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Osteoarthritis as Debilitating Medical Condition: Pharmaceutical Treatment and Management-An Updated Review

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Abstract:

Background: Osteoarthritis (OA) is a common, debilitating condition marked by chronic pain, which significantly affects the quality of life, physical functionality, and mental health of affected individuals. While there are no disease-modifying treatments available, pain management remains a critical component of OA treatment. This review highlights the pharmacological options used for managing OA pain, evaluating their mechanisms, pharmacokinetics, potential side effects, and toxicity.

Aim: The aim of this review is to provide an updated analysis of the pharmaceutical treatments for OA, focusing on their effectiveness, safety profiles, and application in clinical practice, with an emphasis on current guidelines.

Methods: A comprehensive review of the latest clinical guidelines and recent studies was conducted to assess various pharmacological treatments for OA. Specific focus was placed on nonsteroidal anti-

inflammatory drugs (NSAIDs), including both oral and topical forms, as well as other treatments like COX-2 inhibitors and duloxetine.

Results: NSAIDs, both oral and topical, remain the most commonly prescribed medications for OA pain management. Oral NSAIDs, although effective, carry risks of gastrointestinal, cardiovascular, and renal toxicity. Topical NSAIDs have a better safety profile with fewer systemic side effects and are recommended for knee OA and individuals with comorbidities. COX-2 inhibitors, while offering reduced gastrointestinal toxicity, are linked to cardiovascular risks and are not recommended for frail or Cardiovascularly compromised patients. Duloxetine is conditionally recommended for knee OA in patients with depression, offering a potential alternative to opioids in certain cases.

Conclusion: While pharmaceutical treatments, particularly NSAIDs and COX-2 inhibitors, remain central to OA pain management, their use requires careful consideration of patient-specific risk factors. Newer treatments like duloxetine offer additional options, especially for those with comorbidities, although further evidence is needed to fully support their widespread use.

Keywords: Osteoarthritis, Pain management, NSAIDs, COX-2 inhibitors, Duloxetine, Pharmacological treatments, Guidelines, Safety, Efficacy

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Introduction:

For people with osteoarthritis (OA), chronic pain is a common and incapacitating problem that severely reduces their physical functionality, mental health, and quality of life. Even though there are now no authorized disease-modifying treatments for OA, pain management is still developing. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), the American College of Rheumatology (ACR), the American Academy of Orthopedic Surgeons (AAOS), the European Alliance of Associations for Rheumatology (EULAR), and the Osteoarthritis Research Society International (OARSI) have all updated their guidelines in the last five years to consider the most recent research on treatment approaches [1, 2, 3, 4, 5, 6]. For the management of OA, these guidelines suggest a wide range of therapy, including behavioral, psychological, educational, physical, mind-body, and pharmaceutical approaches. An overview of the currently approved pharmacological therapies for OA is provided in this study. These medications continue to be a vital component of clinical pain management. In order to support the creation of patient-centered treatment programs, it investigates the pharmacokinetics, mechanisms of action, and possible toxicity of various medicines.

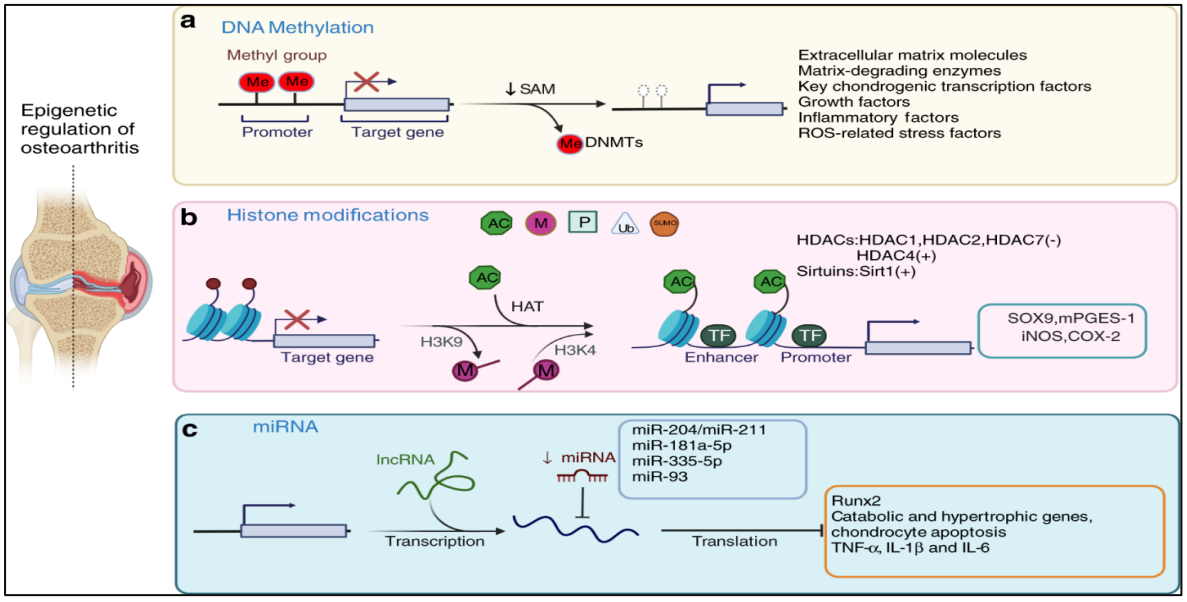

Figure 1: Pathogenesis of Osteoarthritis.

Oral Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Oral nonsteroidal anti-inflammatory medicines (NSAIDs) remain the most often prescribed pharmaceutical treatment for pain associated with osteoarthritis (OA), despite worries about their possible toxicity. Although toxicity hazards have prompted caution, guidelines support their use in managing OA. In the absence of comorbidities, OARSI conditionally advises oral NSAIDs for individuals with polyarticular, hip, or knee OA [1]. NSAIDs are highly recommended by the ACR/Arthritis Foundation and AAOS for the treatment of OA of the hand, hip, or knee [2, 3, 4]. According to EULAR, people with hand OA may benefit from short-term usage of oral NSAIDs to reduce their symptoms [5]. Their usage in patients with chronic symptomatic knee OA is strongly recommended by ESCEO [6]. However, the risk profile of each patient should be taken into consideration while making clinical decisions. For instance, NSAID use should be closely monitored in people with increased cardiovascular or renal risks; in these situations, the ESCEO advises limiting or avoiding the drug [6]. Because NSAIDs have been linked to an increased risk of cardiovascular events, OARSI also advises against giving them to individuals who are at higher risk for cardiovascular events [1, 7]. OARSI conditionally advises co-administration of non-selective NSAIDs with a proton-pump inhibitor due to the gastrointestinal hazards of NSAIDs, including acid reflux and gastric irritation [1]. NSAIDs are generally not recommended for weak individuals, but if they are, they should be used for a brief period of time and at a low dosage [1].

The cyclooxygenase (COX) isoenzymes COX-1 and COX-2 are reversibly inhibited by NSAIDs, which lowers the production of prostanoids, such as prostaglandins. Both analgesic and anti-inflammatory effects result from this activity [8]. NSAIDs can either selectively target one isoform of the COX-1 and COX-2 enzymes more than the other, or they can inhibit both enzymes non-selectively. These medications have different kinetic profiles and different ways of inhibiting COX, such as covalent binding (like aspirin), competitive binding (like ibuprofen), weak binding with time-dependent effects (like naproxen, oxicams), and tight binding with time-dependence (like indomethacin) [9]. With the exception of aspirin, the majority of oral NSAIDs are weak acids that are completely absorbed from the digestive system, mostly through the intestinal mucosa [10]. NSAIDs are mostly restricted to the extracellular compartments due to their potent binding to serum proteins like albumin. Within a few hours of dosing, the well-perfused synovial tissues reach NSAID concentrations comparable to plasma levels. The metabolism of NSAIDs, which includes oxidation and conjugation to inactive metabolites that are subsequently eliminated in the urine, is primarily carried out by the liver [10]. Bile is used to eliminate certain NSAIDs [12]. Some medications, including naproxen, nabumetone, meloxicam, and piroxicam, have slower metabolism (>6 hours), whereas others, like ibuprofen, diclofenac, ketoprofen, and indomethacin, have comparatively short half-lives (<6 hours) [10]. Particularly, oxicams have extended half-lives, lasting anywhere from 20 to 60 hours [12].

Observational studies show a greater connection with adverse outcomes, which is probably due to selection biases and variations in patient demographics, even though many routinely used NSAIDs show minimal toxicity in controlled clinical trials [13, 14]. Renal, cardiovascular, and gastrointestinal toxicity are associated with non-selective oral NSAIDs. Higher dosages and longer treatment duration increase the likelihood of developing stomach mucosal lesions from long-term use [15]. Due to their cytotoxic effects on the stomach mucosa, NSAIDs can cause nausea, duodenal or stomach ulcers, and in extreme situations, gastrointestinal bleeding. This is explained by the inhibition of COX enzymes, which lowers the creation of mucus, decreases the flow of blood to the stomach, and increases the secretion of acid [16]. Nephrotoxicity is another danger associated with NSAIDs. NSAIDs may lower glomerular filtration rates by blocking prostaglandins, which have vasodilatory effects. This is especially true for people who already have heart failure, hypertension, or diabetes. Acute renal failure, fluid and electrolyte abnormalities, nephrotic syndrome, interstitial nephritis, and renal papillary necrosis are among the renal problems that may result from this. The first 30 days of treatment are significantly more likely to result in such negative consequences [16, 17]. Additionally, especially at higher dosages and during the first month of usage, NSAIDs are linked to a higher risk of acute cardiovascular events, such as myocardial infarction [15, 18]. There is also a higher chance of cardiac failure. By encouraging water and salt retention and decreasing the synthesis of prostacyclin, a vasodilator present in blood vessel walls, NSAIDs can increase blood pressure [19].

Topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

Due to their alleged lower toxicity from focused action and decreased systemic exposure, topical NSAIDs are typically recommended above oral formulations in current guidelines [2, 3, 6]. The Osteoarthritis Research Society International (OARSI) conditionally recommends topical NSAIDs for people with polyarticular OA who do not have concomitant diseases and strongly supports its usage in patients with knee OA [1]. OARSI strongly recommends topical NSAIDs for patients with concomitant gastrointestinal, cardiovascular, or frailty disorders because of their modest benefits in pain relief and low side effects, which are usually restricted to mild, temporary skin responses [1]. For people with knee OA who also have generalized pain or depression, OARSI conditionally recommends topical NSAIDs [1]. To make sure that the overall NSAID dosage, when paired with oral NSAID use, does not go beyond the advised limits, they advise vigilance and monitoring [1]. For individuals with polyarticular OA or extensive pain problems who also have depression, OARSI does not recommend topical NSAIDs [1]. Much like OARSI, the American College of Rheumatology (ACR) strongly advises topical NSAIDs for knee OA and conditional NSAIDs for hand OA [2]. Their usage in patients with hand OA is also strongly supported by the European League Against Rheumatism (EULAR) [5]. The deep position of the hip joint may limit the therapeutic effectiveness of topical NSAIDs, hence none of the guidelines recommend its use for hip OA.

The same mechanism that oral NSAIDs use to produce their pharmacological effects applies to topical NSAIDs: cyclooxygenase (COX) enzyme inhibition reduces prostaglandin synthesis, which in turn reduces pain and inflammation. Topical NSAIDs can effectively penetrate the layers of the skin because they are usually lipophilic substances with both hydrophilic and hydrophobic qualities [20]. The medicine must achieve high enough concentrations to inhibit COX enzymes once it reaches its target site. When applied topically, NSAID concentrations in the muscle, joint cartilage, dermis, and synovium are frequently high enough to have a therapeutic impact. For example, concentrations in the subcutaneous skin layers, muscles, and fascia were higher following topical application of ibuprofen than following oral treatment [21]. Plasma levels usually stay below 10% of those seen after oral treatment, even though local areas close to the application site can reach therapeutic amounts [22]. Compared to their oral counterparts, topical NSAIDs typically have fewer systemic side effects, which lowers their toxicity [23]. At the application site, they may, however, result in localized adverse effects such dry skin, erythema, irritation, paresthesia, and pruritus. Mild systemic side effects, such as headaches and gastrointestinal distress, might also happen in certain situations [24].

COX-2 Inhibitors

For individuals without comorbidities who have knee, hip, or polyarticular OA, OARSI conditionally recommends COX-2 inhibitors [1]. It is also advised that people with gastrointestinal comorbidities use COX-2 inhibitors [1]. However, because COX-2 inhibitors are linked to an increased risk of cardiovascular disease, they are not recommended for people with cardiovascular problems [1, 7]. NSAIDs, particularly COX-2 inhibitors, are generally not advised in frailty instances [1]. Because they have a better safety profile, selective COX-2 inhibitors and non-selective NSAIDs combined with a proton-pump inhibitor are both thought to be better than non-selective NSAIDs alone [1]. A subclass of NSAIDs known as COX-2 inhibitors selectively blocks the COX-2 enzyme rather than the COX-1 isoform. By reducing prostaglandin synthesis, this specific inhibition lowers inflammation and eases pain [25]. Targeting COX-2 has the advantage of maintaining the protective effects on the stomach that COX-1 offers, which lowers the risk of gastrointestinal toxicity linked to non-selective NSAIDs. Celecoxib is quickly absorbed when taken orally, peaking in serum levels about three hours after ingestion [26]. Only a small portion (about 2.6% of the medication) is eliminated in urine or feces after significant metabolism [27]. The liver is where celecoxib undergoes the majority of its metabolism, turning it into inactive metabolites. Compared to non-selective NSAIDs, COX-2 inhibitors have a lower frequency of gastrointestinal adverse effects, but they are nonetheless dangerous. Notably, edema, thrombosis, blood pressure instability, and myocardial infarction are among the enhanced cardiovascular toxicity linked to COX-2 inhibitors [28]. Changes in sodium and potassium excretion, renal blood flow, and water retention can all have an impact on renal toxicity, which is

comparable to that seen with non-selective NSAIDs and can result in symptoms such edema, hypertension, and acute renal failure [29].

Duloxetine:

Due to its effectiveness as a serotonin and norepinephrine reuptake inhibitor that reduces depressed symptoms, duloxetine is conditionally recommended by the OARSI guidelines for the treatment of knee osteoarthritis (OA) in patients with extensive depression [1]. Due to the possibility of gastrointestinal side effects, duloxetine is not advised for those with knee OA who are frail or do not have any comorbidities, nor for those who have cardiovascular or gastrointestinal comorbidities [1]. Additionally, due to a lack of evidence, OARSI does not recommend duloxetine for the treatment of hip or polyarticular OA [1]. The ACR, on the other hand, takes a more positive stand, conditionally recommending duloxetine for patients with hand, hip, or knee OA. However, they admit that the majority of the evidence is focused on knee OA and think its effects might be comparable for hip and hand OA [2]. Although careful monitoring of adverse effects is required, duloxetine can be used as a stand-alone therapy or in combination with NSAIDs [2]. When other pharmaceutical alternatives (such as oral NSAIDs) prove inadequate, ESCEO recommendations propose it as a weak alternative to mild opioids for individuals with knee OA, especially those with severe and persistent symptoms [6]. Duloxetine is a well-established medication for neuropathic pain, including peripheral neuropathy pain linked to chronic musculoskeletal pain in OA patients, even if it is not specifically addressed for these individuals [30]. The central nervous system's sense of pain is altered by duloxetine, a strong inhibitor of serotonin and norepinephrine reuptake. It is believed that duloxetine reduces excessive sensory input to the brain by altering serotonergic and noradrenergic neurons in the descending spinal pathway, though the exact processes are yet unknown [31].

When taken orally, duloxetine is well absorbed and reaches peak plasma concentrations about six hours after the dose [32]. The acidic environment of the stomach causes it to hydrolyze, hence an enteric coating is required for protection. The medication accumulates in the cerebral cortex at greater concentrations than in blood plasma after crossing the blood-brain barrier [33]. With an average of 12 hours, the elimination half-life varies from 8 to 17 hours. Less than 1% of the drug is eliminated unaltered, with the rest of the drug being metabolized in the liver and expelled mostly as urine (70%) and feces (>20%) [32]. There have been instances of hepatitis, hepatomegaly, and increased levels of bilirubin and transaminase, raising concerns about hepatotoxicity. Long-term exposure to high serum levels can seriously harm the liver. Moreover, syncope and orthostatic hypotension might happen, especially if the dosage is increased during the first week of treatment. Duloxetine users have also been found to have elevated systolic and diastolic blood pressure [32, 34]. Dry mouth, constipation, nausea, exhaustion, decreased appetite, tiredness, and dizziness are other side effects, but less severe [32, 34].

Intra-Articular Corticosteroids (IACS):

IACS, which usually last less than four weeks, are injected directly into joints to give temporary pain relief [1]. For patients with knee OA in all comorbidity groups, the OARSI conditionally recommends IACS [1]. The ACR, on the other hand, conditionally recommends IACS for hand OA because of a lack of data, but strongly endorses its use for patients with knee and hip OA [2]. The AAOS provides moderate recommendations for patients with symptomatic knee OA and strong recommendations for IACS in patients with hip OA [3]. However, unless there is painful interphalangeal OA, EULAR does not advise IACS for hand OA [5]. When exogenous glucocorticoids are injected into a joint, they diffuse across cell membranes and attach to nuclear steroid receptors. This changes the creation of proteins and mRNA, which in turn changes the functioning of immune cells as well as the amounts of pro-inflammatory cytokines and enzymes. IACS also reduces the inflammatory derivatives of arachidonic acid by inhibiting the activity of phospholipase A2 and p11/calpactin binding proteins [35]. By suppressing receptor expression and causing eosinophil apoptosis, corticosteroids increase T-cell death by inhibiting interleukin-2 [36]. These effects are slow-acting and typically last for a long time since they are mediated via intracellular receptors.

The purpose of contemporary corticosteroid formulations, which frequently use crystalline suspensions or nanoparticles, is to improve localization in joint tissues by keeping medications inside joint spaces [38, 39]. Usually, systemic effects last between one and four weeks [40]. Corticosteroid elimination half-lives range from 8 to 12 hours to 36 to 72 hours. Triamcinolone acetonide extended-release microsphere formulations have a half-life of up to 634 hours, whereas normal crystalline solutions have a half-life of 147 hours [41]. Plasma concentrations drop 24–48 hours after intra-articular injection [42], with inflammatory cytokines rapidly declining within hours and other indicators, such as C-reactive protein, perhaps declining over a few days or months [42]. The liver is the primary site of corticosteroid metabolism [43]. Although certain in vivo studies indicate possible cytotoxicity to cartilage, the long-term effects of IACS on articular cartilage are yet unknown [44]. In a two-year randomized controlled experiment, knees treated with quarterly IACS injections of triamcinolone showed more cartilage loss than knees injected with saline [45]. Due to the crystalline formulation, post-injection responses may include local flare-ups (6–12 hours after injection), which are usually rare and go away on their own in 3 days [46]. Following injection, IACS may result in decreases in sex hormones such androgens and estrogen. There have been reports of short-term cardiovascular consequences, such as raised blood pressure. Femoral head osteonecrosis and other joint-related problems have been reported in the literature, notwithstanding their rarity [40].

Intra-Articular Hyaluronic Acid (IAHA)

Intra-articular injections of hyaluronic acid, a crucial component of synovial fluid, are used to treat osteoarthritis (OA). Because IAHA has fewer long-term safety concerns than other treatments and may provide pain relief that lasts longer than 12 weeks of treatment, the Osteoarthritis Research Society International (OARSI) conditionally recommends it for people with knee OA across all comorbidity categories [1]. The American College of Rheumatology (ACR), on the other hand, strongly advises against using IAHA for hip OA and conditionally advises against using it for knee or hand OA [2]. In a similar vein, IAHA is not recommended by the American Academy of Orthopaedic Surgeons (AAOS) for OA symptoms in the knee or hip [3,4]. The present literature, which varies greatly in terms of IAHA's perceived effectiveness, is reflected in this discrepancy in recommendations. Meta-analyses frequently contain studies with a significant risk of bias, even when some of them indicate minor effects. However, the effects of IAHA seem to be similar to those of saline injections when meta-analyses are limited to low-risk-of-bias trials [2,47].

There are two types of IAHA formulations: native and cross-linked. The latter is intended to increase endurance by minimizing joint deterioration. Neither form has been demonstrated to change the course of OA, although it is still uncertain if greater molecular weight hyaluronic acid is more effective than its lower molecular weight counterpart [49,50,51,52]. Although the exact ways in which IAHA works are yet unknown, it is thought to have both structural and signaling properties and may have the ability to alter illness. In addition to regulating cell migration, division, inflammatory mediators, and tissue remodeling, high molecular weight hyaluronic acid may enhance joint viscoelasticity, hydration, and structural integrity. In order to modulate the expression of collagen, osteopontin, and matrix metalloproteinases, IAHA mainly binds to three cell-surface receptors: intracellular adhesion molecule 1, the receptor for hyaluronate-mediated motility, and the glycoprotein CD44 [53,54]. With half-lives varying from 17 hours to 1.5 days, depending on its molecular weight, hyaluronic acid is quickly removed after injection. Hyaluronic acid with a higher molecular weight has a longer half-life. Hyaluronidases in lysosomes are the main enzymes responsible for the metabolism of hyaluronic acid in tissues, lymphatics, and the vasculature. The liver is the primary site of endocytosis, while the kidneys also experience some endocytosis. Animal studies employing radiolabeled hyaluronic acid reveal that 96–97% of the material is eliminated by feces, despite the fact that human pharmacokinetics are still poorly known [56,57]. IAHA has a minimal toxicity profile and is typically regarded as safe. Severe adverse effects are uncommon in individuals with knee OA, and only 2-4 percent of patients experience mild, temporary local responses at the injection site [46].

Acetaminophen

Although its effectiveness is still up for discussion, acetaminophen is frequently used to treat early-stage OA pain. Acetaminophen is highly recommended by the AAOS for the treatment of knee OA [3]. For knee,

hip, and hand OA, the American College of Rheumatology (ACR) conditionally recommends acetaminophen, but notes that long-term, stand-alone use of this medication is unlikely to be beneficial [2]. However, due to drug contraindications, it may be taken for a brief period of time in patients with few pharmacological choices. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) encourages using acetaminophen for knee OA in the short term (less than 3 g/day) after other symptomatic therapies have been tried, but it weakly advises against using it as a long-term treatment [6]. Given its potential for short-term usage and reservations regarding its effectiveness, the European League Against Rheumatism (EULAR) cautiously recommends acetaminophen for hand OA [5]. Citing acetaminophen's poor effectiveness and possible hepatotoxicity, OARSI deviates from other recommendations by not suggesting it for any OA patients [1].

Acetaminophen works as an analgesic by mildly suppressing prostaglandin production and stimulating descending serotonergic pathways. Acetaminophen has analgesic and antipyretic qualities similar to those of nonsteroidal anti-inflammatory medicines (NSAIDs), but it has no anti-inflammatory actions. Clarifying its effects on COX-1, COX-2, and especially COX-3—which is particularly susceptible to acetaminophen—is the goal of ongoing study. These behaviors imply that acetaminophen influences peripheral (COX isoforms) and central (serotonergic pathways) processes of pain [58,59]. When taken orally, acetaminophen is quickly absorbed from the digestive system, with a systemic availability of 70–90%. Food consumption and stomach emptying are two examples of variables that might affect the absorption rate and cause delays in absorption. After consumption, peak plasma concentrations happen about 90 minutes later. At normal dosages, acetaminophen's plasma protein binding varies from 10 to 25%, while about 10–20% of it binds to red blood cells. Acetaminophen is mostly broken down by the liver into glucuronide and sulfate conjugates. Acetaminophen typically has a half-life of two to three hours, and within twenty-four hours, 90% of the dosage is eliminated as metabolites in the urine, leaving less than 5% as unconjugated acetaminophen [60,61]. Although modest allergic skin reactions might happen, acetaminophen is usually well tolerated at therapeutic levels with little side effects [61]. High dosages or long-term use, however, may result in severe hepatotoxicity, which could include thrombocytopenia, hypoglycemia coma, and renal tubular necrosis [58].

Tramadol

Patients with OA are taken Tramadol, a synthetic opioid and serotonin/norepinephrine reuptake inhibitor, to manage their pain. Tramadol was conditionally advised by the ACR for those with hand, hip, or knee OA [2]. Tramadol may be appropriate if patients have contraindications to other drugs (such as NSAIDs) or lack therapeutic choices (such as surgery), but it shouldn't be used as a first-line treatment because of its limited benefits [2]. Contrary to the AAOS's recommendation, tramadol and other opioids should not be used to treat knee OA because of their limited efficacy and significant risk of side effects [3]. While citing a paucity of evidence for hand OA, EULAR lists tramadol as an alternate oral analgesic for its management [5]. Two active enantiomers with distinct roles make up the combination known as tramadol. Centrally active μ-opioid receptor agonists include the enantiomer (+)-tramadol and, in particular, its main metabolite (+)-O-desmethyl-tramadol (M1) [62,63]. Additionally, κ- and δ-opioid receptors can be bound by tramadol. Since (+)-tramadol inhibits serotonin reuptake and (−)-tramadol inhibits norepinephrine reuptake, each unique enantiomer has the ability to inhibit distinct molecules. Alpha2-adrenoreceptors, neurokinin-1 receptors, the voltage-gated sodium channel type II alpha subunit, and glial cells, cytokines, and prostaglandin E2 can all be inhibited by tramadol to modify pain [64]. Additionally, this medication may impact muscarinic receptors (M1 and M3), GABA(A) receptors, and N-methyl-d-aspartate receptors (NMDA) [65].

Tramadol is often taken orally for the treatment of OA. Tramadol exhibits 68% bioavailability and reaches maximum serum concentrations after around two hours. While the (+)-O-desmethyl-tramadol (M1) derivative has a longer half-life at 8–9 hours, tramadol has an elimination half-life of approximately 5 hours [66]. The medication has a strong affinity for tissues. Regardless of the concentrations at low dosages, about 20% of the dose binds to plasma proteins in the blood [67]. Tramadol is metabolized in the liver. The kidneys eliminate 90% of the metabolites, with the remainder being eliminated by feces [67]. Only around

30% of tramadol is eliminated unaltered in the urine; the remainder is eliminated as metabolites [68]. Dry mouth, headache, nausea, dizziness, and drowsiness are dose-dependent side effects. Similar to typical opioids, some people may develop more severe side effects, such as constipation, respiratory depression, and dysphoria. Because of the higher death rates linked to opioids, there is some reluctance to use them for OA. The safety of tramadol for individuals with OA is also questioned due to a higher risk of hip fractures, venous thromboembolism, and death when compared to widely recommended NSAIDs [69,70]. However, fatal intoxications are rare because tramadol is milder than many other opioids. The cardiovascular, respiratory, renal, musculoskeletal, endocrine, gastrointestinal, and central neurological systems are among the systems that Tramadol can affect. Consciousness disorder (30%), seizures (15%), agitation (10%), and respiratory depression (5%), are all possible outcomes of tramadol intoxication [71,72]. Tramadol use may result in serotonin syndrome, a disorder marked by an excess of serotonergic activity in the central nervous system [73].

Capsaicin

In patients with OA, capsaicin is sometimes applied topically as an analgesic. Topical capsaicin was conditionally recommended by the ACR for people with knee OA [2]. Because of its minor side effects, capsaicin is conditionally advised against use in individuals with hand OA [2]. Due in part to the frequent local side effects (such as stinging and burning sensations on the skin), EULAR also did not suggest capsaicin for hand OA [5]. Unlike ACR, OARSI does not advise topical capsaicin for people with knee OA because of safety and effectiveness issues [1].
The natural irritant found in chili peppers, capsaicin, is artificially produced for use in medicine. It lowers the activation threshold of TRPV1 and is a transient receptor potential vanilloid subfamily member 1 (TRPV1) receptor agonist. Physical abrasion, elevated proton concentration (i.e., lower pH), and heat can all activate TRPV1, a member of the transient release potential family. TRPV1 has a lengthy refractory state after activation, which affects nociceptor fiber "defunctionalization" and lessens pain [74]. TRPV1 inhibits the transport of substance P and somatostatin in neurons while simultaneously releasing sensory neuropeptides. As a result, neuropeptide availability is decreased [74]. Typically, capsaicin is applied topically to treat OA. It does not diffuse well into the blood or other aqueous solutions, while being lipophilic and quickly absorbed through the skin's outer layers. With a mean population elimination half-life of 1.64 hours, capsaicin levels rapidly decreased following the application of a high-concentration (640 microg/cm2) capsaicin patch. The dosage and mode of administration determine the half-life. For instance, the half-life was roughly 24 hours following topical administration of a 3% capsaicin solution. Notably, previous in vitro research indicates that its metabolism and biotransformation in human skin occur at a very sluggish pace [75]. The adverse effects of using capsaicin topically are not very severe. The main side effects at the administration site may be erythema, pruritus, and localized, temporary pain. Edema, swelling, dryness, hypertension, nausea, and vomiting are possible additional adverse effects [75,76]. Small and temporary elevations in arterial pressure were noted in clinical trials, most likely as a result of the discomfort encountered during the application process [77].

Treatment Recommendations Based on Guidelines

The guidelines for the management of osteoarthritis (OA) pain vary across different professional organizations, reflecting the complexities of treating this condition. Oral NSAIDs are conditionally recommended for knee and hand OA by the Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology (ACR), while the American Academy of Orthopaedic Surgeons (AAOS) and the European Alliance of Associations for Rheumatology (EULAR) strongly endorse their use for knee OA. Topical NSAIDs are strongly recommended by OARSI for knee OA and have conditional recommendations for hand OA by ACR. COX-2 inhibitors receive conditional recommendations from OARSI for both knee and hand OA, but are not recommended by ACR, AAOS, or EULAR. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is conditionally recommended by both OARSI and ACR for knee and hand OA, though the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) weakly recommends it. Intra-articular corticosteroids (IACS) are

conditionally recommended by OARSI and ACR for knee and hand OA, with AAOS strongly recommending their use for knee OA. For intra-articular hyaluronic acid (IAHA), OARSI conditionally recommends it for knee OA, though it is not addressed by other organizations. Acetaminophen is conditionally recommended for knee and hand OA by ACR but is weakly recommended by ESCEO, with a stronger recommendation by AAOS for knee OA. Tramadol, while conditionally recommended by ACR for knee and hand OA, is weakly recommended by EULAR for hand OA. Finally, capsaicin has limited recommendation in OA treatment, with ACR conditionally recommending it for knee OA but not addressed by other organizations like AAOS and EULAR.

Personalized Treatment Approach

When formulating individualized treatment plans for OA, clinicians must account for various factors such as patient risk profiles, comorbid conditions, toxicity risks, and potential contraindications with other medications. Although first-line treatments like NSAIDs should be prioritized for managing pain, there is still a role for medications with more controversial standing, such as tramadol, especially when alternative treatments fail to provide adequate relief. Therefore, conducting a thorough risk-benefit analysis for each medication is essential, ensuring that patients are actively involved in the decision-making process. This shared decision-making fosters informed choices and helps clinicians monitor treatment outcomes effectively.

Broader Therapeutic Options

This review specifically focuses on the pharmacological approaches for OA treatment as outlined in updated guidelines. However, it is important to recognize that other therapeutic strategies can be effective in alleviating pain for individuals with OA. For instance, OARSI suggests complementary treatments like patient education, structured exercise programs, and dietary weight management as foundational strategies for OA management. While we primarily address pharmaceutical therapies, other increasingly popular treatment modalities, such as platelet-rich plasma, are often overlooked in the guidelines but show promise. Additionally, the pharmaceutical landscape for OA management is dynamic, with new treatments continuously emerging. Some medications that were once considered standard, like acetaminophen, are now receiving less emphasis due to concerns over their efficacy and safety. Therefore, clinicians must stay abreast of the latest evidence and treatment recommendations to ensure they are offering the best care possible.

Future Perspectives and Plans for Osteoarthritis (OA) Treatment

Osteoarthritis (OA) is a progressive, degenerative joint disease that affects millions worldwide, presenting substantial challenges in terms of its management and treatment. As the global population ages and the prevalence of obesity rises, the burden of OA is expected to increase significantly, emphasizing the need for more effective, tailored, and innovative approaches in its management. Despite advances in understanding the pathophysiology of OA and the development of various treatment modalities, there remains a considerable gap in optimal therapeutic options. This section explores future perspectives and strategic plans for the treatment of OA, focusing on evolving pharmacological therapies, personalized medicine, and innovative non-pharmacological interventions [78].

Personalized and Precision Medicine in OA Treatment

One of the most promising directions for future OA treatment lies in the concept of personalized medicine. Currently, OA treatment approaches are largely symptom-based, focusing on pain management and functional improvement. However, these treatments often fail to address the underlying biological mechanisms of the disease. Personalized medicine aims to tailor interventions based on individual genetic, phenotypic, and environmental factors. Genetic studies have revealed several genetic markers associated with OA susceptibility, including variations in genes involved in cartilage degradation, inflammation, and joint repair. Understanding the genetic predisposition to OA can help in the development of targeted therapies that address the specific pathophysiological processes in each patient. Future research will likely focus on integrating genetic screening and biomarker identification into clinical practice, enabling clinicians

to predict which patients are more likely to respond to certain treatments. For example, patients with specific genetic profiles may benefit from targeted biological therapies aimed at modulating inflammation or enhancing cartilage repair. Additionally, personalized medicine could involve tailoring the intensity and duration of treatment based on a patient's unique disease progression, comorbidities, and response to previous therapies. As the field of genomics continues to evolve, it is anticipated that precision medicine will significantly impact the effectiveness and safety of OA management, reducing the trial-and-error approach currently prevalent in clinical settings [78].

Regenerative Medicine and Cell-Based Therapies

In addition to pharmacological and surgical treatments, regenerative medicine is becoming an exciting avenue for OA management. The goal of regenerative therapies is to repair or regenerate damaged tissues, rather than simply masking symptoms. Among the most investigated regenerative strategies are stem cell therapies and platelet-rich plasma (PRP) injections. Stem cells, particularly mesenchymal stem cells (MSCs), have demonstrated the potential to differentiate into cartilage and other joint tissues, thereby promoting tissue repair and potentially halting disease progression. Early clinical trials suggest that stem cell injections into the affected joints may help reduce pain, improve function, and possibly slow cartilage degeneration. However, more extensive randomized controlled trials are needed to establish the safety, efficacy, and long-term benefits of stem cell therapies for OA. PRP therapy, which involves the injection of concentrated platelets from the patient's own blood into the affected joint, has gained traction as a treatment for OA. Platelets contain growth factors that promote tissue healing and regeneration. While early studies have shown promise, the effectiveness of PRP therapy remains debated, with varying results across different OA populations. The standardization of PRP preparation techniques, as well as identification of optimal dosing regimens and treatment intervals, are critical areas of ongoing research. As regenerative medicine continues to evolve, the integration of stem cell therapies and PRP injections into clinical practice could offer significant advantages in OA management, particularly for younger patients or those with early-stage OA.

Biologic Therapies and Targeted Drug Development

Biological therapies, which have revolutionized the treatment of autoimmune diseases, are now being explored for their potential in OA treatment. Biologic drugs are designed to target specific molecules involved in inflammation and cartilage degradation, offering a more targeted approach than traditional systemic therapies. One of the most studied targets in OA is interleukin-1 (IL-1), a pro-inflammatory cytokine implicated in cartilage breakdown. Several clinical trials are investigating the efficacy of IL-1 inhibitors, such as anakinra, in OA patients. Other biologics targeting tumor necrosis factor-alpha (TNF-α) and other inflammatory pathways are also under investigation, although their success in OA treatment has been more limited compared to their effectiveness in diseases like rheumatoid arthritis. Another promising area of biologic therapy involves growth factors that promote cartilage regeneration. For instance, the administration of transforming growth factor-beta (TGF-β) and insulin-like growth factor (IGF) has shown some success in preclinical studies in stimulating cartilage repair. However, clinical trials have not yet demonstrated consistent positive results, and further research is necessary to determine the efficacy and safety of these biologic agents in OA. A major challenge in the development of biologic therapies for OA is the complexity of the disease, which involves multiple factors such as inflammation, mechanical stress, and cartilage degeneration. Future biologic treatments may focus on a multi-target approach, simultaneously addressing various aspects of the disease process to provide more comprehensive relief. Additionally, advancements in biomarker identification will help clinicians predict which patients will benefit from biologic treatments, reducing the potential for ineffective or unnecessary therapy [78].

New Pharmacological Agents and Treatment Modalities

In recent years, there has been a growing interest in developing new pharmacological agents that target different aspects of OA pathophysiology. These include novel anti-inflammatory drugs, pain modulators, and cartilage protectants. For example, JAK inhibitors, which block the Janus kinase signaling pathway

involved in the inflammatory response, are being investigated for their potential to reduce inflammation and pain in OA. The advantage of JAK inhibitors lies in their ability to act on multiple cytokines involved in the disease process, making them a promising option for patients with inflammatory OA. Another area of interest is the development of pain-modulating drugs that specifically target the pain pathways in OA, without affecting the underlying disease process. These drugs aim to provide more effective pain relief while minimizing side effects associated with current pain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Drugs such as capsaicin, duloxetine, and gabapentinoids are being studied for their role in managing OA-related pain, with varying degrees of success. The future will likely see the development of more specific, targeted pain-relieving medications with fewer adverse effects, improving the quality of life for OA patients. Additionally, cartilage protectants that aim to slow or halt the degradation of joint cartilage are an area of active research. For example, diacerein, a drug that inhibits the activity of interleukin-1 and reduces cartilage breakdown, has shown some promise in clinical trials. However, more evidence is needed to confirm its effectiveness in OA management. Other approaches, such as the use of hyaluronic acid and glucosamine supplements, continue to be explored, although their efficacy remains controversial.

Non-Pharmacological Interventions and Lifestyle Modifications

In parallel with pharmacological treatments, non-pharmacological interventions will continue to play a critical role in the management of OA. Exercise therapy remains one of the cornerstones of OA treatment, with strong evidence supporting the benefits of structured, land-based exercise programs in improving joint function and reducing pain. The future will likely see more personalized exercise regimens, tailored to individual patients' abilities, needs, and disease severity. Moreover, technological innovations such as wearable devices and telemedicine will enable healthcare providers to monitor patients remotely and provide ongoing guidance on exercise and lifestyle changes. Weight management is another key component of OA management, particularly in patients with knee OA, where excess weight exacerbates joint stress. Future OA treatment strategies will likely incorporate more comprehensive weight loss programs, utilizing both dietary interventions and physical activity. In addition, education about the disease and its management will continue to be a core part of OA treatment, empowering patients to take an active role in their care and make informed decisions about lifestyle modifications.

Collaborative Care Models and Multidisciplinary Approaches

Finally, the future of OA treatment will likely involve more collaborative care models and multidisciplinary teams. Given the complexity of OA, effective management requires the expertise of a variety of healthcare professionals, including primary care physicians, rheumatologists, orthopedic surgeons, physiotherapists, occupational therapists, and dietitians. A coordinated, team-based approach will help address the diverse needs of OA patients, from pain management to mobility enhancement, lifestyle modifications, and psychological support. Integrating these professionals into a cohesive treatment strategy will improve patient outcomes, enhance satisfaction, and reduce healthcare costs in the long term. The future of OA treatment lies in the continued evolution of both pharmacological and non-pharmacological interventions. Personalized medicine, regenerative therapies, biologics, and targeted pharmacological treatments hold significant promise in improving disease management and patient outcomes. However, challenges remain in translating these innovations into routine clinical practice. The integration of personalized care, effective pain management strategies, and collaborative care models will shape the future landscape of OA treatment, providing patients with more effective, tailored options to manage their condition. As research continues to unfold, the hope is that OA treatment will shift from a largely symptomatic approach to one that not only alleviates pain but also addresses the underlying causes of the disease, ultimately improving the quality of life for individuals living with OA [78].

Conclusion:

Osteoarthritis (OA) remains a prevalent and debilitating condition, with chronic pain as a hallmark symptom that significantly impairs an individual’s quality of life. The management of OA pain has evolved

significantly, with a variety of pharmaceutical treatments available to address the underlying inflammation and provide symptomatic relief. Despite the absence of disease-modifying treatments, effective pain management is central to improving outcomes for OA patients. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used, yet their safety profile raises concerns, particularly with regards to gastrointestinal, renal, and cardiovascular toxicity. While NSAIDs are effective in alleviating pain, the risk of adverse effects necessitates cautious use, especially in individuals with pre-existing comorbidities. The introduction of selective COX-2 inhibitors, which offer a better gastrointestinal safety profile, provides an alternative for patients at higher risk for stomach-related side effects, though these agents are not without their own risks, particularly in terms of cardiovascular health. Topical NSAIDs present a promising option for localized pain management, especially for knee OA, and they are recommended for individuals with other health complications, due to their lower systemic absorption and reduced toxicity. By focusing on the therapeutic effects at the site of pain, these treatments minimize the risks associated with oral formulations, making them a safer choice for long-term management in many cases. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is an emerging treatment for OA, especially in patients with comorbid depression. Its use in knee OA patients, particularly those who have not responded well to other pain management options, is encouraged, although its application for other forms of OA remains less well-established. As a weak alternative to opioids, duloxetine can offer significant benefits in reducing chronic pain without the high risks of addiction and adverse side effects typically associated with opioid use. Ultimately, the pharmaceutical treatment of OA requires a personalized approach, considering individual patient profiles, including comorbid conditions and the severity of symptoms. While significant progress has been made in understanding and treating OA, more research is needed to explore new medications and further refine existing treatments. The continued development of guidelines and evidence-based treatment protocols will be essential for optimizing outcomes for OA patients and improving their long-term quality of life. Future therapeutic strategies should focus on both enhancing the efficacy and minimizing the toxicity of pharmacological treatments, alongside exploring potential disease-modifying therapies that can slow or halt the progression of OA.

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الملخص:

الخلفية: التهاب المفاصل العظمي (OA) هو حالة شائعة ومدمرة تتميز بالألم المزمن، مما يؤثر بشكل كبير على جودة الحياة والوظائف الجسدية والصحة النفسية للأفراد المتأثرين. في حين أنه لا توجد علاجات معدلة للمرض متاحة، يظل إدارة الألم جزءًا أساسيًا من علاج التهاب المفاصل العظمي. تسلط هذه المراجعة الضوء على الخيارات الدوائية المستخدمة لإدارة ألم التهاب المفاصل العظمي، مع تقييم آلياتها، وحركتها الدوائية، وآثارها الجانبية المحتملة، وسموميتها.

الهدف: الهدف من هذه المراجعة هو تقديم تحليل محدث للعلاجات الصيدلانية لالتهاب المفاصل العظمي، مع التركيز على فعاليتها، وملفات الأمان، وتطبيقاتها في الممارسة السريرية، مع التأكيد على الإرشادات الحالية.

الطرق: تم إجراء مراجعة شاملة لأحدث الإرشادات السريرية والدراسات الحديثة لتقييم العلاجات الصيدلانية المختلفة لالتهاب المفاصل العظمي. تم التركيز بشكل خاص على مضادات الالتهاب غير الستيرويدية(NSAIDs) ، بما في ذلك الأشكال الفموية والموقعية، بالإضافة إلى العلاجات الأخرى مثل مثبطات COX-2 والدولوكستين.

النتائج: تظل مضادات الالتهاب غير الستيرويدية، سواء كانت فموية أو موضعية، هي الأدوية الأكثر وصفًا لإدارة ألم التهاب المفاصل العظمي. على الرغم من أن مضادات الالتهاب غير الستيرويدية الفموية فعالة، إلا أنها تحمل مخاطر التسمم في الجهاز الهضمي، والقلب والأوعية الدموية، والكلى. تتمتع مضادات الالتهاب غير الستيرويدية

الموضعية بملف أمان أفضل مع آثار جانبية جهازية أقل، ويوصى بها لحالات التهاب المفاصل العظمي في الركبة وللأفراد الذين يعانون من أمراض مصاحبة. توفر مثبطات COX-2تقليلًا في سمية الجهاز الهضمي، ولكنها مرتبطة بمخاطر قلبية وعائية ولا يُوصى بها للمرضى الضعفاء أو الذين يعانون من مشاكل قلبية وعائية. يُوصى بدولوكستين بشكل مشروط لالتهاب المفاصل العظمي في الركبة لدى المرضى الذين يعانون من الاكتئاب، كبديل محتمل للأفيونيات في بعض الحالات.

الخلاصة: على الرغم من أن العلاجات الصيدلانية، وخاصة مضادات الالتهاب غير الستيرويدية ومثبطاتCOX-2 ، تظل مركزية في إدارة ألم التهاب المفاصل العظمي، إلا أن استخدامها يتطلب أخذ العوامل الخطرة الخاصة بالمريض بعين الاعتبار. تقدم العلاجات الأحدث مثل الدولوكستين خيارات إضافية، خاصة لأولئك الذين يعانون من أمراض مصاحبة، على الرغم من أنه لا يزال هناك حاجة لمزيد من الأدلة لدعم استخدامها الواسع.

الكلمات المفتاحية: التهاب المفاصل العظمي، إدارة الألم، مضادات الالتهاب غير الستيرويدية، مثبطاتCOX-2 ، الدولوكستين، العلاجات الصيدلانية، الإرشادات، لأمان، الفعالية