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Osteoarthritis Treatment: An In-depth Review of Conventional and Nonconventional Interventions for Symptomatic Relief and Novel Disease Modifying Modalities

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Abstract
Osteoarthritis (OA) is characterized by degradation of joint cartilage which produces severe pain and swelling leading to immobility of the joint. OA can affect people of all age, gender and geographical locations, and the cost associated with long term medication, hospitalization and the loss of daily work hours stigmatizes the patient's life. Conventionally, the treatment of OA is done with analgesic to relieve pain, but due to notorious side effects profile of NSAIDs and corticosteroids, dependence phenomenon with opioids and continuous underlying degradation of joint, the analgesics cannot be relied upon as sole therapeutic agent. Physical therapies, exercise, modification of lifestyle and use of supportive devices have shown effectiveness in prevention and treatment of mild OA. With the application of multidisciplinary approaches in medical research, many pharmacological and non-pharmacological interventions have evolved with optimistic claims of relieving joint pain and swelling. More recently, disease modifying OA drugs (DMOADs) have shown promising results in preventing cartilage degradation and induction of cartilage regeneration in experimental models as well as initial phases of clinical trials. The diversity of individual needs and complex comorbidities calls for patient oriented treatment plan, a goal which can be achieved effectively by multidisciplinary health care team. This review will provide an in-depth review of all clinically accepted conventional and nonconventional interventions for symptomatic relief of pain as well as novel disease modifying pharmacological and non-pharmacological modalities.
Keywords: Diacerein, DMOADs, Glucosamine, Osteoarthritis, Prevalence in Pakistan.

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INTRODUCTION

Osteoarthritis (OA) is a chronic disease of joints characterized by degeneration and progressive loss of articular cartilage. Bone degradation in OA is followed by bone remodeling. This degeneration and remodeling cycles may lead to permanent deformity of the joints. OA affect people of all ages however it is more common in old age groups of all races. OA may be initiated by multiple factors including genetic, developmental, traumatic and metabolic factors (Ellis *et al.,* 2011).

OA is primarily a disease of cartilage. It usually affects specific joints including knee, hip, hands (fingers and thumb) and spine (neck and lower back). In osteoarthritis, the surface layer of cartilage breaks and wears away. This allows bones under the cartilage to rub together, causing pain, swelling and loss of motion of the joint (Shari and Joan, 2015). OA should be differentiated from rheumatoid arthritis (RA) which is an autoimmune disease. RA also involves autoimmune reactions against skin, liver and eyes etc. which are not affected in OA. Additionally, OA mostly involves only one joint while RA is symmetrical, that is, if one joint is

affected, the same joint on the opposite side of the body is also affected.

Arthritis is the most common cause of physical disability and has big economic impact on patient life. Osteoarthritis is the most prevalent of arthritic diseases, almost 15 times more prevalent than rheumatoid arthritis (Myasoedova *et al.,* 2010). In USA, about 7.9% young adults report OA, 29.8% persons of the age of 45-65 years are diagnosed with OA while another study found that almost every person above 75 years has at least one joint involved. In osteoarthritic adults, 66% doctors reported cases are obese (Cheng *et al.,* 2010; Margaret *et al.,* 2002). In Pakistan a large number of persons report OA. In 2005, 30% Pakistani males and 47% Pakistani females self-reported OA (Shaikh and Shaikh, 2005). Rheumatoid arthritis is a disease of modern civilization attacking people in every part of the world. Ashraf et al. (2016) reported that the prevalence of rheumatoid arthritis was more in males (55%) compared to females (45%) in Narowal, Pakistan. Akhter et al. (2011) compared Pakistani and Indian arthritic population to European and North American arthritic population and found that the prevalence of OA is higher in developed countries as compared to developing countries including India and Pakistan. They also observed clear difference in the presentation patterns of the disease, especially in younger age groups.

OA management includes changes in lifestyle, pharmacological interventions as well as innovative supportive devices. Allopathic, ayurvedic and nutritional supplements are pharmacological options which are widely used for OA management. Many classes of pharmacological agents have been reported to treat OA including pain relieving analgesics and disease modifying OA drugs (DMOAD). However the claim of these treatment options ranges from sub-optimistic to highly pessimistic. This review highlights epidemiology and etiology of OA, and the advances in treatment options including discovery of novel targets for therapeutic applications and their effectiveness in clinical set ups.

ETIOLOGY

To understand the etiology of OA, it is first desirable to understand the structure of the joint (Figure 1). A joint consists of cartilage, joint capsule, synovium, synovial fluid and surrounding tissues of ligaments, tendons and muscles. Cartilage is a hard but slippery tissue that covers the ends of bones where they meet to form a joint. Healthy cartilage allows bones to glide over one another during physical movement. Joint capsule is a membrane sac that encloses joint bones and it surrounding tissues. Synovium is a membrane inside joint that secretes synovial fluid, the fluid that lubricates the joints. Tissues, ligaments and tendons help joint to bend and move. Ligaments and tendons are tough and cord-like tissues that connect bones with bones and tissues, respectively. The elasticity and compressibility in cartilage is imparted by extracellular matrix which consists of chondrocytes (1-2%), liquid phase (70-80%) and solid phase consisting of collagens and proteoglycans. Ligaments connect one bone to another while tendons connect a muscle with a bone (Ellis *et al.,* 2011).

Nature has kept an intelligent balance of remodeling process in which low levels of catabolic and anabolic enzymes work side by side. OA arises when this balance is shifted to catabolic side i.e. cartilage breakdown rate exceeds the cartilage synthesis rate. This degradation in OA is caused by matrix metalloproteinases (MMPs) which can degrade collagen and proteoglycans of joints. These enzymes are secreted as pro-enzymes by synovium membrane and chondrocytes, and require enzymatic cleavage for activation. Normally, activity of these enzymes is controlled by tissue inhibitors of MMPs (TIMPs) (Muroski *et al.,* 2008). Synthesis of MMPs can be induced by pro-inflammatory interleukin-1 (IL-1) and to some extent by tumor necrosis factor alpha (TNF-alpha). IL-1 degrades cartilage in two ways i.e. by inducing catalytic pathways and by suppressing remodeling pathways (Shari and Joan, 2015).

Induction of Cartilage Catalysis: In normal circumstances, the action of IL-1 is antagonized by the IL-1 receptor antagonist (IL-1RA). But in arthritis, excessive synthesis of IL-1 or reduction in IL-1RA level leads to excessive synthesis of MMPs that outweigh the synthesis of inhibitory TIMPs. This imbalance in the favor of MMPs over-production produces cartilage degradation. IL-1 is also associated with production of nitric oxide (NO) and prostaglandins that further induce cartilage catalysis.

Suppression of remodeling processes:

Remodeling process is regulated by insulin-like growth factor-1 (IGF-1). IL-1 has ability to inhibit transforming growth factor-beta which is responsible for chondrocytes proliferation. This inhibition of chondrocyte proliferation will suppress the production of type II collagen and proteoglycans which are building blocks of joint cartilage. IL-1 is also associated with apoptosis of chondrocytes as well as production of nitric oxide (NO) and prostaglandins.

The complete understanding of these events and the underlying molecular mechanisms provides the opportunity to explore new potential therapeutic targets that can inhibit the degradation events or induce the regeneration events.

It has been found that OA has genetic determinants in some families. The increased incidence of osteoarthritis (OA) in some families and identification of mutation in these genes encoding structural cartilage matrix proteins are strong indication of the genetic component in OA etiology. Specific mutations in these genes results in structural changes that lower the threshold at which biochemical stresses tend to induce OA (Markenson, 2015).

Chang et al. (2010) studied effect of weight bearing habits of OA patients and found that dynamic knee alignment during weight bearing phase of walking is a

predisposing factor of knee OA. This phenomenon is more evident in old age and in obese.

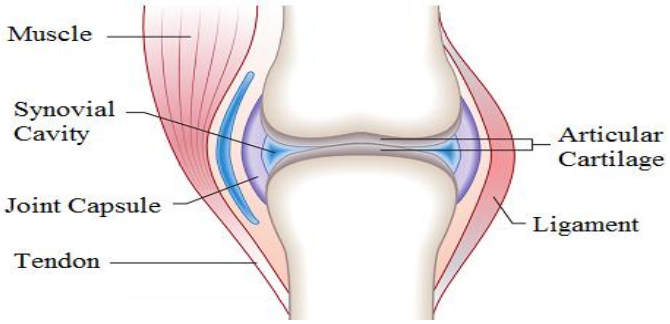

Fig. 1. This figure provides visual description of clinically important components of the joint.

OSTEOARTHRITIS TREATMENT

The goal of osteoarthritis treatment is to control symptoms, prevent disease progression, and improve functionality and quality of life. A successful treatment plan should include changes in lifestyle as well as non-pharmacological and pharmacological options. A patient with osteoarthritis can live active and productive life despite limitations of OA. Only currently available and clinically accepted modification of lifestyle, non-pharmacological and pharmacological interventions, surgical replacement of joint and quality of life enhancing devices are discussed here.

Modification of Lifestyle

Most of the clinician considers lifestyle changes as the first line management option after the diagnosis of OA. This can be achieved by modifications in lifestyle such as rest, exercise, diet control, learning self-care and having a "good attitude".

Rest

It is the basic preventive option which can limit the degradation of the joint. Progressive degradation of joint can be avoided by avoiding prolonged exposure to vocational and recreational activities that require repetitive motions, bending and heavy weight lifting. However mild recreational activities such as walking may not effect joint degradation and should not be avoided (Sun *et al.,* 2007).

Exercise and physical therapy:

Exercise and physical therapy are very useful options for improving muscle strength as well as improving joint health and functionality. Exercise will help in weight control and strengthening joint. Physical therapy is required when a patient do not respond to exercise. Deyle et al. (2000) found that physical therapy has significantly improved OA management outcomes as compared to ultrasound therapy. A clinician should devise an exercise or physical therapy regimen which is feasible for social and occupational needs of the patients. Usually low-impact aerobic exercises are recommended such as walking, bicycling and swimming. Physical therapy significantly controls OA symptoms and improves strength of quadriceps, adductor and abductor muscles that further facilitate hip and knee joint functionality.

Diet Control

As evident from the studies of Chang et al. (2010), obesity is the major predisposing factor of OA in 66% patients. The studies of Wang et al found obese patients have three to four time greater risk of primary joint replacement. David and Yuqing, (1998) concluded in his study that reducing as little as 11 pounds weight reduces the chances of OA by 50% in women. Thus diet control to reduce weight and body mass index (BMI) is the first line treatment options for these patients. Taking low fat and controlled amount of carbohydrates significantly helps in weight loss. Supplementation of the specific digestive enzymes in feed improves its nutritional value by increasing its digestion efficiency and enzymes help in the breakdown of anti-nutritional factors (Imran *et al.,* 2016). Most clinicians recommend combination of diet control and exercise as means to reduce body weight.

Learning self-care

Education of self-care principles should be the first step after the diagnosis of OA and should be continued even after the disease is controlled. A patient should be educated about the disease pathology, treatment options and self-care. A patient should be properly educated about the exercise or diet control plans and should be actively involved while planning the treatment regimen. A patient should also learn proper resources for self-care information and patient oriented support programs available in his community.

Non-Pharmacological Interventions for the Management of OA

The interventions, other than drugs, that are used to control the symptoms of osteoarthritis are discussed here;

Joint Surgery

Joint Surgery is performed when OA medications fail to manage symptoms. The effectiveness of joint surgery depends upon the assessment of need of surgery and evaluation of risks versus benefits ratio. Medicines must be given first preference and if joint surgery is requisite, the whole plan must be discussed with the patients. There are two types of joint surgeries that have gained clinical acceptance for Osteoarthritis of weight bearing joints.

- **Total Joint Replacement (Arthroplasty):** Total joint replacement is required when drugs fail to manage pain and it becomes very difficult to perform the household tasks (MBHPM, 2013; CCHL, 2015; MHS, 2013).

- **Osteotomy:** In osteotomy, a small part of the lower joint part is remove which shifts the weight on the other parts of the joint and may prevent damaged bones from rubbing with each other. This prevents deteriorated parts of the joints from further stress (WebMD, 2013; Mehta and Parihar, 2012).

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a non-invasive technique which involves electrical excitations of nerve in order to reduce pain. Both high frequency (>50Hz) and low frequency (<10Hz) electrical currents may be used (Robinson and Lynn, 2007). TENS are effective in controlling the symptoms of the OA but there is also a significant role of "placebo effect". However, many clinicians are using this technique especially in hip osteoarthritis.

Rational Field Quantum Magnetic Resonance (RFQMR)

This technique exposes the affected joint to quantum electromagnetic radiation wbhich leads to the activation of chondrocyte and the stimulation of regeneration pathways (Vasishta *et al.,* 2004).

Thermotherapy and Cryotherapy

Thermotherapy involves the application of the heat to the effected joint. Application of heat with heating pads and towels improves circulation and relaxes the muscles (Brosseau *et al.,* 2003). Cryotherapy involves the application of cold to the effected joint. Application of cold with cold compresses and ice bags reduces pain and swelling, constricts blood vessels and block nerve impulses to the joint (Carol Eustice, 2015).

Mobility Shoes

It has long been understood that walking with thin and flexible shoes mimics the walking barefoot. Najia et al. (2013) have designed "mobility shoes" that adapt the patients gait after long term use. The sole of these shoes have cuts and grooves that shift the body weight from knee joint and the gait adaptation persists even after the shoes are removed. In a 6 month study, they showed mobility shoes can prevent disease progression and may be used to train osteoarthritis patients to beneficially adapt their gait mechanics. From these results, mobility shoes appear to be an ideal supportive device.

Pharmacological Interventions for OA Management

Most clinicians consider pharmacological agents as first line treatment option for the relief of pain. Clinically acceptable pharmacological interventions range from over the counter analgesics to topical preparations to intra-articular injections to new disease modifying osteoarthritis drugs (DMOADs). Today, the pathways leading to joint degradation and their molecular mechanism are completely understood. This provides the opportunity to selectively inhibit destructive pathways or to induce constructive pathways (Figure 2).

Usually analgesic like NSAIDs, selective COX-2 inhibitors, corticosteroids, narcotics derivatives and some topical preparations are prescribed for pain relief. But these drugs do not alter the course of joint degeneration. Last decade has witnessed the evolution of DMOADs which prevent joint degeneration or induces joint regeneration. All these pharmacological classes of drugs and their clinical effectiveness is reviewed here.

Acetaminophen

Acetaminophen or paracetamol has proved to be effective in the management of mild to moderately OA. Acetaminophen relieves OA associated pain but it lacks anti-inflammatory properties. Acetaminophen is a selective cyclooxygenase-2 (COX-2) inhibitor but its anti-inflammatory properties are limited due to high concentration of peroxides at the inflammation site (Hinz *et al.,* 2008). However, better safety profile of acetaminophen compared to NSAIDs makes it the drug of choice as first line treatment. Panadol and Tylenol are two common brands prescribed by orthopedics in recommended dose of 500mg every 4 hours or 1000mg every 8 hours, not exceeding 4g a day. Alcohol is contraindicated with acetaminophen because it increases the risk of hepatic damage, thus an alcoholic should consult his pharmacist before he starts acetaminophen (FPC, 2013). Madni et al. (2016) documented that immediate release tablet released all contents at acidic pH in less than one minute.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The patients who do not respond to acetaminophen are treated with NSAIDs. They effectively reduce pain and inflammation in mild to moderate OA. The clinical efficacy of all NSAIDs is almost equal thus a pharmacist should select a drug or brand on the basis of safety profile and financial status of the patient.

Over The Counter (OTC) NSAIDs: These drugs inhibit both isoforms of cyclooxygenase (COX) enzymes, COX-1 and COX-2. They provide effective relief from mild to moderate OA pain due to inhibition of COX-2 enzymes. Inhibition of COX-1 enzyme inhibits production of prostaglandin mediators of inflammations (Knights *et al.,* 2010). But Inhibition of prostaglandin also exposes gastric mucosa to acidic degrading environment. Gastric ulceration and renal failure are two serious complications that are associated with the prolonged use of the NSAIDs. Almost 30 to 40 percent patients tend to discontinue NSAIDs due to these problems. These are advised to be taken with food or antacids at the lowest effective dose. Ibuprofen (Brufen and Actifen) 400mg every 6 or 8 hours and Naproxen (Arthrox and Aproxen) 500mg every 12 hours are two common OTC drugs used for OA pain and swelling. However, some clinician may prefer

Diclofenac sodium (Voltaren), Piroxicam (Feldene) and Sulindac.

Selective COX-2 Inhibitors: Celecoxib is the only clinically accepted drug of this class which selectively inhibits COX-2 enzymes. Celecoxib lacks gastro-intestinal side effects and shows activity comparable to the NSAIDs. However, use of Celecoxib has been associated with increased incidence of myocardial infarction (Deeks *et al.,* 2002). Celecoxib (Osteoxib) is given orally as 200mg every 12 hours or 100mg every 6 hours.

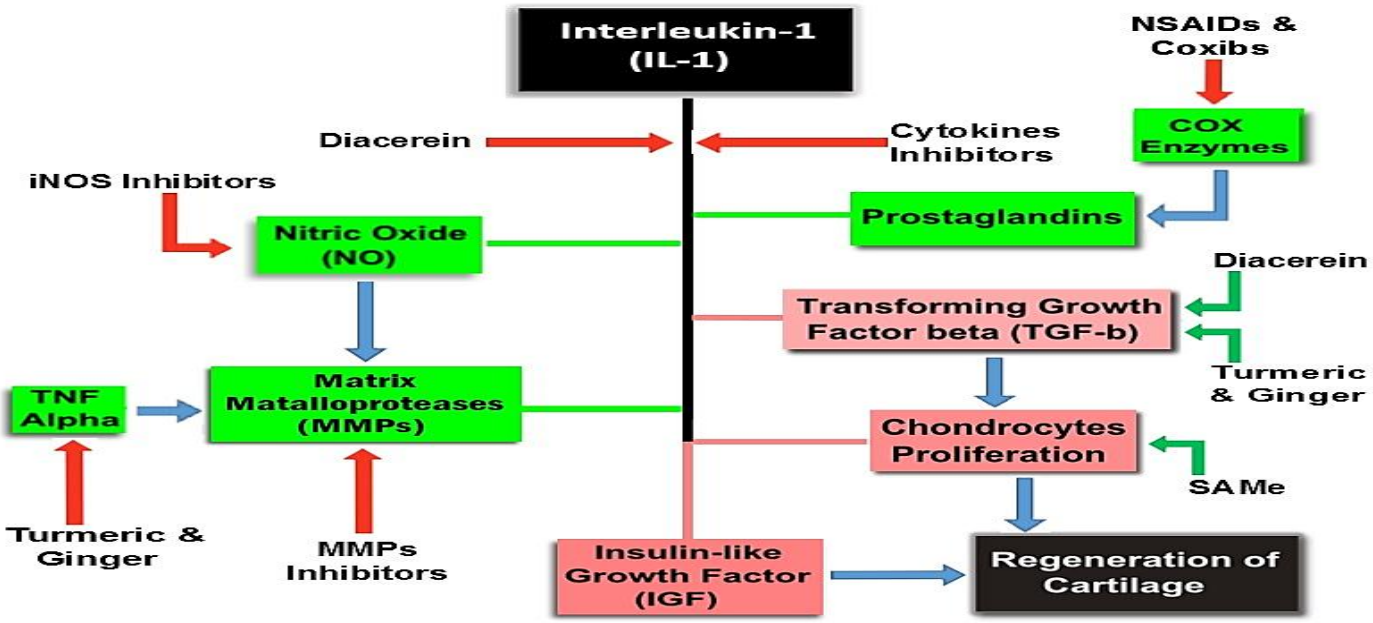

Fig. 2. An elaboration of induction of cartilage degradation pathways (green) and inhibition of regeneration pathways (red), and drug targets in these pathways to cure osteoarthritis.
The boxes shows potential of Interleukin-1 to induce some steps (green box) and to inhibit some steps (red box) as well as the inductive effect of these steps on one another (blue arrows). Different therapeutic agents can target Interleukin-1 pathway at different steps to inhibit (red arrows) or induce (green) these steps.

Topical Analgesics

Many pain relieving creams, ointments and sprays are available over the counter with proven efficacy in the management of Osteoarthritis symptoms. Methyl salicylate (Metsal, Iodex, Wintogeno) and topical formulations of other NSAIDs are helpful to patients who cannot tolerate these drugs systematically (Lin *et al.,* 2004). Capsaicin (Zostrix, Finalgon) acts by inhibiting the synthesis of neuropeptide "substance P". It also increases blood circulation and produces heat. Topical Capsaicin has also been prescribed in combinaton with other analgesics (Altman *et al.,* 1994). Methanol has been used as an ingredient of topical preparation. Methanol produces feeling of cold by the activation of cold-sensitive TRPM8 receptors and produces analgesia due to activation of k-opioid receptors (Eccles, 1994). Lidocaine 5% patches are available for OA management. One comparative clinical trial has proved that lidocaine patches are as effective as selective COX-2 inhibitors (Kivitz *et al.,* 2008).

Narcotic Derivatives

The long term use of narcotics is allowed only in cancer and its chronic use in other diseases, including OA, is controversial amid risk of addiction, dependence and hyperalgesia. Narcotics act by selectively binding endogenous opioid receptors. They are prescribed in OA in lowest effective dose for shortest possible time. Many clinicians use narcotics in combination with non-pharmacological therapies. Narcotics provide effective analgesia and moderately improved joint functioning. Codeine and oxycodone are discouraged as first line treatment for OA pain (Goodwin *et al.,* 2009). In another, Langford et al. (2006) showed that fentanyl patch improve pain and functionality in hip and knee OA. Fentanyl administration through patches is more tolerable and provides continuous medication for hours. Fentanyl transdermal (such as patches) is especially considered for patients who develop tolerance to other opioids. Extended release formulations of oxycomorphone have been rated from excellent to good by 80% clinical practitioners for

effective analgesia and improve functioning of joints (Gibofsky and Barkin, 2008).

Tramadol is codeine like molecule but it is not considered narcotic. Tramadol acts on central mu-receptors and inhibits the reuptake of norepinephrine and serotonin. Its analgesic effects are better than NSAIDs but it lacks anti-inflammatory effects. Its clinical acceptance is limited due to tolerance and withdrawal effects. Tramadol (Merlon, Opadol SR) is given 50mg every 6 hours.

Corticosteroids

Corticosteroids also known as glucocorticoids are powerful anti-inflammatory hormones that are prescribed for acute pain and inflammation that is not responsive to NSAIDs. Prednisolone (Deltacortril), betamethasone (Betnovate, Betnesol), triamcinolone (Kenacort) and misoprostol (Cytotec) are the corticosteroids commonly prescribed by the physicians for knee OA (Schumacher, and Chen, 2005). Misoprostol (200mcg) is also available in combination with diclofenac sodium (50mcg and 75mcg) as Arthrotec tablet. Corticosteroids inhibit the production of inflammatory mediators including interleukins, interferons and TNF alpha etc. In OA, corticosteroids are applied topically or administered intra-articularly i.e. directly into joints and their effect lasts for 4 to 6 weeks. Dose of the injection depends upon the size of the joint and it should be administered by a trained health professional to avoid complications like infection or joint injury (Bellamy *et al.,* 2006).

Disease Modifying Osteoarthritis Drugs

Abbreviated as DMOADs, these drugs are capable of stimulating regeneration of articular cartilage. DMOADs have made big impact on osteoarthritis treatment during last decade. Currently, a large number of drugs from different pharmacological classes that inhibit one or more OA pathophysiological pathways are under research, however, only Diacerein and hyaluronic acid are available in market for oral administration. This review will highlight the DMAODs that have shown promising efficacy in research and clinical trials.

Matrix metalloproteinase (MMP) Inhibitors

MMPs are the major component of cartilage damage. Today, activation of MMPs and their mechanism of cartilage degradation are understood. Thus, inhibition of MMPs provides an interesting target for disease modifying treatment. Broad spectrum MMP inhibitory drugs like BAY 12-9566 (Leff *et al.,* 2003) and PG-116800 (Krzeski *et al.,* 2007) have demonstrated improved cartilage regeneration in clinical trials. However, emergence of mild to moderate musculoskeletal problems including pain and swelling has restricted further research. Recently, MMP-13 and ADAMTS-5 have been recognized as chief metalloprotease enzymes of cartilage and targeting these catalytic enzymes will provide safe disease modifying treatment (Stanton *et al.,* 2005). Recently, Baragi et al. (2009) have proposed a new class of MMPs inhibitors non-hydroxamic acid containing compounds that have high degree potency against MP-13 and show improved safety and pharmacokinetic profile. Researches have also evaluated Doxycycline as DMOAD due to its ability to inhibit MMPs. Early clinical trials showed promising data but a recent study has concluded that Docxycycline has very little to no benefit in osteoarthritis (da Costa *et al.,* 2012).

Biophosphonates

Biophosphonates are antiresorptive agents that have proved to be effective in preventing the degradation of the bony components of the joints. Two clinical trials on a biophosphonate drug risedronate by Spector et al. (2005) and Bingham et al. (2006) have shown that the prevention of radiographic degradation of OA has been insignificant. Most recently, results of clinical trials of two biophosphonate drugs tiludronate (Moreau *et al.,* 2011) and zoledronic acid (Laslett *et al.,* 2012) showed promising results in reducing osteoarthritis pain and disease progression.

Cytokines Inhibitors

Cytokines, especially interleukin-1 (IL-1), are involved in the degradation of cartilage through induction of MMPs and suppression of remodeling process. Cytokines are released by cartilage as well as synovium and bone (Pelletier *et al.,* 2001). Thus cytokines and cytokine receptors have emerged as interesting research topic for drug developing researchers. In rheumatoid arthritis, Interleukin-1 receptor antagonist (IL-1RA) (Caron *et al.,* 1996) and transfection of IL-1RA genes into knee joints (Fernandes *et al.,* 2000) have proved their efficacy but they are not yet tested in OA. Inhibition of Interleukin-1 converting enzyme has also been shown to be effective for the prevention of articular cartilage degradation (Saha *et al.,* 1999). Cytokines inhibitors have shown to reduce the degradation of the human cartilage in in-vitro experiments (Kobayashi *et al.,* 2005). Only a few drugs of this class have been tested in clinical trials for osteoarthritis treatment with no evidence of significance effectiveness. In 2005, a clinical trial was conducted with cytokines inhibitor drug Anakinra injected intra-articularly as a single dose. Anakinra did not show significant beneficial effects on the management of symptoms and prevention of disease progression (Chevalier *et al.,* 2005).

Calcitonin

Calcitonin is a thyroid hormone which has been used for the treatment of osteoarthritis for more than three decades. Oral Salmon Calcitonin has been safe, and effective for increasing bone mineral density and reduction in bone resorption. Recently, the study of Manicourt et al. (2006) showed that 1mg of Salmon Calcitonin improved physical functions after 42 days of treatment and reduced levels of circulating MMP-13 after 84 days of treatment. On March 5, 2013, U.S. Food and Drug Administration (FDA) have

approved Salmon Calcitonin for postmenopausal OA (FDA, 2013.

Inducible Nitric Oxide Synthase (iNOS) Inhibitors

Nitric oxide plays a major role in the pathogenesis of OA in three ways. First, it can induce and promote the production of MMP enzymes. Second, it can cause apoptosis of chondrocytes. Third, it promotes inflammatory component of OA thus worsening the symptoms. This production of nitric oxide is induced by nitric oxide synthase. Naproxcinod, a derivative of naproxen, is first compound of this class undergoing clinical trials for safety and efficacy (Geusens, 2009). Pfizer Inc. has now conducted clinical trials on a drug SD-6010 which has been shown to be safe tolerable and effective in obese and overweight OA patients (Pfizer Incorporation, 2016).

Diacerein

Diacerein, a semisynthetic anthraquinone, is a symptomatic disease modifying OA drug. Diacerein directly inhibits interleukin-1 (IL-1) and stops the cascade of pathways modulated by IL-1. It suppresses the IL-1 induced production of MMPs and pro-inflammatory agents. Diacerein promotes the expression of TGF beta-1 and TGF beta-2 thus promoting the synthesis of articular chondrocytes (Mahajan *et al.,* 2006). Thus, diacerein appears to be an ideal DMOAD which can control OA symptoms, prevents degradation of joint and promotes the synthesis of new cartilage. Its daily dose is 80mg to 100mg in two divided doses. It provides symptomatic control after 4 weeks of administration and remains for up to 12 weeks after discontinuation. Its oral bioavailability is 35-55%. During absorption, diacerein is converted to its active metabolite Rhein (Tamura *et al.,* 2001). Diacerein is the only DMOAD available in market for OA. In India and Pakistan, Diacerein tablets (50mg) are available with brand name Dicerin, Diora, Diritis, Karty and Rein. The clinical acceptability of oral diacerein has been marred by the gastrointestinal adverse effects like increased gastric motility and diarrhea (Louthrenoo *et al.,* 2007). This requires the need of a “para enteral” and joint specific formulation which can avoid gastrointestinal exposure and subsequent first pass effect. Jain et al. have reported solid lipid nanoparticles of diacerein to target drugs joint bypassing GIT (Jain *et al.,* 2013). Recently, we took research in this field one step ahead by preparing solid lipid nanoparticles that can sustain drug release action for as long as three days. In addition, we were able to get thermoresponsive drug release which shows promise to enhance drug release at inflamed joints (Rehman *et al.,* 2015). Another strategy which we have used to enhance bioavailability of diacerein and to bypass GIT is by encapsulating it inside vesicles of non-ionic surfactants, also termed as niosomes. These vesicles showed the potential to sustain drug release rate for more than 12 hours and improve solubility of drug as well as bioavailability in rats (Khan *et al.,* 2015a; Khan *et al.,* 2015b). Madni et al. (2017) demonstrated that dialysis tube cab affect drug release behavior independent of drug delivery system.

Hyaluronic Acid

Hyaluronic acid is a mucopolysaccharide which maintains lubrication of synovial fluid. It is administered intraarticularly into affected joint. Hyaluronic acid and its several derivatives are commercially available. Bellamy et al. (2006) conducted a comparative study of various hyaluronic acids derivatives and found that all are effective in reducing OA pain and functioning to some extent. Their action remains for 5 to 12 weeks after injections. Euflexxa, Hyalgan, Orthovisc, Supartz and Synvisc are most accepted brands of hyaluronic acid and its derivatives. Intraarticular administration should be conduct by an expert physician or technician because an improper injection may damage joint and its components (WebMD, 2017).

Dietary Supplements

Supplements constitute an important part in OA treatment regimen. Supplements are used in combination with OA drugs and usually lack any side effects. These supplements are not controlled by regulatory authorities and have very little clinical data to prove their effectiveness. It is usually thought that a costly supplement is better than a cheaper one but this is not the case. Concomitant use of supplements with OA drugs may lead to serious interaction or overdosing, thus, a patient should consult his physician or the pharmacist before spending large amount of money on these supplements.

Glucosamine Sulphate

The most common OA supplement, glucosamine sulpahte, is a carbohydrate with an amino and a sulphur group. It is building block of cartilage. After oral administration, it is taken up selectively by cartilage and it may be used as building block of chondroitin Sulphate. Perry at al. (1972) demonstrated that Glucosamine Sulphate primarily protects joints from degradation and promotes cartilage regeneration. Its analgesic and anti-inflammatory effect has slow onset but later equal to most of the NSAIDs. Vaz (1982) studied that action of glucosamine after two weeks was lower than that of Ibuprofen but glucosamine showed better results after four weeks and so on. Its daily recommended dose 1000mg in single or two divided doses and it may be taken with milk or soft drinks.

Chondroitin Sulfate

It is a glycosaminoglycan which provides elasticity and resistance to cartilage. The results of clinical trials have shown that chondroitin sulfate is an effective supplement for management of osteoarthritis pain and slows the degeneration of joints (Uebelhart *et al.,* 1998). However it is not superior to chondroitin sulfate. Its daily oral dose is 1000mg once daily or in two divided doses (Leffler *et al.,* 1999).

Glucosamine and Chondroitin Sulfate are most commonly used and are also available in combination which, hypothetically, provides a better management of moderate to severe arthritis. Forever Freedom® is a glucosamine sulfate and Chondroitin Sulfate supplement which also contains very low levels of Methylsulfonylmethane and Aloe Vera (Forever living products, 2015).

SAMe

SAMe (s-adenosylmethionine) is a compound which is synthesized in our body. It exerts its action by inducing the synthesis of hormones, neurotransmitters and phospholipids. Studies have demonstrated that SAMe promotes production of cartilage from chondrocytes and also shows analgesic effects. It is better tolerated than NSAIDs and contraindicated in patients with depressive disorders. However, its use is limited due to high cost and relatively slower onset of action, almost thirty days (Hardy *et al.,* 2002). It is not currently available in India or Pakistan.

MSM

Methylsulfonylmethane (MSM) is found in green vegetables, fruits and also in human adrenal gland. Short term clinical trials have showed that MSM is modestly anti-inflammatory and analgesic. MSM is a second line OA supplement and usually available in combination with other supplements such as glucosamine sulfate (Kim *et al.,* 2006).

Turmeric and Ginger

Turmeric (*Curcuma longa*) and Ginger (*Zingiber officinale*) belong to family Zingiberaceae and have been found to be a second line supplement for OA. Turmeric has anti-inflammatory effect due to active ingredient curcumin which inhibits cyclooxegenase-2, prostaglandins and leukotrienes. Ginger exerts its effects due to inhibition of cyclooxygenases (subtypes 1 and 2) and lipoxygenases. Ginger may also inhibit TNF-alpha and prostaglandins. Clinical trials have shown that ginger has modest improvement in OA pain during walking phase (Altman and Marcussen, 2001). There are no clinical trials for turmeric however results of some preliminary research showed that it relieves the symptoms of OA (Deodhar *et al.,* 1980).

Devil's Claw and Cat's Claw

Devil's Claw (*Harpagophytum procumbens*) and Cat's Claw (a common term for many plants especially *Uncaria guianensis and Uncaria tomentosa)* are native to Africa and get the name "claw" due to the shape of their fruits. Devil's claw activity is attributed to glycoside harpagoside. Harpagoside inhibits cyclooxygenase-2 and it is well tolerated. Usually Devil's Claw supplements are recommended in combination with NSAIDs (Wegener and Lüpke, 2003). Cat's Claw inhibit TNF-alpha and, to a lesser extent, prostaglandins (Piscoya *et al.,* 2001). Devil's Claw is most commonly used second line supplement for the management of OA. It inhibits the hepatic metabolism of many drugs including warfarin and NSAIDs. Thus patient taking warfarin or NSAIDs should consult their physician and the pharmacist before starting the supplement.

Vitamins

Patients with Vitamin D deficiency are at three time higher risk of getting OA. The study of Jon Giles (2009) showed that Vitamin D and exposure to sunlight reduce the degeneration and loss of cartilage in OA patients. Vitamin B6 has demonstrated reduced inflammatory response in arthritis (Huang *et al.,* 2010) while Vitamin B12 and folic acid (Vitamin B9) have shown significant management of OA of hands (Flynn *et al.,* 1994).

DESIGNING AN OSTEOARTHRITIS TREATMENT REGIMEN

OA is generally a disease of elderly who have complex comorbidities. According to U.S. National Institute of Health guidelines on OA treatment, to facilitate the routine working of patients, it is devisable to optimize every aspect of patient's treatment plan (NIAMS, 2016). Ideally, the treatment plan should be designed on the basis of severity of disease as shown in the Table 1.

THE CONCEPT OF MULTIDISCIPLINARY HEALTH CARE TEAM

It is clear that any clinical stage of OA has complex treatment regimens and involves different services of physicians, pharmacist and nurses. Thus an effective patient care plan must involve the synergistic efforts of these entire health professional in accordance with the patient's needs. Physician is responsible for diagnosis of the patient, prescribing the drug and counsel about the precautions and lifestyle modifications. Nursing care is confined to hospitalized patients and involves assessment of symptoms, psychological status, treatment related problems and the administration of medicines. Pharmaceutical care of a patient includes preventing drug related problems, counseling and educating patients about the treatment and ancillary devices, helping physicians in developing patient oriented treatment plan. In the same way, a patient should also take responsibility of his health by knowing about OA, its risk factors, treatment options, precaution and changes he should adapt. Recently, Grotle et al. (2010) evaluated the current trends of health care teams and proposed that physicians and nurses alone cannot manage the treatment of complex chronic diseases like osteoarthritis. The concept of multidisciplinary health care team incorporates a broader range of health professional under same umbrella. According this concept, the complete diagnosis, treatment, prevention of further treatment and the reduction of socio-economic limitations requires a multidisciplinary health care team as shown in Table 2.

Table 1. Recommendations for designing treatment plan on the basis of osteoarthritis severity

Severity of osteoarthritis	Recommended Treatment Regimen*	
	Non-pharmacological Approach	**Pharmacological Approach**
Mild cases or as prevention after the treatment	Modification of life style including diet control and exercise, and supplements	Analgesic should be used on when needed basis
Mild to moderate	Modification of lifestyle including reductions in weight and rest	Drugs like analgesics or a DMOADs
Moderate to severe	Modification of lifestyle including reduction in weight, exercise, adaptation of gait and rest, and novel non-pharmacological OA treatment	Drugs like like analgesic, intra-articularly injected drugs and DMOADs
Severe cases	Modification of lifestyle including rest and modification of gait, novel non-pharmacological interventions and/or surgical procedures	Drugs like analgesics and DMOADs. If patients does not respond to medication, joint surgery is performed

*These recommendations only outline the components of the treatment plan. Choice of drugs may vary depending upon local laws, availability of interventions or the personal experience.

Table 2. Structure of multidisciplinary health care team (MHCT) for osteoarthritis patients

Health Care Professional	Responsibilities
General (Primary care) Physician	GP is the person who diagnoses OA and help you in establishing the whole team.
Rheumatologist	The doctor specialized in arthritis and related diseases will perform further diagnosis and design the treatment plan.
Orthopedic Surgeon	Orthopedist is specialized in surgery of joints and bones, and should be included in the teams for moderate to severe OA patients.
Pharmacist	Pharmacist may guide patient as well as other members of the team about medicine, its administration, economic aspects and side effects. In some setups, the follow up visits and monitoring of ambulatory patients is also carried by the pharmacist.
Physical, acupuncture and occupational Therapist	May guide the patient on how to protect joint, how to conserve energy and how to perform routine activities without pain. These services must be conducted by registered practitioners.
Nurse	Nurse may care hospitalized patients and may educate the patients on how to walk or sleep, how to take medicines. Nurse may also specialize in rheumatology.
Social workers	Social workers may help patients by assisting them in avoiding social limitations, home care and unemployment problems.
Others	In certain cases, a psychiatric or geriatric may also be hired to assist in physical and mental activity of the patient.
The concept of teamlet	Teamlet means a little team. According to this concept, a health coach first meets the patient and inquires about his needs. In a MHCT, a health coach design the necessary members of teams and guides the team to design his treatment plan.

The study of Brenda Goodman also suggested the need of multidisciplinary approach for OA treatment and stressed that the structure of Multidisciplinary Health Care Team should be based on individualized patient needs (Goodman, 2015). This may also be affected by local job structures of different health professional as well as regulatory affairs. However, establishment of an effective treatment plan, it's monitoring and achievement of better treatment outcomes is possible only by close collaborative work of these professionals, preferably in multidisciplinary health care teams.

CONCLUSION

Osteoarthritis is a chronic disease that reduces functionality of affected joint and restricts patient's daily life. Treatment of OA should be based on evidence based approach keeping in mind the patient needs. Modification of life style significantly improves routine function and should be given first consideration. As evident from above discussion, several non-pharmacological and pharmacological interventions are available that can control the pain and swelling of joints. The choice of intervention also depends upon many factors like age, gender, profession, weight, joint type and severity of damage. The evolution of DMOADs has made promises of preventing joints from injury and recovering degraded cartilage. However, association of mild to severe side effects with these agents has called for the joint specific formulations. Effective osteoarthritis treatment should embrace the concept of "health care team" in which physician, specialists, pharmacist and nurse work together to define effectively the complete treatment plan including modification of life style, non-pharmacological supportive interventions and pharmacological therapeutic agent.

Novelty Statement

This comprehensive review article is first of its kind (to our knowledge) in that;

1. It covers all conventional and modern, pharmacological and non-pharmacological treatment options. Attempt has been made to cover all new therapeutic agents in market and those in various phases of clinical trials.
2. Pathogenesis of osteoarthritis and the opportunity of new therapeutic targets has been elaborated with easy to understand flow diagram (Figure 2).
3. The concept of clinical stage of disease based treatment plan and multidisciplinary health care team has been highlights.

This review articles has been compiled with special emphasis on clinical data and will be very helpful to readers who are active practitioners or want to conduct research on any aspect of osteoarthritis.

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CONFLICT OF INTEREST

I hereby declare that this review articles has neither been submitted nor under consideration for publication anywhere. All authors have participated in this publication and I (corresponding author) have obtained the consent for publication from all authors.

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