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Review Article

Pharmacological management of osteoarthritis: Position statement of the Indian Orthopaedic Rheumatology Association

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Abstract

Osteoarthritis (OA) is the most common form of arthritis in the general population, accounting for more pain and functional disability than any other musculoskeletal disease. There remains a paucity of effective and safe pharmacologic options for the management of OA, with oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs) being the primary medications recommended. Therefore, nutraceuticals and supplements have emerged as possible adjuncts or alternatives. Undenatured collagen type II has been studied for its potential benefits during OA supportive care in preclinical and clinical studies, demonstrating positive results with substantially lower therapeutic doses. This review article aims to provide a scientific rationale for a treatment algorithm for the management of OA, including analgesics and nutraceuticals such as undenatured collagen type II and other nutrients.

Keywords: Osteoarthritis, Oral analgesia, Non-surgical management, Topical medication, Intra-articular delivery, Nutraceuticals, Undenatured type II collagen

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1. Introduction

Globally, osteoarthritis is a leading cause of chronic pain and disability and is the most common musculoskeletal disorder with a growing prevalence due to aging populations and increased obesity. The Global Burden of Disease (GBD) study 2021, reported an alarming increase in age-standardized incidence rate of 15% between 1990 and 2021. Furthermore, in 2021, the burden of hip OA in India was 3.6 million, knee OA was 48.4 million, and hand OA was 25.5 million. The prevalence of OA was highest in the 60-64 age group (11.9 million), while the incidence of OA was highest in the 50-54 age group (1.04 million).[1] A study in rural India reported that the community prevalence of knee OA was 34.6%, with a mean Western Ontario and McMaster Universities Arthritis Index (WOMAC) score of 57.38±12.16.[2] The prevalence of primary knee OA is reported to be higher in big cities compared with villages, small cities, and towns (33.2% vs. 29.9% vs. 18.3% vs. 19.3%).[3]

There are several methods for OA staging, including radiographically derived evaluations, joint space narrowing (JSN) measurements, and the Kellgren-Lawrence (KL) scoring system:[4]

0: No radiological findings of osteoarthritis
I: Doubtful narrowing of (JSN) joint space and possible osteophytic lipping
II: Definite osteophytes and possible JSN
III: Moderate multiple osteophytes, definite narrowing of joint space, with or without small pseudocystic areas with

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sclerotic walls and possible deformity of bone contour may be seen
IV: Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour

OA frequently coexists with other chronic conditions particularly in older populations.[5] Multimorbidity increases the complexity of care, and healthcare providers must balance the management of OA with the treatment of other chronic conditions.[6,7] Despite this, conventional pharmacological options only offer symptomatic relief, efficacy is often limited, and adverse effects are common with long-term use.[8] There are no pharmacological agents that alter or slow the progression of OA. Surgical management is undertaken when conservative measures fail to control symptoms and cause significant morbidity to the patients Activities of Daily Living. Total joint replacement is effective, and prostheses may last for up to 20 years.[9] Therefore, there is a growing interest in exploring nutraceuticals and supplements, as potential adjuncts in OA support to address unmet needs and improve patient outcomes.[10]

This article reviews the evidence on pharmacological management of OA using topical, systemic, and intra-articular pharmacological agents for pain management. An expert opinion on the use of currently available pharmacological agents, including supplements, for the management of OA is presented, along with a rational treatment algorithm to healthcare providers to enable effective, safe, and individualized treatment to OA patients.

2. Management of OA

2.1. Pharmacological management: Systemic

2.1.1. Paracetamol

Paracetamol or acetaminophen is a common mild analgesic medication and is included in the World Health Organization's List of Essential Medicines. As part of OA management, paracetamol is commonly recommended for analgesia at an early stage in the treatment recommendations.[11] Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), it does not exert anti-inflammatory action. The central mild analgesic effect is mediated through interfering with the serotonergic descending pain pathways. It is also likely that paracetamol might inhibit prostaglandin synthesis.[12] While paracetamol is a widely used over-the-counter (OTC) analgesic, safety concerns may prevent its use for the management of chronic pain.[11] Recent guidelines from the National Institute for Health and Care Excellence (NICE) recommend that paracetamol should be used infrequently for short-term relief from pain and if other pharmacological options are not tolerated or ineffective or contraindicated, due to the lack of strong evidence of benefit. [13] However, guidelines from the American College Rheumatology conditionally recommend paracetamol for patients with knee, hip, and/or hand OA. [14]

2.1.1.1. Efficacy

A systematic review and meta-analysis of 13 randomized trials including reported that while paracetamol did not significantly reduce the intensity of pain, it did have a significant (yet not clinically important) effect on pain and disability in patients with knee or hip OA in the short term.[15] Combination of paracetamol and NSAID has demonstrated better short-term pain relief compared with NSAID alone without increased risk of AEs in patients with OA. The meta-analysis of 22 studies examining patients with low back pain and OA. Moderate certainly evidence indicated a reduction in pain for paracetamol plus aceclofenac vs aceclofenac (mean difference [MD] -4.7, 95% CI -8.3 to -1.2) and paracetamol plus etodolac vs etodolac (MD -15.1, 95% CI -18.5 to -11.8) among OA patients. Similarly, moderate certainly evidence indicated reduction in pain at intermediate term for paracetamol plus oral tramadol compared with placebo OA (MD -6.8, 95% CI -12.7 to -0.9).[16]

2.1.1.2. Safety

Paracetamol has generally been considered safer than other analgesics drugs. However, higher doses of paracetamol have a considerable degree of toxicity and a dose-response trend has been reported for cardiovascular and renal AEs.[11] Furthermore, the incidence of withdrawals due to adverse effects with paracetamol is significantly higher than that of placebo (77/1,000 participants vs. 65/1,000 participants, risk ratio 1.19), as is the incidence of abnormal liver function (70/1,000 for paracetamol vs. 18/1,000 for placebo, risk ratio 3.79). Thus, patients taking paracetamol are nearly four-fold more likely to have abnormal liver function.[14,17]

2.1.2. Nonsteroidal anti-inflammatory drugs

Guidelines routinely recommend the use of oral NSAIDs for the management of OA pain. These drugs are prescribed in 50-60% of OA patients in USA and Europe. [18] The use of NSAIDs has to be balanced with the potential for adverse effects, through limited duration of use, or use only in patients with persistent pain while also considering the risk profile of individuals. The anti-inflammatory and analgesic effects of NSAIDs are attributed to the inhibition of cyclooxygenase isoenzymes (COX-1 and COX-2) leading to reduced levels of prostaglandins. NSAIDs may be selective (targeting only one isoform of cyclooxygenase) or nonselective (targeting both isoforms).[8]

2.1.2.1. Efficacy

A network meta-analysis analyzing 76 randomized controlled trials (RCTs) evaluated the efficacy of seven NSAIDs, paracetamol and placebo in patients with OA. A clinically important pain reduction was noted for diclofenac 150 mg/day, etoricoxib 30 mg/day, 60 mg/day, and 90 mg/day, and rofecoxib 25 mg/day and 50 mg/day (effect size [ES] -0.37), with the highest probability of pain reduction noted for diclofenac 150 mg/day and etoricoxib 60 mg/day.

Furthermore, diclofenac 150 mg/day and rofecoxib 25 mg/day significantly improved physical function. A dose-dependent response was noted for the interventions analyzed.[19]

A network meta-analysis reported that diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day have high efficacy in pain reduction. The probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain was ≥99%, while it was ≤53% for opioids. Furthermore, the risk of treatment dropout due to adverse effects is higher for opioids compared with NSAIDs (89.5% vs. 29.8%). [20]

2.1.2.2. Safety

Oral NSAIDs have a risk of adverse effects that is recognized by the United States Food and Drug Administration (US FDA) leading to a black box warning on this class of drugs. There is an increased risk of cardiovascular (CV) and gastrointestinal (GI) adverse effects. [21] Upper GI complications include peptic ulcer perforation and bleeding. Oral NSAIDs have up to fivefold higher risk of such complications, and thus, lower doses for limited durations of treatment are preferred. Diclofenac increases the risk of major vascular events by 41% while coxibs increase this risk by 37%. Ibuprofen, but not naproxen, increases the risk of major coronary events. In addition, naproxen carries a lower risk of vascular events.[22]

Older patients have an increased risk of these adverse events. Polypharmacy is common in older adults and can lead to drug interactions with NSAIDs. Older patients are more likely to have CV disease and age-related decline in renal function, increasing the risk of CV, hematologic, and renal AEs. Due to this, guidelines recommend topical NSAIDs over oral NSAIDs for patients aged over 75 years.[18]

It has been reported that over 40% of patients using oral NSAID users are at higher risk for cardiovascular AEs, and over 85% of oral NSAID users are at significant risk for gastrointestinal AEs. The gastrointestinal AEs resulting from oral NSAID use are often asymptomatic and thus unrecognized by patients and providers until they become clinically significant. [23]

2.1.3. Opioids

Opioids act on G protein-coupled opioid receptors, primarily the μ-opioid receptors which inhibits calcium influx and cAMP production, thus inhibiting the release of neurotransmitters. Despite the widespread use of opioids, there is an apparent lack of efficacy as well as a risk of adverse effects and overdose.[24] This is reflected in guidelines, wherein the use of non-tramadol opioids is conditionally recommended against, and can be used only when alternatives are exhausted. [14] Osteoarthritis Research Society International (OARSI) guidelines also strongly recommend against the use of oral as well as transdermal opioids due to the risk of chemical dependency and the limited impact on symptom.[25]

2.1.3.1. Efficacy

A meta-analysis of 22 studies evaluated the efficacy of opioids versus placebo in patients with OA. No clinically relevant benefit of opioids over placebo was noted for pain relief of 50% or more, disability, and patient global impression much or very much improved. Opioids did not have a clinically relevant benefit in improving mean pain intensity. [26]

The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial evaluated opioid and nonopioid medication therapy in patients with chronic back pain or knee/hip OA pain of moderate or severe intensity despite analgesic use. Multiple medication options were prescribed in three steps. Patients in the opioid group received immediate-release morphine, oxycodone, or hydrocodone/ acetaminophen. Patients in the nonopioid group received acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug. At 12 months, the treatment groups did not differ in pain-related function, functional response (≥30% improvement in Brief Pain Inventory [BPI] interference), and health-related quality-of-life (HRQoL). However, pain intensity was significantly improved in the non-opioid group at 12 months. [27]

2.1.3.2. Safety

Opioids have an increased burden of adverse effects compared with placebo, including nausea (relative risk [RR] 3.17), constipation (RR 3.57), vomiting (RR 3.65), dizziness (RR 3.06), somnolence (RR 3.61), fatigue (RR 2.52), hyperhidrosis (RR 4.85), and pruritus (RR 4.88). Overall, the risk of experiencing severe adverse effects was 3.12 times higher for opioids compared with placebo. The rate of treatment discontinuation due to adverse effects was significantly higher in the opioid group. [28]

A meta-analysis by Welsch, et al., also reported that more patients receiving opioids discontinued treatment due to adverse effects (26.4% vs. 7.1%, $p<0.0001$) and therefore, clinically relevant harm due to opioids was apparent. Subgroup analysis revealed that the risk difference (RD) for dropout rates due to adverse effects for pure opioids was 0.25 and for tapentadol and tramadol was 0.12.[26] In the SPACE trial, the opioid group had significantly more adverse effects. The findings did not support the use of opioid medication for knee/hip OA pain.[27]

2.1.4. Symptomatic slow-acting drugs for OA (SYSDOA): Chondroitin sulfate and glucosamine

Pharmacological options for the management of OA largely provide only symptomatic relief without addressing the pathophysiology of OA, have known adverse effects. This led to the development of symptomatic slow-acting drugs

(SYSADOAs) such as chondroitin sulfate (CS) and glucosamine which have better tolerability and safety compared to traditional pharmacological options.[36,37] Glucosamine and CS are naturally occurring compounds that are important for the synthesis of proteoglycans which maintain the integrity of articular cartilage. Chondroitin is present in the connective tissues and the extracellular matrix of articular cartilage. [37,38] CS has a delayed onset of action and provides symptomatic relief as well as disease modification by slowing the progression of joint space narrowing. While several clinical trials have demonstrated the efficacy of these two molecules, guidelines do not recommend their use. [36]

CS has been shown to reduce the number of apoptotic chondrocytes in studies *in vitro and in vivo*. It increases the production of proteoglycans and type II collagen (anabolic effect). CS might also have an anti-catabolic effect by limiting the synthesis/activity of metalloproteases, which are responsible for the degradation of ECM components. [37]

Though the ACR had conditionally recommend d the use of glucosamine in patients with OA, the 2019 guidelines strongly recommended *against* the use of glucosamine in patients with knee, hip, and/or hand OA. While CS is strongly recommended against for patients with knee and/or hip OA, it is conditionally recommended for patients with hand OA.[14] NICE guidelines do not recommend the use of glucosamine due to the lack of sufficient evidence of benefit.[39]

2.1.4.1. Efficacy

A clinical trial comparing glucosamine and CS alone and in combination compared with placebo reported statistically significant reduction in JSN at 2 years. Monotherapy with either glucosamine or CS did not significantly reduce JSN or knee pain at 2 years. JSN at 2 years was 0.12 mm with the combination compared with 0.22 mm with placebo, but knee pain did not significantly reduce with the combination treatment.[38]

A meta-analysis reported the effect of glucosamine and CS in patients with OA. While glucosamine alone and in combination with CS did not significantly reduce OA pain compared with placebo, CS monotherapy had a significant effect on pain. In addition, glucosamine significantly reduced stiffness and improved function, while chondroitin sulfate alone and in combination with glucosamine significantly improved function.[36] In contrast, a recent meta-analysis CS (with decreased pain intensity and improvement in the physical function), and GS (with significant reduction in the joint space narrowing) have significant therapeutic benefits. However, their combination did not significantly improve the symptoms or modify the disease.[40]

2.1.4.2. Safety

CS is extracted from animal and fish cartilage and undergoes purification to minimize the presence of contaminants. However, other glycosaminoglycans, bacteria, viruses and prions, and other polysaccharides (hyaluronic acid, dermatan sulfate, and keratan sulfate) can contaminate preparations of chondroitin sulfate. Infective contaminant can cause severe adverse effects, while contaminating proteins can cause allergic and immunologic reactions.[37] Glucosamine, though well-tolerate, can interact with coumarin anticoagulants[41] may worsen glucose intolerance for patients with untreated or undiagnosed glucose intolerance or diabetes.[42] Combinations of CS with glucosamine and vitamins/minerals have been banned in India due to the lack of therapeutic justification.[43]

2.1.5. Undenatured collagen type II

The long-term use of drugs for symptomatic relief of pain has limitations including lack of slowing disease progression, risk of adverse effects, particularly CV and gastrointestinal adverse effects, and lack of treatment compliance due to these adverse effects.[10] Interest in nutraceuticals led to the development of undenatured collagen type II (UCII, Lonza) as a supplement with preventive or therapeutic effects in patients with OA. Collagen is a crucial component of extracellular matrix (ECM) and connective tissue and it has been demonstrated that collagen supplementation leads to accumulation of collagen in cartilage. UCII is resistant to gastric acid and digestive enzymes. [44]

UCII maintains the triple helical structure and preserves active antigenic epitopes that are effective in OA patients. It modulates the humoral and cellular response, and presents a cartilage regeneration benefit. The antigenic epitopes undergo uptake by dendritic cells leading to the differentiation of naïve T cells to regulatory T cells (Tregs). Tregs pass through the systemic circulation and exert anti-inflammatory effects at the articular cartilage. This occurs through the secretion of anti-inflammatory mediators (transforming growth factor-beta [TGF-β], interleukin 4 [IL-4], and interleukin 10 [IL-10]). This reduces joint inflammation and permits cartilage repair.[10,44]

2.1.5.1. Efficacy

UCII vs glucosamine + CS: Among patients with unilateral or bilateral OA of the knee, UCII treatment for 180 days led to significant reduction in WOMAC scores compared with the placebo and G + C groups (-39.4% vs. -29.9% vs. -32.5%, respectively. Furthermore, significant reduction in VAS score (-38.7% vs. -29.2% vs. -31.1%, respectively) and total Lequesne's functional index (LFI) score (-36.7% vs -27.1% vs. -37.8%) was also reported.[45] Treatment with UCII compared with glucosamine + chondroitin sulfate for 90 days led to greater improvement in WOMAC scores (33% vs. 14%), decrease in VAS score (40% vs. 15.4%), and reduction in LFI (20.1% vs. 5.9%).[46]

UCII vs placebo: Placebo-controlled studies have demonstrated the favorable effect of UCII on joint health. Sadigursky, et al., reported that 90 days of UCII treatment led

to improved pain using the VAS score (difference from baseline -3.8±1.8 -1.3±2.0, p<0.001) and WOMAC scores (-6.6±4.8 vs. -1.0±3.8, p<0.001), improved fitness using the WOMAC score (-0.5±0.9 vs. 0.1±1.1, p=0.001), as well as improved quality-of-life.[47] Supplementation with UCII in addition to physiotherapy increases quadriceps muscle strength, and active and passive knee flexion mobility. UCII augmented the effect of muscle strengthening exercises. [48] **Table 2** summarizes the key clinical trials evaluating the efficacy of UCII.

Table 1: Summary of key clinical studies evaluating efficacy of paracetamol, NSAIDs, and opioids

Study design	Subjects	Intervention	Outcomes
Paracetamol			
Randomized, double-blind, double-dummy, parallel, phase 3 study[29]	Moderate to moderately severe OA	Paracetamol 1000 mg SR x 2 tablets plus 2 placebo tablets twice daily Paracetamol 665 mg x 2 tablets plus 2 placebo tablets three times daily For 12 weeks	**Efficacy:** SR 2 x 1000 mg paracetamol BID had 41% change over baseline in WOMAC pain subscale
Prospective, randomized, open-label, parallel-group, active-controlled study[30]	Patients aged ≥45 years with symptomatic knee OA for ≥3 months; mild-to-moderate pain (VAS score ≥3) while not taking analgesics	Paracetamol 650 mg dual-release (325 mg IR + 325 mg ER) twice-daily vs. paracetamol 500 mg IR three times daily For 6 weeks	**Efficacy:** Paracetamol 650 mg dual release had significantly greater reduction in pain intensity vs. paracetamol 500 mg IR at weeks 2, 4 and 6 (p<0.0001), and greater improvement in KOOS score **Safety:** Rate of AEs: 5.5% vs. 13.7%
NSAIDs			
Systematic review and meta-analysis[22]	280 trials of NSAID vs. placebo including 124,513 patients and 474 trials of NSAID vs. NSAID including 229,296 patients	NSAIDs and placebo	**Safety:** Major vascular events were increased by about 33% for coxib and diclofenac.
SUCCESS-I study: Multicenter, multinational, randomized, double-blind, 3-arm, active-comparator trial[31]	Age ≥18 years, hip or knee or hand OA for≥6 months, ; required daily anti-inflammatory agents or other analgesic therapy; Functional Capacity Classification I-III	Celecoxib 100 mg twice-daily vs. celecoxib 200 mg twice-daily vs. naproxen 500 mg twice-daily vs. diclofenac 50 mg twice-daily For 12 weeks	**Efficacy:** Both dosages of celecoxib were as effective as NSAIDs **Safety:** More ulcer complications with non-selective NSAIDs than celecoxib (0.8/100 patient-years vs 0.1/100 patient years) CV complications were low and not significantly different between the groups
Opioids			
Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial[32]	Age ≥18 years, functional class I-III primary OA of the knee meeting ACR diagnostic criteria, morning stiffness <30 minutes and/or crepitus, treatment taken for ≥75 of the past 90 days, VAS ≥40 mm	Tramadol ER 100 mg daily; uptitration to 200 mg daily between days 4-8; uptitration to 300 mg or 400 mg after the first week Placebo control	**Efficacy:** Tramadol group had a greater change in Arthritis Pain Index VAS over 12 weeks (30.4 mm vs. 17.7 mm), and WOMAC pain subscale (120.1 mm vs. 69 mm), WOMAC physical function subscale (407 mm vs. 208.5 mm), WOMAC stiffness subscale (48.9 mm vs. 27.3 mm)
Pragmatic, randomized-trial[27]	Chronic back pain, or hip or knee OA with moderate-to-severe pain despite analgesic use	Opioid group: Morphine, oxycodone, or hydrocodone/acetaminophen IR	**Efficacy:** The non-opioid group had significantly better pain intensity at 12 months

		Nonopioid group: Paracetamol or NSAID	No significant different in BPI severity, HRQoL **Safety:** Medication-related symptoms were higher in the opioid group: 1.8 vs. 0.9
Comparison between drug classes			
Randomized, double-blind, double-dummy, parallel-group, multicenter clinical trial[33]	Aged 30-75 years, with primary knee OA degrees II or III (KL classification), history of knee pain for ≥3 months in the last year, current knee pain ≥30 mm on VAS scale, and ACR functional classes I-III	Paracetamol 1,000 mg plus placebo tablet three times daily vs. aceclofenac 100 mg plus placebo tablet three times daily For 6 weeks	**Efficacy:** Aceclofenac group had significantly greater improvement sin VAS (mean treatment difference 7.64 mm), Lequesne OA index (mean treatment difference 1.41), patient's global assessment (mean treatment difference 0.33), and physicians global assessment (mean treatment difference 0.23) **Safety:** Rate of AEs: 32% for aceclofenac vs. 29% for paracetamol Rate of AEs related or possible related to the study drug: 61% for aceclofenac vs. 35.5% for paracetamol
Pragmatic open-labelled randomised controlled trial[34]	Age ≥45 years; new episode of non-traumatic knee pain; knee pain severity of ≥2 (on a 0–10 scale); ACR clinical criteria for knee OA fulfilled	Diclofenac maximum 50 mg three times daily for 12 weeks vs paracetamol maximum 1,000 mg three times daily for 12 weeks	**Efficacy:** No significant difference in daily knee pain over 2 weeks and 4 weeks follow-up, and in KOOS pain over 12 weeks follow-up **Safety:** More patients reported AEs in the diclofenac group: 63.5% vs. 46.2%
Systematic review and meta-analysis[20]	192 clinical studies including 102,829 patients	90 active preparations or doses (NSAIDs, opioids, and paracetamol)	**Efficacy:** Compared to the minimal clinically relevant reduction in pain, (diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day) had ≥99%, and all opioids had ≤53% probability of more pronounced treatment effects **Safety:** Oxymorphone 80 mg/day had the highest risk of dropouts due to adverse events (51%) and any adverse event (88%)
Systematic review and meta-analysis[35]	17 clinical studies	27 active treatment arms (NSAIDs and opioids)	**Efficacy** No clinically important or statistically significant difference among NSAIDs, less potent opioids, and potent opioids Trend for NSAIDs to result in larger WOMAC Pain changes than opioids

ACR: American College of Rheumatology; AE: Adverse effects; BID: Twice-daily; BPI: Brief Pain Inventory; CV: Cardiovascular; ER: Extended-release; IR: Immediate-release; HRQoL: Health-related quality-of-life; KL: Kellgren-Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score (KOOS); OA: Osteoarthritis; NSAID: Nonsteroidal anti-inflammatory agent; SR: Sustained-release; VAS: Visual Analog Scale; WOMAC: Western Ontario McMaster Universities Arthritis Index.

Table 2: Summary of key clinical studies evaluating efficacy of undenatured collagen type II

Study design	Subjects	Intervention	Outcomes
Multicenter, randomized, double-blind, placebo-controlled study[45]	Age 40–75 years with unilateral or bilateral OA of the knee (moderate-to-severe); BMI 18–30 kg/m^2; knee pain for ≥3 months; LFI score 6–10, VAS 40–70 mm; K-L radiograph score 2 or 3	UCII 20 mg, two capsules once-daily vs. glucosamine 1,500 mg + chondroitin 1,200 mg daily vs. placebo **For 180 days**	**Efficacy:** UCII group compared with the placebo and G + C groups, had significant reduction in WOMAC (-39.4% vs. -32.5% vs. -29.9%), VAS (-38.7% vs. -31.1% vs. -29.2%), LFI (-36.7% vs. -37.8% vs. -27.1%) **Safety:** Similar findings were reported across the groups
Non-interventional real-life study[49]	Clinically or radiologically diagnosed knee OA	UCII 40 mg daily For 90 days	**Efficacy**: Significant reduction from baseline in WOMAC (-40.11%) and VAS (-52.26%) scores at 90 days **Safety**: Rate of treatment-emergent adverse events: 4.47%
Prospective study[50]	Age 45–65 years, moderate or severe OA in one or both knees, BMI 24–30 kg/m^2, pain for ≥3 months, LFI 6–10, VAS 40–70 mm, K-L score 2–3	UCII 40 mg daily For 120 days	**Efficacy:** Reduction in WOMAC mean subscores (-95.5% for pain, -60% for stiffness, -80% for physical function), mean VAS scores (p=0.002) and LFI scores (p=0.008)
Prospective study[51]	Age ≥18 years with grade 2-3 knee OA	UCII 40 mg daily For 24 weeks	**Efficacy:** Improvement in Leken index vs. baseline (13.3±3.90 vs. 9.97±4.14), WOMAC score (39.6±13.5 vs. 26.5±11.55), right knee joint cartilage thickness (0.18±0.03 sm vs. 0.20±0.03 sm) and left knee joint cartilage thickness (0.17±0.03 sm vs. 0.20±0.03 sm) **Safety:** No adverse effects related to the study drug
AE: Adverse effects.			

2.1.6. Vitamin and minerals

2.1.6.1. Vitamin K2

Vitamin K2 is an important regulator of bone and cartilage mineralization acting as a cofactor for gamma-carboxylation of G1a proteins.[52] Vitamin K2 activates the expression of glutathione peroxidase 4 (GPX4) in chondrocytes which in turn regulates the degradation of extracellular matrix (ECM). The delayed degradation of ECM, promotion of chondrocyte proliferation, and increase in type II collagen accumulation contributes to the anti-OA affects of vitamin K2. Animal studies demonstrated that IA injection of vitamin K increases bone volume/total volume (BV/TV) and cartilage thickness in the tibia subchondral bone.[53] Vitamin K2 deficiency increases the risk of incident radiographic knee OA by 56% and cartilage lesions by approximately two-fold.[52]

2.1.6.2. Vitamin D3

Inadequate intake of vitamin D is associated with a higher prevalence of radiographic knee OA, higher levels of pain and a greater risk of progression.[54] A 3.3-fold higher risk of incident Joint space narrowing is reported for adults with low levels of vitamin D (25(OH)D <75 nmol/L). A greater loss of joint space over eight years is reported for OA patients with vitamin D ≤55 nmol/L compared to those with 25(OH)D ≥ 75 nmol/L.[55]

On a physiological level, inadequate vitamin D adversely affects the structure and function of articular cartilage. This contributes to the progression of OA with increasing joint pain, reduced muscle strength and limitations to physical activity.[56] It is possible that vitamin D and the vitamin D receptor VDR interferes with the activation of the TGFβ

pathway, or interact with SMAD3 or MMP13 to ameliorate OA. The findings of *in vivo* studies have shown that high-dose vitamin D supplementation leads to an increase in the expression of TGFβ1 and type-II collagen.[55] **Table 3** summarizes the key clinical trials evaluating the efficacy of vitamin D in management of OA

Deficiency of vitamin D accelerates the development of age-related knee OA, while vitamin D supplementation can improve the articular cartilage structure, reduce joint pain, and enhance functionality and quality of life in OA patients.[54,58,61]

Table 3: Summary of key clinical studies evaluating efficacy of vitamin D

Study design	Patient selection criteria	Intervention	Outcomes
Systematic review and meta-analysis[54]	4 RCTs involving 1,136 patients	Daily dosage of vitamin D supplementation: 800 IU to 60,000 IU	Vitamin D supplementation was associated with a significantly greater reduction in WOMAC pain and WOMAC function compared with placebo
Vitamin D Effect on Osteoarthritis (VIDEO) study: Multicenter randomized, double-blind, placebo-controlled[57]	Symptomatic knee OA and low 25-OH(D) 12.5-60 nmol/L	Cholecalciferol 50,000 IU (1.25 mg) monthly for 24 months vs. placebo control	**Efficacy:** Patients achieving 25-OH(D) >60 nmol/L: 79% vs. 43% No significant difference in WOMAC pain and tibial cartilage volume between the groups at 2 months **Safety:** Rate of AE: 27% vs. 18%
Double-blind, randomized, placebo-controlled trial[58]	Aged >50 years, ambulatory, radiological evidence of knee OA at medial tibio-femoral knee compartment (Modified KL score 2/3, JSW >1 mm) and knee pain for most days of the previous month	Cholecalciferol 800 IU daily vs. placebo	**Efficacy:** No significant difference in the rate of JSN over three years in the medial compartment of the index knee between treatment groups No significant difference in WOMAC pain, stiffness, and physical function between the groups **Safety:** Rate of serious AE: 25% vs 27%
Prospective, randomized double-blind, parallel, placebo-controlled pilot trial[59]	Knee OA, age ≥50 years, BMI <30 kg/m^2, morning stiffness <30 minutes, knee pain for 6 months, WOMAC pain score >4, on conventional OA treatment for >6 months	Cholecalciferol 60,000 IU/day for 10 days followed by 60,000 IU once a month for 12 months vs. placebo one capsule/day for 10 days followed by once a month for 12 months	**Efficacy**: Patients in the vitamin D group had less knee pain at 12 months on the WOMAC (-0.55 vs. 1.16, p<0.001) and on the VAS (-0.26 vs. 0.13, p=0.02) pain scale, and better WOMAC physical function (-1.36 vs. 0.69, p<0.001)
Single center, randomized, placebo-controlled, double-blind, clinical trial[60]	Symptomatic knee OA, age ≥45 years, BMI <30 kg/m^2, at least mild pain on one of the weight-bearing questions of the WOMAC pain subscale	Cholecalciferol 2,000 IU daily with increments at 4, 8, and 12 months to target a 25-OH(D) level between 36-100 ng/mL	**Efficacy:** No significant difference in knee pain (-2.3 vs. -1.5) and cartilage volume (-4.3 vs. -4.3) between the groups **Safety:** Rate of AE was not significantly different between the groups (serious AEs: 31 vs. 23; no. of participants with AE: 16 vs. 16)

AE: Adverse effects; BMI: Body mass index; JSW: Joint space widening; KL: Kellgren and Lawrence; OA: Osteoarthritis; RCT: Randomized controlled trial; WOMAC; Western Ontario and McMaster Universities Index.

2.1.6.3. Calcium

Calcium salts are suggested to have anti-inflammatory effects. Animal studies have indicated that calcium gluconate improves cartilage damage, reduces articular thickness, and articular stiffness that is characteristic of OA. Calcium gluconate protects chondrocytes against apoptosis. Anti-inflammatory action of calcium gluconate is evident through inhibition of COX-2 expression, which can lower levels of caspase-3 and chondrocyte death. Thus, calcium gluconate might slow the progression of OA. [62]

2.1.6.4. Zinc

Zinc plays a role in enhancing the growth and maturation of cartilage and promoting the differentiation of mesenchymal stem cells into chondrocytes.[63] A significant fraction (30%) of the zinc in the body is stored in the bones.[64] Zinc stimulates the synthesis of metallothionein and is required for improving the activity of vitamin D. Zinc deficiency leads to disorganization of chondrocytes and inhibition of the proliferation of chondrocytes. In vitro studies have shown a 40-50% increase in the proliferation of cultured chondrocytes exposed to low doses of zinc (<0.5 μM).63 In vivo experiments demonstrated that zinc supplementation at a dose of 1.6 mg/kg/day can prevent the progression of OA measured through smooth joint surfaces, lower OARSI scores and preservation of proteoglycan.[65] Among patients with OA, increased intake of zinc reduced the likelihood of deterioration in trabecular number (odds ratio 0.967), trabecular thickness (OR 0.958), and trabecular separation (OR 0.967), thus potentially delaying the progression of subchondral sclerosis.[66]

2.1.6.5. Manganese

Manganese acts as a cofactor for enzymes such as glycosyltransferase which is involved in the synthesis of components of the ECM including proteoglycan and collagen. Manganese is involved in the metabolism of articular cartilage, and is necessary to slow the degeneration of cartilage. Manganese dioxide exhibits antioxidative effects which an reduce the oxidative stress in the articular cartilage.[63]

2.1.6.6. Copper

The regeneration of articular cartilage and subchondral bone is regulated by copper, through activation of the immune response of cartilage. This facilitates the recovery of cartilage lesions. Inhibition of the inflammatory response by copper can ameliorate damage to the cartilage and promote the proliferation of chondrocytes.[63] Animal studies have demonstrated that copper-containing topical formulation of indomethacin reduced serum interleukins and improved mobility and motor function.67 Copper reduces the release of nitric oxide (NO) which prevents the decomposition of cartilage matrix proteoglycan. Deficiency of copper can negatively impact bone strength, and impair cartilage integrity. Copper supplementation improves collagen cross-linking and can thus reduce the severity of osteochondrosis and cartilage lesions.[63]

3. Pharmacological Management: Topical NSAIDs

Topical NSAIDs are recommended universally by guidelines as the first treatment option for managing OA pain based on the efficacy as well as the greater safety compared with oral NSAIDs. Furthermore, topical NSAIDs can be prescribed to elderly patients including those with comorbidities and increased cardiovascular risk in whom oral NSAIDs may be contraindicated.[68] Topical NSAIDs have led to lower systemic exposure compared with oral NSAIDs while achieving therapeutic concentrations in target tissue including muscle, patella, cruciate ligament, and patellar tenson. Serum concentrations remain in the range of 0.4-2.2% of that achieved with oral NSAIDs.[68,69] Therefore, topical NSAIDs overcome the safety limitations of oral NSAIDs while providing symptomatic relief.

3.1. Efficacy and safety

A meta-analysis reported that topical diclofenac, ketoprofen, and ibuprofen reduce pain, and improve physical function more effectively than placebo in patients with knee OA (with moderate effect size).[68] Topical and oral NSAIDs are equally effective in reducing pain, improving function as assessed by the WOMAC, Osteoarthritis Index, and improving stiffness in patients with OA.[70]

A network meta-analysis evaluated topical NSAIDs against oral paracetamol and oral NSAIDs. Topical NSAIDs were more effective than paracetamol in improving function at 4 weeks of treatment, with a 48% lower risk of gastrointestinal AEs. The risk of cardiovascular AEs and withdrawal due to AEs was not significantly different. The risk of death was 41% lower among users of topical NSAIDs compared with paracetamol (16.9/1,000 person-years vs. 28.8/1,000 person-years, rate difference -11.9). Similarly, topical NSAIDs were associated with a 27% lower risk of major CV diseases, 19% lower risk of venous thromboembolism, and 47% lower risk of gastrointestinal bleeding compared with oral paracetamol. Topical and oral NSAIDs had a similar impact on pain and function after 4 weeks and 12 weeks of treatment, and topical NSAIDs had a 54% lower risk of gastrointestinal AEs. The risk of death was 41% lower among users of topical NSAIDs compared with oral NSAIDs (17.3/1,000 person-years vs. 29.5/1,000 person-years, rate difference -12.2). Similarly, topical NSAIDs were associated with a 26% lower risk of major CV diseases, 27% lower risk of venous thromboembolism, and 29% lower risk of gastrointestinal bleeding compared with oral NSAIDs. Overall, efficacy of topical NSAIDs was greater than paracetamol and similar to oral NSAIDs, with greater safety. [71]

Basic principles of management

Combination of treatment modalities (pharmacological and non-pharmacological) is recommended

Lifestyle management (for all grades of OA)

- Weight loss if overweight
- Exercises including aerobic, strengthening, and/or resistance exercises depending on the grade of OA
  - Weight-bearing exercises are not appropriate for severe OA

Management of comorbidities

- Comorbidities (overweight/obesity, type 1 or 2 diabetes, hypothyroidism, hyperthyroidism, hypertension) should be managed appropriately
- Vitamin D status should be corrected

STEP 1 (for grade 1, 2, and early grade 3 OA with undisturbing comorbidities)

After making a correct diagnosis and excluding inflammatory arthropathies

If symptomatic:
Undenatured type II collagen
± paracetamol as required

↓

If still symptomatic:
Add topical NSAIDs depending on the surgeon's choice

Include as required:
Walking aids (stick, walker, crutches)
Thermal agents
Bandage tape
Hydrotherapy
Mechanotherapy or manual therapy

STEP 2 (for grade 1, 2, and early grade 3 OA with undisturbing comorbidities)

If still uncontrolled, add oral NSAIDs (intermittent or longer cycles)

Risk group	Preferred agent	Caution
Normal GI risk	Non-selective NSAID or COX-2 selective NSAID with PPI	
Increased GI risk or use of low-dose aspirin	COX-2 selective NSAID (celecoxib) with PPI	Monitor for complications with NSAID
Increased CV risk	COX-2 selective NSAID (celecoxib) with PPI	
Increased renal risk	Avoid NSAIDs if GFR <30 cc/min	

If still uncontrolled, intra-articular modalities including hyaluronic acid or regenerative orthobiologic modalities may be used under aseptic measures based on the surgeon's experience
If *corticosteroids are preferred, a single injection of intra-articular corticosteroid (preferably the hexacetonide salt) may be given once in a year*

STEP 3 (for grade 1, 2, and early grade 3 OA with undisturbing comorbidities)

If still uncontrolled, add

- Short-term weak opioids
- Duloxetine (with appropriate dose titration) may be included depending on the case

STEP 4 (for grade 3 and 4 OA)

Management of advanced disease not responding to the above modalities

If severely symptomatic, total joint replacement or arthroplasty or other surgical modalities can be carried out depending on the case and the surgeon's experience

COX-2; Cyclooxygenase 2; CV: Cardiovascular; GFR: Glomerular filtration rate; GI: Gastrointestinal; NSAID: Nonsteroidal anti-inflammatory drug; OA: Osteoarthritis; PPI: Proton pump inhibitor.

Figure 1: Treatment algorithm for the management of OA

4. Pharmacological Management: Intra-Articular Injections

Intra-articular (IA) injections (including corticosteroids and hyaluronic acid [HA]) are used to provide short-term relief from pain, and can improve function as well. IA injections are used for patients are unresponsive to oral medication or do not tolerate oral medication, and to delay or avoid surgical management.[8,72,73]

Exogenous HA injections provide lubrication and mechanical support to the joint. A number of formulations are available. Cross-linked HA may provide long-lasting efficacy and reduce joint degradation, improve elasticity and structural integrity of the joints.[8] HA inhibits enzymatic degradation of cartilage and also inhibits nociceptors. Furthermore, antioxidant action and stimulation of endogenous HA synthesis have been reported. IA corticosteroids provide short-term to medium-term relief from pain, and reduce synovial inflammation by downregulating collagenases and proinflammatory mediators. Therefore, IA corticosteroids can slow the progression of cartilage damage. [72]

NICE guidelines recommend that IA corticosteroid injections can be considered when other pharmacological treatments are ineffective or unsuitable, and as a supplement to exercises.[39] The ACR guidelines recommend IA glucocorticoid injections for patients knee and/or hip OA, with a conditional recommendation for patients with hand OA. However, the ACR guidelines recommend against IA HA injections due to the failure of establishing benefit and the possibility of harm.[14]

4.1. Efficacy and safety

A comparative clinical trial recently evaluated the efficacy of IA injections of glucocorticoids, HA, platelet-rich plasma, and placebo in patients with mild or moderate OA of the knee. The study reported that none of the treatments had short-term or long-term effects on pain or function compared to placebo.[73] Five weekly IA injections of sodium hyaluronate have demonstrated efficacy in improving the 50-foot walking test compared to placebo (change from baseline to 25 weeks: 30.85±14.16 vs. 23.62±16.38, p=0.002) in patients with knee OA. Patients receiving sodium hyaluronate had significantly better WOMAC pain scores and WOMAC function scores at 5 weeks compared with placebo. Sodium hyaluronate was considered well-tolerated, with all AEs being mild or moderate in intensity.[74]

A study by Hangody, et al., compared the efficacy of cross-linked HA with the combination of HA and triamcinolone hexacetonide in patients with knee OA. Patients received a single injection of cross-linked HA, HA plus triamcinolone hexacetonide, or placebo and were followed up for 26 weeks. The combination of HA plus triamcinolone hexacetonide significantly improved WOMAC pain score up to 26 weeks compared with placebo, and up to 3 weeks compared with cross-linked HA. Improvement in WOMAC Pain from baseline was 70% and 64% at 12 weeks with combination therapy and monotherapy, respectively, while it was 72% and 65% at 26 weeks with combination therapy and monotherapy, respectively. There were significantly more responders in the combination *versus* the placebo group (93% vs. 84% at 26 weeks), and compared with the monotherapy group (92% vs. 83% at 3 weeks).[75]

Leopold, et al, compared the frequency of acute local reactions in patients receiving multiple cycles of IA Hylan to those patients receiving only 1 course. It was reported that multiple cycles led to an 8-fold increase in the risk of local adverse effects. A post-marketing survey reported that the use of avian high-molecular weight crosslinked HA injections caused inflammatory reactions including pseudo sepsis/severe acute inflammatory reactions.[76]

5. A Treatment Algorithm for the Management of Osteoarthritis

A suggested treatment algorithm for the management of OA is presented in **Figure 1**.[77]

6. Conflicts of Interest

Dr. Atul Sharma is on the payrolls of Haleon/ GlaxoSmithKline Asia Private Limited, India.

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