose for multiple injections separated by 1 - 4 weeks are available. Relative rest is given for 2 - 3 days with the resumption of normal activity over 4 weeks [22]. Prolotherapy with dextrose and with prolozone (intra-articular ozone) achieve same on WOMAC (pain relief) score among patients with mild to moderate KOA [28].

Anti-nerve growth factor (e.g. Tanezumab)

Exogenous nerve growth factor depending on dose and route of administration increases local or systemic pain. They increase the inflamed tissues of arthritis patient; so, pharmacological inhibition of their activity can reduce or block signs of pain [29]. Tanezumab is an antinerve growth factor (NGF) monoclonal antibody working to reduce joint inflammation in OA whilst also providing pain relief. Osteonecrosis is a serious side-effect following its use. Understanding of better safety and tolerability issues and exploration of its clinical potential as an alternative to current pharmacological treatments is possible with longer trials involving larger samples.

Topical treatment for osteoarthritis

Topical NSAIDs and capsaicins as alternatives or adjunctive to oral analgesics are safe and well-tolerated. These creams are

popular amongst KOA patients. The efficacy of this treatment in relieving pain has been evaluated by Hasel., *et al*. in a randomized, double-blind study. Homeopathic gel versus Piroxicam gel were equally effective for short-term management of painful KOA [16]. Bruhlmann., *et al.* conducted randomized, double-blind controlled study proved the efficacy and safety of Diclofenac hydroxyl ethyl pyrrolidine (DHEP) patch on symptomatic arthritic knee [30]. Topical use of NSAID has known side effects: local burning sensation and dry skin.

Nutraceuticals

Recent awareness on role of nutritional supplements (nutraceuticals) is based on presumption that they may have a specific effect on disease pathophysiology. Though mechanism of actions and efficacy continue to be; they can be used as disease-modifying agents.

Glucosamine

Glucosamine Sulfate (GS) is a natural building block of proteoglycans. Along with its mild anti-inflammatory property, it normalizes articular cartilage metabolism. GS has a carryover effect like disease modifying agents [31]. In a randomized, double-blind placebo-controlled trial of GS it was not any better than placebo [32]. But 21% pain reduction and 11% increase in function is noted by Cochrane Review [22].

Chondroitin

Natural glycosaminoglycan found in human cartilage, bone, cornea, skin, arteries and extracellular matrix. Mild improvement in pain and function (6 - 10% absolute change) can be brought about by chondroitin sulfate (CS). It decreases expression of cytokines and proteases and may also slow down the progression of OA on X-ray.

Clinical trials have suggested its long-term safety in absence of overdose and significant side effects [33]. However a multicentric double blind placebo and Celecoxib-controlled study [Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)] found that GS and CS alone or in combination did not reduce pain effectively in the overall group of patients with OA of the knee [34].

Methylsulfonylmethane (MSM)

It is naturally present in human body but its mechanism in OA is unclear. It may be associated with decreased inflammatory markers *in vitro*. A significant reduction in pain and increase in function is reported with MSM but is inferior to NSAIDs.

Collagen hydrolysates (CHs)

Enzymatically hydrolysed collagen, the collagen peptide, is absorbed and distributed to joint tissues. It has analgesic and anti-inflammatory properties. Collagen hydrolysates have attained improvement of OA in several investigations. Stimulation of chondrocytes and the increased synthesis of extracellular matrix may rebuild the cartilage damaged during osteoarthritic process [35]. The therapeutic mechanism of counteracting the degenerative process of OA remains unsolved. Pharmaceutical grade collagen hydrolysate (PCH) is obtained by hydrolysis of pharmaceutical gelatin. In clinical studies PCH 10 g daily reduced pain in KOA patients [35] the adverse effects are limited to GIT, characterized by fullness or unpleasant taste. The high level of safety is the attractive feature of CH in its long-term use for chronic disorders like KOA. WOMAC score values proved high effectiveness of CH in improving joint function. A double-blind, placebo-controlled, randomized trial demonstrated collagen peptide's potential as therapeutic nutritional supplement for management of osteoarthritis and maintenance of joint health [36].

Diacerin

Slow but persistent symptomatic relief was reported with Diacerin, an oral interleukin-1 inhibitor. A meta-analysis on diacerin has put forth it as an alternative to Paracetamol [37]. Its combination with diclofenac sodium decreases pain and improves joint function significantly than diclofenac alone in KOA [38].

Boswellia serrata extracts

Boswellia serrata), a common tree in India. The part used is gum resin. It possess excellent anti-inflammatory, anti-arthritic and analgesic activity. Boswellia serrate extract (BSE) is well tolerated by KOA subjects except for minor gastrointestinal ADRs [39]. Curcuma longa and Boswellia serrata extracts (CB formulation, 500 mg BD) was well tolerated and did not produce any adverse effect in patients, as judged by the vital signs, hemogram, liver and renal function tests [40].

Vitamin D

A small but statistically significant clinical benefit to vitamin D treatment in patients with knee OA is presented by randomized controlled pilot trial. Still a long-term study to establish it with clinical and radiologic confirmation is needed [41].

Conclusion

OA is a common disease that can cause significant morbidity. No therapies can retard structural damage in OA, unlike for rheumatoid arthritis. The treatment strategies discussed here target symptoms but not the disease process itself. Understanding of the complex pathogenic mechanisms of this disease is itself an active area of research. Novel therapies that both improve symptoms and prevent disease progression are expected in near future. Managing OA requires a multifaceted and multidisciplinary approach that combines nonpharmacological and pharmacological therapies. Physicians may have a significant effect on the quality of life of patients

with OA by providing education, collaborating with other specialties, knowing the available resources, and incorporating appropriate pharmacological therapies into treatment regimens.

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