Review Article

Pharmacological Treatment Of Osteoarthritis In A Nutshell

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ABSTRACT:

Osteoarthritis, an inflammatory, degenerative disease of joints mostly affects weight bearing joints in old age. Treatment modalities are categorized into non-pharmacological, pharmacological and surgical. Among pharmacological options, oral formulations are mostly used. Acetaminophen is considered as first line though, NSAIDs are well established choice for the management of osteoarthritis and mostly employed for the same. However NSAIDs are associated with gastric adverse effects. Symptomatic slow acting osteoarthritis drugs like glucosamine, chondroitin sulfate, diacerein and avocado soybean saponifiables are considered as maintenance therapy as they have shown to reserve joint space width. Topical formulations are good for patients with co-morbidities. For patient not responding to other modalities, opioids and duloxetine are employed but with caution. Intra-articular injections like corticosteroids, hyaluronic acid and Platelet rich plasma are ranked highest in efficacy. Newer agents like Nerve growth factor-α inhibitors, Interleukin-1 antagonists and certain neutraceutical preparations are under investigation for osteoarthritis management.

Key words: osteoarthritis, treatment, pharmacological modalities, conservative

INTRODUCTION:

Osteoarthritis (OA) is an inflammatory and degenerative disease of joints in which mostly weight bearing and hand joints are affected[1]. In OA there is damage of articular cartilage that causes bones to rub against each other leading to pain and loss of movement[2]. It is the most common arthritis and one of the leading causes of disability in world[3]. Commonly affected age is above 50 years and gender is female[4]. According to WHO, worldwide 9.61% of males and 18.0% of females over 60 years of age have symptomatic osteoarthritis[5]. India showed the prevalence to be 5.8% and mostly people over 65 years of age were affected. Prevalence of OA in Northern areas of Pakistan was found to be 3.7% and there was predominance of knee joint involvement that is 95%[6]. Because of increasing life expectancy and obesity, prevalence of OA is expected to increase steeply worldwide in next few years[7].

OA is classified into primary OA, with unknown etiology and secondary OA, having a known etiology. Predictors of OA are: mechanical injury, age, gender, obesity, genetics, metabolic disorders etc. Pathology of osteoarthritis begins with loss of articular cartilage then spreading to subchondrial bone. The bone shows sclerotic changes, formation of osteophytes and synovitis. Loss of cartilage, synovitis along with some other causes, leads to pain[8].

Common complaints of OA patient are pain and stiffness after long period of movement (exercise)[9]. There can be tenderness, swelling, crepitus and decrease in range of movement on examination. X-ray shows decrease in joint space and osteophytes[10]. Joint space width (JSW), measured on x-ray is considered gold standard for detection of loss of articular cartilage[11]. OA can be graded on plain radiograph according to Kallgren Lawrence grading system[12]. Diagnosis is done using American College of Rheumatology criteria for knee,[13] hip[14] and hand joints[15].

Treatment of OA is non-pharmacological, pharmacological modalities and surgical intervention. (table 1) Long term monitoring course of the disease, follow up and review is also essential[16,17]. Non-pharmacological and pharmacological approaches are conservative management modalities. Pharmacological modalities are the mainstay and commonly employed for the management of osteoarthritis. However succinct information regarding this subject has been found to be lacking. This review is a meek effort to provide current

Type of treatment	Examples
Conservative A. Non-pharmacological	Exercise, weight loss, physical therapy, walking cane, shock absorbing foot wear, acupuncture etc
B. Pharmacological	a. Oral Acetaminophen, oral and topical NSAIDs, SYSOADs, opoids, duloxetine b. Topical NSAIDs, capsaicin etc c. Intra-articular injection Corticosteroids, hyaluronic acid etc
Surgical	Microfracture, arthroscopy, arthroplasty etc

Table 1. Treatment modalities for osteoarthritis

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and approved pharmacological treatment of osteoarthritis.

METHODOLOGY:

Literature search was done using electronic data bases 'Google scholar' and 'Pubmed' from 2008-2018. Key words and phrases used were osteoarthritis, alone and with treatment, pharmacological treatment, acetaminophen, NSAIDs, diacerein, capsiacin, corticosteroids, hyaluronic acid, duloxetine, platelet rich plasma. Initially 150 articles were selected. Inclusion criteria were original and review articles. Exclusion criteria were animal studies, non-pharmacological and surgical interventions in OA. 60 articles meeting inclusion criteria were included to write this review.

LITERATURE REVIEW:

Pain is the main and early symptom of OA and other types of arthritis. The core ingredient for management of pain is the pharmacological treatment.[18] This includes primarily oral, topical and intra-articular formulations.

a. Oral

i) Acetaminophen

Acetaminophen is recommended as first line treatment of OA and is well tolerated. It is a non-prescription drug and suitable for OA of mild to moderate severity. Acetaminophen is a non-opioid with anti-pyretic and analgesic properties. Acetaminophen has not proven to be very effective for OA pain in many studies[19,20], but it has lesser gastric adverse effects as compared to NSAIDs. However patient should be counseled about maximum dose (that is 4g) that can be used per day and concomitant use of any other over-the- counter drugs containing Acetaminophen, as over dosage can cause hepatic toxicity[21]. Recently investigated extended release (ER) Acetaminophen has proven to provide more effective pain relief in OA[22].

ii) NSAIDs

Non steroidal anti-inflammatory drugs are well established treatment option for OA[23,24]. These are inhibitors of cyclo-oxygenase (COX) enzyme thus halting conversion of arachidonic acid to prostaglandins responsible for inflammation and pain. They are classified as non-selective (inhibiting both COX 1 and 2) and COX-2 selective NSAIDs[25]. Nonselective NSAIDs like Diclofenac, Ibuprofen, Naproxen are significantly associated with gastric adverse effect (because of COX-1 inhibition), hence a proton pump inhibitor is recommended with their use[26,27]. COX-2 selective inhibitors like Celeoxib, Etoricoxib etc have lesser gastrointestinal effects but more prone to cardiovascular events (myocardial infarction, stroke etc)[28]. Based on these facts systemic NSAIDs should be used cautiously especially in elderly OA with co-morbidities or where long term use is required.

iii) Symptomatic Slow acting Drugs for Osteoarthritis (SYSADOA)

SYSADOA include Glucosamine, Chondroitin sulfate, Diacerein and Avocado-Soybean Unsaponifiables (ASU).[29] Glucosamine and chondroitin sulfate are naturally occurring compounds in body and are substrates for proteoglycan.[30] Chondroitin sulfate and glucosamine are available in pharmaceutical grade and neutraceutical preparations; however there is striking difference among the two preparations. As pharmaceutical grade preparations are prepared under high quality checks they have shown to be more effective to improve pain and function in OA[31]. Chondroitin sulfate and glucosamine are recommended to be used as maintenance therapy alone or in combination. Moreover use of this combination for 2 years has shown to reduce joint space loss[32].

Diacerein is an anthraquinone derivative, and its active metabolite is rhein. The key mechanism of action of Diacerein is to inhibit the interleukin-1α (IL-1α) system and subsequent signaling. IL-1α has been found to be increased in synovial fluid of joint affected, hence its inhibition benefits in improving signs and symptoms of OA[33]. Diacerein can cause stomach upset (dose related), mild skin reactions and rarely hepato-biliary problems but these are much less than adverse effects of NSAIDs[34]. European Society for Clinical and Economic Aspects of Osteoarthritis (ESCEO) recommends Diacerein for patients of OA for whom NSAIDs are not suitable[35].

ASU are unsaponifiable fraction of avocado and soybean oils. Its anti-OA properties are attributed to many mechanisms like inhibition of interleukin-1 (IL-1), IL-6, IL-8 and TNF-α. It has also chondro-protective role by stimulating collagen synthesis[36]. Hence it has shown to inhibit deterioration in joint space width (JSW) and demonstrated efficacy in relieving symptoms of knee and hip OA. Moreover safety profile of ASU is good[37].

iv) Opioid analgesics and duloxetine

Opioid are potent analgesics that act through spinal and supra-spinal opioid (μ) receptors and provide physical as well as psychological part of pain. These should be prescribed with cautious and weak opioids should be prescribed first, as there is risk of sedation, respiratory depression, misuse, overdose and dependency. Moreover opioids are to be prescribed for short duration of time[38].

Duloxetine is an anti-depressant drug and is approved by FDA as analgesic for arthritis[39]. It is a potent serotonin and nor-epinephrine reuptake inhibitor (SNRI). These neurotransmitters also play role in central pain pathways. Hence role of Duloxetine is implicated in chronic pain conditions like OA[40]. Opioids and Duloxetine are treatment options for OA patients who are unresponsive to other pharmacological treatment options, unwilling to undergo surgery or if total arthroplasty is contraindicated, due to higher risk of serious adverse effects[1,41].

b. Topical

i) NSAIDs

Topical NSAIDs are used as alternate to oral formulation. They reduce systemic exposure to NSAIDs, hence beneficial for patients having OA with co-morbidities or elderly. Its mechanism has been discussed above, however considered as safer option than oral NSAIDs as there are no related serious adverse effects[42]. Topical application of ibuprofen, diclofenac, ketoprofen, peroxicam etc are available[43].

ii) Capsaicin

It is active ingredient of chilies. It provides warmth and desensitizes the nerve endings by inhibiting a pain neurotransmitter, Substance P. There is abundance of nociceptive innervations in joint cartilage and capsaicin is also known to cause selective and reversible destruction of primary afferent fibers. Burning sensation and local skin irritation are main adverse effects[44]. Its use in OA has been recommended by OARSI 2014 and ACR 2012[16,41].

c) **Intra-articular**

i) Corticosteroids

Intra-articular corticosteroid injections are proven to be quite effective but are reserved for patients not responding to other pharmacological options[41]. Steroids have anti-inflammatory and anti-nociceptive actions[45]. Crystalline triamcinolone and non-crystalline prednisolone, methylprednisolone are frequently used[46]. These injections are not recommended more than 3-4 times in a year. Patient's response for pain relief and functional improvement may vary with intra-articular steroids[47]. The effect last for 3 weeks to no more than 6 months[46].

ii) Hyaluronic acid (HA)

Intra-articular injection of hyaluronic acid and its derivatives is called viscosupplementation. This injection has been approved by FDA, only for knee OA. It is naturally present in synovial fluid, proposed underlying mechanism to reduce pain is restoration of viscoelastic properties of the synovial fluid and reductions in friction within the joint[48]. The evidence for efficacy of this treatment option is controversial. Local adverse reactions are main risk of the injection[49].

Combination of corticosteroid and hyaluronic acid intra-aricular injection has been shown more effective as compared to monotherapy[50].

iii) Platelet rich plasma (PRP)

PRP is an autologous blood product that is obtained when whole blood is centrifuged to obtain a specific concentration of platelets. The use of PRP is thought to provide cellular and humoral mediators (growth factors) including vascular endothelial growth factor, Fibroblast growth factor b, epidermal growth factor, ?broblast growth factor and platelet-derived growth factor for tissue healing especially cartilage repair[51]. PRP has shown to be superior or equally effective as HA in treating knee OA. Moreover PRP has not been found to produce serious local or systemic adverse effects[52].

Among all the conservative treatment options intra-articular injections are ranked highest in efficacy for management of OA by most of authors and researchers[53].

d) Others

Despite the fact here is a long list of drugs for management of OA, an increasing trend has been observed in patients for the use of alternate medicines for few decades[46,54]. This is because of long term use of the drugs for chronic and debilitating disease like osteoarthritis and troublesome adverse effects caused by them. The alternate medicines include herbs like Boswella serrata, curcuminoids, passion fruit peel extract, ginger, rosehip[55] and dietary supplements like methylsulfonylmethane[56], vitamin D and K. Although these herbal and neutraceutical products are being used for management of OA, evidence for their efficacy is weak. Hence more studies are warranted in this regard.

e) Drugs under investigation

Tanezumab is a monoclonal antibody against â-nerve growth factor **α**-(NGF-**α**). NGF is involved in causing chronic pain in OA, hence by inhibiting NGF-**α,** Tanezumab is effective for improving symptoms of OA this drug is still under trial but is facing safety issues[57].

IL-1 receptor antagonists: Anakinra and Orthokin have shown to decrease pain in OA. IL-1 had been shown to increase in synovial fluid of affected joint[58]. Moreover IL-1**α** antibody Gevokizumab is in phase 11 trials for efficacy and safety in treating hand OA[59].

Now focus of research in OA is on disease modifying agents rather than drugs providing only symptomatic relief. Strontium ranelate (SrRa), presently indicated for prevention of fracture in severe osteoporosis, has shown promising results in reducing cartilage volume loss in OA. It is an element similar to calcium, and is incorporated in bones in place of calcium. SrRa has been proved well tolerated and safe so far[60].

Intra-articular injection of DNA to modify chondrocytes to produce TNF- **α**1 and intra-articular injection adipose derived stem cell (ADSC) are also under investigation[36].

CONCLUSION:

When pain and function of joint does not respond to non-pharmacological management, pharmacological treatment should be considered. Different pharmacological treatment options are present for management of OA, but treatment should be chosen in stepwise manner, keeping in consideration, individualized needs and benefit-to-risk assessment.

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