Review Article

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A review on osteoarthritis

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Abstract

Degenerative joint disease, or osteoarthritis (OA), is a prevalent chronic synovial joint condition characterized by non-inflammatory degeneration, leading to pain and restricted joint movement. OA patients navigate a spectrum of therapeutic options, from social media advice to prescriptions from primary care physicians. This article critically assesses evidence-based treatments for generalized or monoarticular OA, advocating multidisciplinary and multimodal therapy. Evaluation covers patient education, pharmaceuticals, complementary and alternative medicine, surgery, manual techniques, acupuncture, bracing, assistive devices, physical therapy, modalities, and interventional procedures (corticosteroid injection, viscosupplementation, pulsed radiofrequency). Optimal benefits emerge from early diagnosis and prevention combined with multidisciplinary and multimodal treatments. The review highlights the synergy of complementary therapies. Healthcare professionals should be well-versed in diverse OA management resources, emphasizing tailored treatment plans aligned with individual needs and encouraging healthier lifestyle choices for optimal patient outcomes.

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INTRODUCTION

The most frequent type of chronic condition affecting synovial joints is osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease (DJD). This illness is non-inflammatory and degenerative, causing pain as well as limited mobility in the afflicted joints. It is defined by the gradual deterioration of the articular cartilages over time, especially in weight-bearing joints. There are two clinical types of OA: primary and secondary [1].

Primary Osteoarthritis: The cause of this type is not known. It affects the elderly, with women experiencing it more frequently than men. By the end of the fourth decade, this process starts, and it then gradually and steadily intensifies to produce clinical signs. The acceleration of the natural ageing process in overused joints could be the cause of the changes. It typically appears in late middle age and affects the hips, knees, and other big weight-bearing joints. Frequently, only one joint is affected.

Secondary Osteoarthritis: Also known as Secondary OA, it can develop at any age and is caused by a variety of prior joint wear and tear events, including hip dislocations caused at birth, fractures, inflammation, as well as loose bodies. The disintegration of collagen type II, most likely caused by IL-1, TNF, as well as nitric oxide, appears to be the molecular process causing injury to cartilage in OA [2].

Morphologic Features [3][4]: Interphalangeal joints in fingers may also be impacted; however, weight-bearing joints, including the hips, knee, and vertebrae, are the most frequently affected. The synovium surrounding bones, as well as articular cartilages, all experience pathologic alterations.

Articular Cartilage: The areas of articular cartilage that bear weight are where the regressive alterations are most noticeable. Normal metachromasia gradually disappears due to the initial loss of the cartilaginous matrix (proteoglycans). This is followed by chondrocyte loss in specific areas and chondrocyte proliferation in other areas leading to the formation of clusters. As the process advances, the articular cartilage loosens, flakes, and fissures, tearing off fragments of cartilage that reveal subchondral bone. Joint mice or loose bodies may develop as a result of cartilage protrusion and dislodgement into the joint space. This progressive cartilage loss is shown radiologically as narrowed joint space.

Bone: The polished ivory-like subchondral bone has been denuded. The subjacent bone may occasionally suffer from microfractures due to rarefaction, microcyst development, and the loss of superficial osteocytes and enhanced osteoclastic activity. These modifications cause the articular end of the bone to flatten and take on the appearance of a mushroom as a result of remodelling the bone and altering the contour of the joint surface. When cartilage is damaged, the edges of the joints generate osteophytes or spurs. These are cartilaginous protrusions at the edge of the joints that will eventually ossify. Osteophytes make the damaged joint appear to be lipping. Fragmented and loosened osteophytes can produce loose bodies or free "joint mice."

Synovium: At the beginning, the synovium shows no pathologic alterations; nevertheless, as the disease progresses, low-grade chronic synovitis and villous hypertrophy develop. A certain degree of synovial effusion could be linked to persistent synovitis.

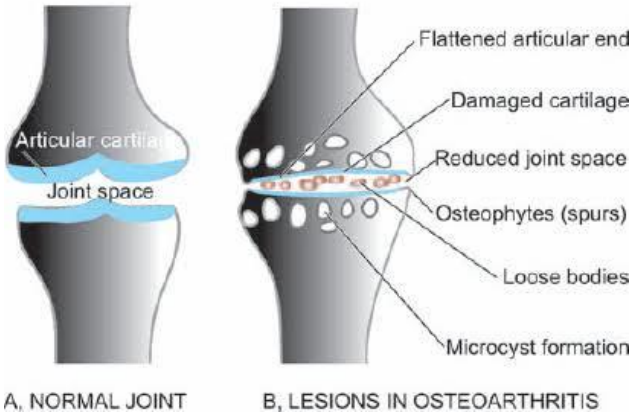

Figure 1 Normal joint and Lesions in Osteoarthritis

Etiology [5]

The disorganized healing and deterioration of articular cartilage are the root causes of OA lesions. As a flow-friction surface, articular cartilage transfers loads to the underlying bone. The extracellular matrix, primarily composed of type II collagen, proteoglycans, and water and released by chondrocytes, exhibits viscoelastic qualities that help cartilage withstand compression. In addition to hereditary variables, such as genes encoding matrix components and signaling molecules, repeated biomechanical stress is a contributing factor in the development of osteoarthritis (OA). These variables are hypothesized to increase the risk of chondrocyte damage, altering the extracellular matrix. While chondrocytes multiply and continuously synthesize and exude proteoglycans, breakdown eventually outpaces synthesis. As the disease worsens, the composition of proteoglycans varies.

The type II collagen network is deteriorated in the interim by MMPs released by chondrocytes. Osteoarthritis (OA) has been linked to cytokines and diffusible substances from chondrocytes and synovial cells, specifically TGF-β (which includes MMPs), TNF, prostaglandins, and nitric oxide. The disease progresses more quickly when there is persistent low-level inflammation. The disease ultimately reaches its late stage when chondrocytes are lost, and the matrix is badly damaged.

MANAGEMENT [6][7]

Lifestyle Advice

One of the most potent treatments for OA of the lower limbs is weight loss, which significantly impacts symptoms if the patient is obese. Strengthening and aerobic exercises are also beneficial for people with osteoarthritis (OA) and should be recommended, ideally with physiotherapy support. Exercises that strengthen the quadriceps are quite helpful for those with osteoarthritis in the knee. The symptoms of painful knee or hip osteoarthritis can be improved by wearing shock-absorbing shoes, timing activities, using a walking stick, as well as providing built-up shoes to equalize leg lengths.

Non-pharmacological Treatment

Acupuncture and transcutaneous electrical nerve stimulation (TCNS) have both been demonstrated to be beneficial in the treatment of knee OA. Local physical therapy, such as heat or cold, can provide brief relief in some cases.

Pharmacological Treatment

If non-pharmacological methods are ineffective, paracetamol should be attempted. Capsaicin is added after a topical NSAID. It can also help with knee and hand OA.

In patients who continue to be symptomatic, oral NSAIDs should be tried. These medications are substantially more effective than paracetamol and can be combined well with paracetamol or complex analgesics.

Pharmacologic Management

Pharmacologic agent trials may have several drawbacks, such as the inability to generalize the results to other patients. The possibility that unfavorable findings will find their way into the published literature may be diminished by publication bias. Results that are statistically significant may indicate benefits to patients that are not clinically relevant due to their limited size. Where applicable, we have underlined these factors [9].

Patients with knee OA should firmly consider topical NSAIDs, while patients with hand OA should consider them conditionally. Topical NSAIDs should be explored before using oral NSAIDs, following the idea that drugs with the least systematic exposure are the best. The voting panel did not look into the use of topical NSAIDs in hip OA due to practical concerns and the lack of direct evidence of efficacy in the hand. Additionally, the depth of the joint beneath the skin's surface suggests that topical NSAIDs are unlikely to confer benefit [10].

It is conditionally advised against using topical capsaicin in people with hand OA and conditionally suggested for those with knee OA. Because of the tiny effect sizes and large confidence intervals seen in the literature, topical capsaicin is conditionally advised for the treatment of osteoarthritis in the knee. Because there is little data to support topical capsaicin use for treating hand OA, as well as a possible higher risk of ocular contamination, we conditionally advise against its use. The depth of the joint below the skin's surface in hip OA indicates that topical capsaicin may be helpful. There is not enough information available to recommend topical lidocaine preparations for OA.

For individuals with knee, hip, and hand injuries, oral NSAIDs are highly advised. It is still highly advised to take oral NSAIDs as the cornerstone of the pharmacologic treatment of OA. Numerous trials have proven to be effective in the short term. All other oral drugs are not recommended for treating osteoarthritis (OA); oral NSAIDs are the first oral treatments of choice, regardless of the anatomic location of the condition.

Although there is evidence that some NSAIDs may have more favorable side effect profiles than others, this recommendation did not discuss the relative benefits of different NSAIDs. Clinical considerations focused on risk mitigation for the safe use of NSAIDs. Notably absent from the GRADE process for recommendation formulation were elements like proper patient selection,

Table 1 Marketed products [8]

S.NO	Name of the drug	Brand Name	Manufacturer	Dose	Type of Dosage form
1	Paracetomol	Dolo-650	Micro labs	650Mg	Tablet
2	Paracetomol	Calpal-650	gsk	650Mg	Tablet
3	Paracetomol	Crocin	gsk	500Mg	Tablet
4	Diclofenac	Voveran50	Novartis India Ltd	50Mg	Tablet
5	Diclofenac	Defenac50	Zydus cadila	50Mg	Tablet
6	Diclofenac	Jonac 50	Zydus cadila	50Mg	Tablet
7	Diclofenac	Nudiclo75	Macleods	75Mg	Tablet
8	Diclofenac	DolokindAqua	Mankind	75Mg	Tablet
9	Diclofenac	Volini	Ranbaxy	1.16% w/w	Gel
10	Diclofenac	Powergesic	Jenburkt	1.16% w/w	Gel
11	Diclofenac	Flexabenz	Macleods	1.0% w/w	Gel
12	Diclofenac	Omni	Cipla	1% w/w	Gel
13	Aceclofenac	Aceclo	Aristo	100	Tablet
14	Aceclofenac & paracetomol	Dolokind	Mankind	Aceclofenac 100mg + Paracetomol 325 Mg	Tablet
15	Piroxicam	Dolonex- DT	Pfizer	20Mg	Tablet
16	Piroxicam	Pirox- DT	Cipla	20Mg	Tablet
17	Piroxicam	Doloforce- DT	Mankind	20Mg	Tablet
18	Piroxicam	Pirox	Cipla	20Mg	Injection
19	Ibuprofen	Brufen	Abbott	400Mg	Tablet
20	Ibufrofen	Emflam	Merck	600Mg	Tablet
21	Naproxen	Naprosyn	RPG life science Ltd	500Mg	Tablet
22	Naproxen	Xenobid	Shreya life science	275Mg	Tablet
23	Etodolac	Etogesic	Zydus cadila	400Mg	Tablet
24	Etodolac	Toldin	Torrent Pharma	400Mg	Tablet
25	Etodolac	Etova	Ipca labs	400Mg	Tablet
26	Etodolac	Etofree	Lupin	400Mg	Tablet
27	Celecoxib	Celedol	Ipca	200Mg	Tablet
28	Celecoxib	Celact MD	Sun Pharma	200Mg	Tablet
29	Celecoxib	Cobix	Cipla	200Mg	Tablet
30	Ketoprofen	Lupinex 4	Lupin	Thiocolchicoside 4Mg+Ketoprofen 50Mg	Tablet
31	Aspirin	Ecosprin	USV	75Mg	Tablet
32	Aspirin	Delisprin	Aristo	75Mg	Tablet
33	Glucosamine Sulphate potassium	Jointace	Meyer	750Mg	Tablet
34	Glucosamine sulphate potassium	Jointace	Meyer	750Mg	Capsule
35	Triamcinolone	Tricort	Cadila	4Mg	Tablet

Table 2 Marketed products [8] (Continued…)

S.NO	Name of the drug	Brand Name	Manufacturer	Dose	Type of Dosage form
36	Triamcinolone acetamide	Kenacort	Abbott	40Mg	Injection
37	Triamcinolone acetamide	Kenacort	Abbott	0.1% w/w	Paste
38	Triamcinolone acetamide	Triora	Unimarck	0.1% w/w	Ointment
39	Indomethacin	Idicin	Indian drugs & pharmaceuticals Ltd	25Mg	Capsule
40	Indomethacin & paracetomol	Idicin-P	Indian drugs & pharmaceuticals Ltd	Insomethacin 25Mg + paracetomol 500 Mg	Tablet
41	Indomethacin	Arcide	Sun pharma	25Mg	Tablet
42	Oxaprozin	Daypro	Pfizer	600Mg	Tablet
43	Oxaprozin	Macprox	Macleods	600Mg	Tablet
44	Ketoprofen	Rhofenoid	Abbott	200Mg	Tablet
45	Ketoprofen	Rhofenoid	Abbott	100Mg	Tablet
46	Ketoprofen	Ostofen	Torrent	50Mg	Capsule
47	Ketoprofen	Rhefenoid	Abbott	5Mg	Injection
48	Flurbiprofen	Flurwell	Wellona pharma	100Mg	Tablet
49	Flurbiprofen	Froben	Abbott	100Mg	Tablet
50	Tolmetin	Tolmetin sodium	Mylan	600Mg	Tablet
51	Prednisolone	Omnacortil	Macleods	5Mg	Tablet
52	Prednisolone	Omnacortil	Macleods	10Mg	Tablet
53	Prednisolone	Omnacortil	Macleods	20Mg	Tablet
54	Prednisolone	Wysolone	Pfizer	5Mg	Tablet
55	Prednisolone	Wysolone	Pfizer	10Mg	Tablet
56	Prednisolone	Wysolone	Pfizer	20Mg	Tablet
57	Methylprednisolone	Medrol	Pfizer	4Mg	Tablet
58	Methylprednisolone	Medrol	Pfizer	8Mg	Tablet
59	Methylprednisolone	Medrol	Pfizer	16Mg	Tablet
60	Methylprednisolone	Predmet	Sun pharma	4Mg	Tablet
61	Methylprednisolone	Predmet	Sun pharma	8Mg	Tablet
62	Methylprednisolone	Predmet	Sun pharma	16Mg	Tablet
63	Methylprednisolone	Nucort M4	Life star	4Mg	Tablet
64	Methylprednisolone	Nucort M8	Life star	8Mg	Tablet
65	Methylprednisolone	Nucort M16	Life star	16Mg	Tablet
66	Methylprednisolone	Nucort M40	Life star	40Mg	Tablet
67	Hydrocortisone	Lycortin-S	Hetero drugs	100Mg	Injection
68	Hydrocortisone	Hydrocort	Abbott	100Mg	Injection
69	Hydrocortisone	Efcorin	Gsk	100Mg	Injection
70	Deflazacort	Dercort	Macleods	6 Mg	Tablet

Table 3 Marketed products [8] (Continued…)

S.NO	Name of the drug	Brand Name	Manufacturer	Dose	Type of Dosage form
71	Dexamethosone	Dexona	Zydus cadila	0.5Mg	Tablet
72	Dexamethosone	Dexona	Zydus cadila	4Mg	Injection
73	Betamethosone	Betnesol	Gsk	5Mg	Tablet
74	Betamethosone	Betnesol	Gsk	10Mg	Tablet
75	Betamethosone	Betnesol	Gsk	4Mg	Injection
76	Hyaluronic acid	Synvisc hylan GF	Genzyme	20Mg	Injection
77	Hyaluronic acid	Hytas one	Intas	8Mg	Injection
78	Vitamin D3	D- rise	USV	60000 IU	Capsule
79	Calcium carbonate + Magnesium hydroxide	Calcimax D 1000	Meyer	Calcium carbonate 500Mg + Magnesiuvicakm Hydroxide 75Mg + zinc sulphate 4Mg+ vitamin D3 1000IU	Tablet
80	Calcium carbonate + Calcitrol	Shelcal-CT	Torrent	Calcium carbonate 500Mg + Calcitrol 0.25Mcg	Tablet
81	Mefenamic acid	Meftal forte	Blue cross	Mefnamic acid 500 Mg + Paracetomol 125 Mg	Tablet
82	Nimesulide	Nise- MD	Dr.Reddy's	100Mg	Tablet
83	Nimesulide	Nise	Dr.Reddy's	100Mg	Tablet
84	Nimesulide	Nise	Dr.Reddy's	75Mg	Injection

routine monitoring for the emergence of potentially harmful gastrointestinal, cardiovascular, and renal side effects, and possible drug interactions. Doses ought to be as little as feasible [11].

For individuals with hip, knee, or hand osteoarthritis, intraarticular glucocorticoid injections are strongly advised; for patients with hand osteoarthritis, they are conditionally indicated. Intraarticular glucocorticoid injection trials have shown some short-term benefit in patients with osteoarthritis. With no data specifically for this anatomic region, intraarticular glucocorticoid injection is conditionally rather than firmly suggested for hand OA. To make an informed decision about using low dosages rather than large ones or selecting short-acting versus long-acting preparations, there is not enough data available. The Voting Panel was unsure of the clinical significance of a recent report that suggested certain steroid preparations, or a particular frequency of steroid injections may be linked to cartilage loss, especially since changes in cartilage thickness were not linked to worsening in pain, functioning, or other radiographic features.

It is highly advised to use ultrasound guidance while administering intraarticular glucocorticoids to hip joints. For knee as well as hand joints, ultrasound guidance is not necessary, although it can help guarantee precise drug administration into the joint when it is available. Nonetheless, it is highly advised to use imaging assistance when injecting into hip joints. For individuals with knee, hip, and/or hand OA, intraarticular glucocorticoid injections are conditionally suggested as opposed to alternative injections. In most cases of osteoarthritis (OA), conditional recommendations favor intraarticular glucocorticoid injection over alternative intraarticular injection methods, such as hyaluronic acid preparations. Although there aren't many head-to-head comparisons, the evidence supporting the effectiveness of

glucocorticoid injections is of a far higher caliber than that of other medications [12].

It is conditionally advised that people with OA of the knee, hip, or hands take paracetamol. Acetaminophen's effect sizes in clinical trials are quite tiny, indicating that few patients receive meaningful benefit, and a meta-analysis has indicated that acetaminophen alone may not be beneficial. For most people, receiving longer-term treatment is no better than receiving a placebo. The majority of people do not benefit from paracetamol, according to the Patient Panel members. If NSAID intolerance or contraindications limit a patient's pharmacologic alternatives, paracetamol might be a suitable short-term and episodic treatment. Patients receiving paracetamol on a regular basis—especially at the recommended maximum dosage of 3 gm daily in divided doses—need to be monitored frequently for hepatotoxicity.

Duloxetine is only advised if the patient has knee, hip, or hand OA. Duloxetine's effects on osteoarthritis (OA) of the hand or hip may reasonably be anticipated, despite the drug's primary research on the knee. Although many different centrally acting medications (such as pregabalin, gabapentin, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants) have been used to treat chronic pain, there is not enough data to recommend the use of duloxetine for osteoarthritis (OA). However, any of these agents may be taken into account as part of a collaborative decision-making process between the patient and the doctor, taking into account all the possible ways that OA may be impacting the patient. Future research focusing on OA may find it acceptable to examine the usage of these drugs, given their usefulness in pain treatment in general. Research indicates that duloxetine, either by itself or in conjunction with NSAIDs, can effectively treat osteoarthritis (OA); nonetheless, concerns have been raised about tolerability and adverse effects. Because there were no direct studies that were relevant to OA, no recommendations were offered for the other centrally acting drugs [13].

Tramadol is only suggested on a case-by-case basis for individuals with knee, hip, and/or OA [14]. Recent research has shown the relatively limited amount of benefit in the long-term (3 months to 1 year) opioid therapy of non-cancer pain. Nonetheless, tramadol or other opioids may be acceptable in the treatment of OA in certain conditions, such as when patients are contraindicated to NSAIDs, find other medications unsuccessful, or have no surgical options. Patient Panel comments revealed a high degree of comprehension of the possibility for addiction, as well as a respect for the role of these drugs when other pharmacologic and physical choices have been ineffectual. However, there is no RCT evidence addressing the use of tramadol and other opioids for periods longer than one year. Clinical trials have shown some symptomatic benefit, but there are still worries about potential side effects. Tramadol is conditionally recommended above nontramadol opioids when considering an opioid. With the understanding that they may be utilized in specific situations, especially when all other options have been explored, non-tramadol opioids are conditionally advised against in patients with knee, hand, or hip OA. The severity of adverse effects, such as dependence and constipation, and the absence of data on the long-term efficacy of opioids in OA caused the Voting Panel to issue conditional recommendations against these drugs. The evidence for opioids was criticized by Panel members, who felt it was insufficient and frequently outdated. Overall, the recommendations provided represent the best current advice, as the Voting Panel was faced with a scarcity of top-quality studies examining the safety and efficacy of opioids in OA treatment.

It is not suggested that individuals with knee, hip, or hand OA use acupuncture. For a range of reasons, including the difficulty of blinding individuals to acupuncture, the absence of clear dose-response relationships, and the observation that even minimal acupuncture has a noticeable impact on OA symptoms, the evidence supporting the use of acupuncture for OA is suspect. The very modest effect sizes for OA relief and the need for frequent treatments mean that the time and financial costs are relatively high, yet the benefit is quite low. No recommendations were made concerning patients with OA of the knee, hip, or hands receiving physical therapy. Despite the fact that physical therapy for OA has not been extensively studied, physical therapy may be considered in a shared decision-making process between the patient and the doctor [15].

Vitamin D

While some osteoarthritis (OA) trials showed modest effect sizes when administering vitamin D, others demonstrated no benefit at all, and combining data from multiple studies resulted in null results. Additionally, other circumstances have revealed that supplementing with vitamin D has limited and dubious health advantages. Patients with hand, hip, or knee osteoarthritis are strongly advised not to use bisphosphonates. The majority of research indicates no improvement in pain or functional results, despite one small trial suggesting an oral bisphosphonate may have analgesic benefits in OA.

Glucosamine

Patients with OA of the knee, hip, or hands should not use glucosamine. There are pharmaceutical-grade glucosamine formulations that have been the subject of numerous studies. Disparities in effectiveness between industry-sponsored and publicly financed studies have sparked grave worries about publication bias. Furthermore, the physiological understanding of how the type of salt under study will affect efficacy is unclear. The least likely to be biased results do not provide any discernible advantages above a placebo. The previous conditional recommendation against the use of glucosamine has been replaced by these recommendations. The overwhelming body of research points to significant placebo effects and a lack of efficacy. However, in the US, glucosamine is still one of the most popular dietary supplements, and doctors need to be aware that many patients believe it to be effective. Patients frequently ask for recommendations on manufacturers and brands because they believe that glucosamine formulations vary in their degree of effectiveness. Although there is little chance of glucosamine being harmful, some people who are exposed to it may have elevated blood glucose levels.

Chondroitin Sulphate

It is highly advised against using chondroitin sulfate in patients with hip, knee, or pelvic OA, as well as combination products that contain glucosamine and chondroitin sulfate. However, people with hand OA may benefit from using it under certain conditions. A single experiment found analgesic efficacy of chondroitin sulfate in hand OA without evidence of damage.

Hydroxychloroquine and Methotrexate

Hydroxychloroquine should be avoided in people with knee, hip, and/or hand OA. Well-designed hydroxychloroquine randomized controlled trials (RCTs) in a subset of individuals with erosive hand OA revealed no effect. Methotrexate is strongly advised against in patients with knee, hip, and/or hand OA. Methotrexate RCTs in a subset of individuals with erosive hand OA have shown no effectiveness.

Hyaluronic Acid Injections

Intra-articular hyaluronic acid injections are contraindicated in patients with knee and/or first carpometacarpal (CMC) joint OA and extremely contraindicated in patients with hip OA. Previously, apparent advantages of hyaluronic acid injections in OA were described in systematic reviews. These assessments, however, did not account for the possibility of bias in the individual main research. Our evaluation found that the benefit was limited to studies with a larger risk of bias: when limited to trials with a low risk of bias, meta-analysis found that the effect size of hyaluronic acid injections versus saline injections approaches zero. The discovery that the best evidence fails to prove a benefit and that these injections may cause damage justified the recommendation against using this medication. Many clinicians desire the ability to administer hyaluronic acid injections in situations where other therapies, such as glucocorticoid injections, are insufficient to control local joint complaints. Given the significance of the contextual effects of intraarticular hyaluronic acid injections, it may be more advantageous in clinical practice to employ hyaluronic acid injections rather than to offer no intervention in patients with osteoarthritis (OA) whose response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids has been insufficient. When other options have been exhausted or have not shown sufficient benefit, the conditional recommendation against is consistent with the use of hyaluronic acid injections within the framework of shared decision-making that acknowledges the limited evidence of efficacy of this treatment. The conditional recommendation against is not meant to sway choices about insurance coverage. On the other hand, the data against hyaluronic acid injection in the hip is of a higher calibre. Thus, we

strongly advise against using hyaluronic acid injections for hip OA.

Other Injections

Patients with hip and/or knee osteoarthritis are conditionally advised not to have intraarticular botulinum toxin injections. There appears to be no evidence of effectiveness for intraarticular botulinum toxin treatment in treating osteoarthritis in the knee or hip. There is no advice about the therapy of hand OA because it has not been investigated in this context. Patients with hip and/or knee OA are conditionally advised not to undergo prolotherapy. Prolotherapy has demonstrated modest effect sizes in knee or hip OA, according to a small number of trials with a small sample size. On the other hand, there have been significant variations in injection schedules, injection sites, and comparators throughout trials. There is no advice about the therapy of hand OA because it has not been investigated in this context. Patients with hip and/or knee osteoarthritis are strongly advised not to have platelet-rich plasma therapy. In contrast to the intraarticular therapies outlined above, there is worry about the variability as well as lack of standardization in accessible platelet-rich plasma preparations, as well as procedures used, making it impossible to determine exactly what is being injected. Because this treatment has not been tested in hand OA, no recommendation is offered for hand OA. Stem cell injections are severely discouraged in patients with knee and/or hip OA. Concerns have been raised about the heterogeneity and lack of standardization in existing stem cell injection preparations and procedures. Because this treatment has not been tested in hand OA, no recommendation is offered for hand OA.

Biologics

Patients with knee, hip, and/or hand osteoarthritis are strongly advised not to use tumor necrosis factor inhibitors or interleukin-1 receptor antagonists. Trials have examined the subcutaneous and intraarticular delivery of interleukin-1 receptor antagonists and tumor necrosis factor inhibitors. Particularly in cases of erosive hand OA, efficacy has not been proven. It is strongly advised against using them for any type of OA due to the known toxicity hazards associated with them. Early findings on the use of anti-nerve growth factor (anti-NGF) medicines point to the possibility of both serious safety concerns and significant analgesic advantages that are not fully understood. A tiny portion of patients receiving these treatments experienced quick joint deterioration, necessitating early joint replacement. As a result, the FDA brought an immediate end to anti-NGF clinical trials; however, they have since been restarted, and longer-term safety and efficacy data are still being collected. We are not able to advocate the use of anti-NGF therapy because none of these drugs had FDA approval for usage, and the longer-term data were unavailable at the time of the literature review and Voting Panel meeting.

These recommendations are based on current evidence and expert consensus, but it's important to consult with healthcare professionals for individualized advice based on specific patient circumstances.

MEDICATIONS IN DEVELOPMENT

Because existing OA medicines have limitations, the continued quest for more effective OA therapies with satisfying therapeutic results (i.e., treating pain, symptoms, and restoring normal joint structure) and minimum side-effects is still important. A few promising new disease-modifying medications have shown potential in slowing the course of OA by modulating cartilage anabolism/catabolism, subchondral bone remodelling, or synovial inflammation. Growth factors, cytokines, monoclonal antibodies, and inhibitors are examples of these, and they help reduce inflammation, promote chondrogenesis, and inhibit osteogenesis and matrix destruction [21].

BMP-7 (Bone Morphogenetic Protein-7)

BMP-7, sometimes referred to as OP-1, is a biologic licensed by the FDA for spinal fusion therapy and bone non-union. It is a member of the transforming growth factor (TGF)-β superfamily. BMP-7 is essential for both embryogenesis and the homeostasis and regeneration of bone and cartilage. In a Phase I, multi-center, placebo-controlled randomized controlled trial (RCT), IA injections of BMP-7 at 0.1 and 0.3 mg improved the WOMAC pain and increased the OARSI response rate compared to placebo. However, IA doses of BMP-7 at 1 mg were linked to injection site discomfort. Even though BMP-7 has been

studied for many years in scientific studies, more clinical trials are necessary to determine whether or not it can be used as a clinical treatment for OA [22].

FGF-18 (Fibroblast Growth Factor)

FGF-18 plays a role in cartilage healing and chondrogenesis. Spifermin, or recombinant human FGF-18, increases the expression of chondrocyte-specific markers while promoting cell proliferation and maintaining chondrocyte phenotype in chondrocytes cultured in vitro. A proof-of-concept randomized, double-blind, placebo-controlled study involving 180 participants was conducted to assess the efficacy and safety of IA sprifermin in the management of symptomatic osteoarthritis. In a dose-dependent way, IA sprifermin considerably reduced the loss of thickness and volume as well as the narrowing of the joint space width in the total and lateral femorotibial cartilage. However, it is not able to stop the loss of cartilage in the central medial femorotibial compartment. A later pre-specified 3-year analysis of the 5-year Phase II FORWARD trial showed that sprifermin 100 µg therapy significantly increased the thickness of the femorotibial joint's cartilage at Year 2 when compared to placebo, and this effect persisted until Year 3. The data to date indicate that sprifermin has an acceptable safety profile and is effective in thickening the cartilage in knee OA. This innovative OA biologics' safety and efficacy will be further assessed in the ongoing Phase II trial [23].

Human Serum Albumin (HSA)

The low molecular weight fraction of 5% HSA (LMWF-5A) has been reported to produce anti-inflammatory effects and be effective in treating osteoarthritis by inducing transcriptional changes in mesenchymal stem cells and increasing COX-2, prostaglandin E2, and D2 in inflammation. Ampiontm, the commercial version of LMWF-5A (<5kda) created by Ampion Pharmaceuticals, has been demonstrated to have anti-inflammatory properties through preventing T-cells from producing pro-inflammatory cytokines. When compared to a vehicle control group, WOMAC pain significantly decreased in a 12-week clinical trial involving 329 patients with moderate to severe OA receiving therapy with AmpionTM. AmpionTM significantly improved WOMAC pain, physical function, and patient global assessment scores, as well as responder rates when compared to saline, according to an analysis of three randomized placebo-controlled studies including 417 patients with severe knee OA (Kellgren-Lawrence grade 4). Additional long-term clinical trials are necessary to further determine the clinical effectiveness of HSA treatment, as there have not been any reported serious drug-related deaths or withdrawals linked to adverse events during the treatment [24].

β-Nerve Growth Factor (β-NGF) Antibody

Monoclonal antibodies are emerging therapeutic options for treating a variety of bone illnesses, including osteoarthritis. Pfizer and Lilly are working together to co-develop tanezumab, an experimental humanized monoclonal antibody that targets β-NGF, to treat chronic pain in OA patients. It has been discovered that β-NGF has the ability to modulate pain through nociceptor sensitization. OA patients' synovial fluid was shown to have increased NGF levels. When compared to a placebo, tanezumab significantly decreased knee pain and improved overall evaluation ($p < 0.001$) in a clinical trial involving 450 individuals with OA in their knees. Tanezumab treatment was linked to a greater frequency of side effects than placebo (68 vs. 55%), including headache, upper respiratory tract infection, and paresthesia. Sixteen individuals developed OA that worsened over time and necessitated total joint replacements. However, later research revealed that using tanezumab in conjunction with an NSAID increased the risk of fast progressing OA, compared to using tanezumab alone. The FDA designated tanezumab as Fast Track for the treatment of OA in June 2017. As a result, a speedy completion of the approval procedure is anticipated [25].

Interleukin-1 (IL-1) Inhibitor

IL-1 contributes to the advancement of osteoarthritis by promoting the manufacture of proteolytic enzymes, cytokines, and other mediators that cause tissue inflammation and destruction, as well as by causing the degradation of cartilage extracellular matrix. In research involving animals, it has been shown that specific reduction of IL-1 production or activity can stop the development of experimentally caused OA. Two different RCTs have documented the usage of

IL-1 receptor inhibitors in OA patients. Anakinra is a recombinant type of IL-1 receptor antagonist that was administered intraarticularly to 160 individuals with OA who had symptoms. The patients were followed up after 12 weeks. An IL-1 receptor antibody called AMG108 was intraarticularly injected into 159 patients with osteoarthritis (OA) once every four weeks for a period of twelve weeks (77). There hasn't been any discernible clinical improvement above placebo in either trial, despite the IL-1 receptor antagonist/antibody's tolerability being adequate. Even though IL-1 inhibitors have demonstrated their efficacy in treating OA in a number of preclinical studies, their inability to significantly reduce OA when compared to placebo control in clinical trials calls for more research into the mechanisms behind their action and the optimization of treatment protocols [26].

PTH and PTHRP (Parathyroid Hormone and Parathyroid Hormone-Related Protein)

PTH or its homolog PTHRP, via the IHH-PTHRP regulatory axis, inhibits chondrocyte hypertrophy and controls endochondral ossification in the growth plate. They have also been found to control the remodeling of subchondral bone and lessen articular cartilage terminal differentiation. The FDA has approved the recombinant human PTH (1-34) teriparatide for the treatment of osteoporosis. In the injury-induced animal model of osteoarthritis, systematic teriparatide treatment can effectively suppress cartilage breakdown and aberrant chondrocyte differentiation. In a rabbit osteochondral defect model, combined therapy with IA recombinant human PTHRP (1–40) and collagen-silk scaffold implantation has been demonstrated to attenuate chondrocyte terminal differentiation and enhance cartilage regeneration 4-6 weeks after damage. For potential clinical applications in the future, PTH/PTHRP research remains intriguing even though the majority of them are in the preclinical stage. Teriparatide is being sought after as a potential chondroregenerative treatment for osteoarthritis (OA) in a prospective Phase II RCT (NCT03072147). There will be an enrollment of 80 participants for a 24-week therapy of symptomatic knee OA [27].

Matrix Extracellular Phosphoglycoprotein (MEPE)

Cartilage hypertrophy and subchondral bone thickening are frequently linked to osteoarthritis. One prospective treatment for osteoarthritis (OA) is the downregulation of mineralization through MEPE, a mineral-regulating protein that is primarily expressed in osteocytes and odontoblasts. In two phase II clinical trials, individuals with mild to severe patello-femoral osteoarthritis have been treated with TPX-100, a new 23-amino-acid peptide produced from MEPE (NCT01925261, NCT03125499). When comparing the TPX100 treated group to the placebo controls, a significant improvement in KOOS and WOMAC ratings was seen. However, during a 12-month period, quantitative MRI did not show any discernible structural alteration. There were no notable side effects linked to the medication. To ascertain its potential therapeutic usefulness, long-term clinical trials are required to confirm its safety and efficacy [28].

TGF-β Inhibitor

The preservation of articular cartilage's structural integrity and metabolic equilibrium depends on TGF-β. In the subchondral bone of surgically produced mice with OA or human OA patients, TGFβ1 expression was observed to be enhanced. Abnormal subchondral bone formation with increased angiogenesis was caused by nestin-positive mesenchymal stem cell (MSC) clusters, which were enhanced by high levels of active TGF-β1. In an experimentally induced OA animal model, the development of OA was reduced by TGF-β type II receptor (TβRII) knockout in nestin-positive MSCs. Moreover, OA degeneration was prevented by blocking TGF-β1 signaling by implanting an antibody to TGF-β (1D11) in alginate beads within subchondral bone or by injecting a TGF-β type I receptor inhibitor (SB-505124). Future OA medication development may focus on the TGF-β inhibitor as a novel target [29].

Retinoic Acid-Related Orphan Receptor Alpha (RORα) Inverse Agonist and Cholesterol Metabolism

The pathophysiology of OA is significantly influenced by the interplay between ROR and cholesterol metabolism. Specifically, the cartilage-specific CH25H-CYP7B1-RORα axis of cholesterol

metabolism is involved. The CH25HCYP7B1 cholesterol metabolism axis has RORα as a downstream target. This axis can be triggered by cholesterol and its oxysterol metabolite, which increases the regulation of cholesterol and its oxysterol metabolite and, in turn, increases the degradation of OA cartilage. According to a study, increasing the severity of OA in mice involves double deletion of INSIG1 and INSIG2, which increases cholesterol production in chondrocytes. In mice with experimental OA, a fairly recent study found that a high-cholesterol diet raised serum cholesterol levels and the severity of OA in comparison to a typical diet. Furthermore, the loss of cartilage resulting from medial meniscus surgery or adenovirus-mediated overexpression of RORα was much lessened by intra-articular injection of SR3335, an inverse agonist of RORα. Additionally, the up-regulation of MMP3 and MMP13 produced by cholesterol and its metabolites was prevented. Consequently, RORα and cholesterol metabolism may present new treatment opportunities for OA [30].

CONCLUSION

Complex alterations surrounding the afflicted joints, such as structural, biomechanical, chemical, and related functional and neurological changes, are a feature of osteoarthritis (OA). Because we are still learning more about the pathophysiology of the condition, OA is still an intriguing entity. But up until now, doctors haven't found a permanent cure for OA. For patients, families, and medical professionals, the knowledge that osteoarthritis (OA) is usually progressive and that there is no known cure can be discouraging. This review demonstrates the potential benefits and synergies between conventional and alternative therapy techniques. Medical professionals need to be aware of the range of resources available for managing osteoarthritis (OA) and its related symptoms. Healthcare professionals that are most adept at customizing treatment regimens for particular patients and motivating them to adopt healthy lifestyle choices will succeed the best outcomes.

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REFERENCES

[1] Felson, D. T. (2009). Developments in the clinical understanding of osteoarthritis. Arthritis Research and Therapy, 11(1), 203.

[2] Dieppe, P. A., & Lohmander, L. S. (2005). Pathogenesis and management of pain in osteoarthritis. Lancet, 365(9463), 965-973.

[3] Pereira, D., Severo, M., Barros, H., Branco, J., Santos, R. A., & Ramos, E. (2013). The effect of depressive symptoms on the association between radiographic osteoarthritis and knee pain: a cross-sectional study. BMC Musculoskeletal Disorders, 14, 214.

[4] Altman, R. D. (2010). Early management of osteoarthritis. The American Journal of Managed Care, 16(Suppl), S41-S47.

[5] Cimmino, M. A., Sarzi-Puttini, P., Scarpa, R., Caporali, R., Parazzini, F., Zaninelli, A., & Marcolongo, R. (2005). Clinical presentation of osteoarthritis in general practice: determinants of pain in Italian patients in the AMICA study. Seminar in Arthritis and Rheumatism, 35(1 Suppl 1), 17-23.

[6] Reginster, J. Y. (2002). The prevalence and burden of arthritis. Rheumatology (Oxford, England), 41(sup 1), 3-9.

[7] Hill, C. L., Parsons, J., Taylor, A., & Leach, G. (1999). Health-related quality of life in a population sample with arthritis. Journal of Rheumatology, 26(9), 2029-2035.

[8] Altman, R., Alarcón, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., ... & Feldman, D. (1991). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis and Rheumatism, 34(5), 505-514.

[9] Felson, D. T., Zhang, Y., Hannan, M. T., Naimark, A., Weissman, B. N., Aliabadi, P., & Levy, D. (1995). The incidence and natural history of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis and Rheumatism, 38(10), 1500-2000.

[10] Murray, C., Marshall, M., Rathod, T., Bowen, C. J., Menz, H. B., & Roddy, E. (2018). Population prevalence and distribution of ankle pain and symptomatic radiographic ankle osteoarthritis in community-dwelling older adults: A systematic review and cross-sectional study. PLoS One, 13(4), e0193662.

[11] Bonnet, C. S., & Walsh, D. A. (2005). Osteoarthritis, angiogenesis, and inflammation. Rheumatology, 44(1), 7-16.

[12] Hulth, A., Lindberg, L., & Telhag, H. (1972). Mitosis in human osteoarthritic cartilage. Clinical Orthopedics and Related Research, 84, 197-199.

[13] Stevens, J. (1970). Osteoarthritis of the hip. A review with special consideration of the problem of bilateral malum coxae senilis. Clinical Orthopedics and Related Research, 71, 152-181.

[14] Lippiello, L., Hall, D., & Mankin, H. J. (1977). Collagen synthesis in normal and osteoarthritic human cartilage. The Journal of Clinical Investigation, 59(4), 593-600.

[15] Brandt, K. D. (1974). Enhanced extractability of articular cartilage proteoglycans in osteoarthritis. Biochemical Journal, 143(2), 475.

[16] Miller, G. D., Nicklas, B. J., Davis, C., Loeser, R. F., Lenchik, L., & Messier, S. P. (2006). Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring), 14(7), 1219–1230.

[17] Flood, J. (2010). The role of acetaminophen in the treatment of osteoarthritis. The American Journal of Managed Care. 16(Suppl Management), S48–S54.

[18] Empson, G. E., Muir, H., Swanson, S. A., & Freeman, M. A. (1970). Correlations between stiffness and the chemical constituents of cartilage on the human femoral head. Biochimica et Biophysica Acta, 215(1), 70–77.

[19] Martel-Pelletier, J., Faure, M. P., McCollum, R., Mineau, F., Cloutier, J. M., & Pelletier, J. P. (1991). Plasmin, plasminogen activators and inhibitor in human osteoarthritic cartilage. Journal of Rheumatology, 18(12), 1863-1871.

[20] van de Loo, F. A., Joosten, L. A., van Lent, P. L., Arntz, O. J., & van den Berg, W. B. (1995). Role of interleukin-1, tumor necrosis factor alpha, and interleukin-6, in cartilage proteoglycan metabolism and destruction. Effect in situ blocking in the murine antigen- and zymosan-induced arthritis. Arthritis and Rheumatism, 38(2), 164-172.

[21] van den Berg, W. B. (1998). Joint inflammation and cartilage destruction may occur uncoupled. Springer Seminars in Immunopathology, 20(1-2), 149-164.

[22] Kollias, G., Douni, E., Kassiotis, G., & Kontoyiannis, D. (1999). On the role of tumor necrosis factor and receptors in models of multiorgan failure, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. Immunological Reviews, 169, 175-194.

[23] Clancy, R. (1999). Nitrous oxide alters chondrocyte function by disrupting cytoskeleton signaling complexes. Osteoarthritis and Cartilage, 7(4), 399-400.

[24] Schumacher Jr., H. R. (1995). Synovial inflammation, crystals, and osteoarthritis. The Journal of Rheumatology, 22(Suppl 43), 101-103.

[25] van de Loo, F. A., Joosten, L. A., van Lent, P. L., Arntz, O. J., & van den Berg, W. B. (2007). The role of T cells in the pathogenesis of osteoarthritis. Arthritis and Rheumatism, 56(2), 409-424.

[26] van de Loo, F. A., Kuiper, S., van Enckevort, F. H., Arntz, O. J., & van den Berg, W. B. (1997). Interleukin-6 reduces cartilage destruction during experimental arthritis. A study in interleukin-6-deficient mice. American Journal of Pathology, 151(1), 177-191.

[27] Uebelhart, D. (2008). Clinical review of chondroitin sulfate in osteoarthritis. Osteoarthritis and Cartilage, 16(3), S19-S21.

[28] Cheng, D. S., & Visco, C. J. (2012). Pharmaceutical therapy for osteoarthritis. PM R, 4(5 Suppl), S82–S88.

[29] Katz, J. N., Mahomed, N. N., Baron, J. A., Barrett, J. A., Fossel, A. H., Creel, A. H., ... & Losina, E. (2007). Association of hospital and surgeon procedure volume with patient-centered outcomes of total knee replacement in a population-based cohort of patients age 65 years and older. Arthritis and Rheumatism, 56(2), 568–574.

[30] Mancuso, C. A., & Salvati, E. A. (2003). Patients' satisfaction with the process of

total hip arthroplasty. Journal for Healthcare Quality, 25(2), 12–18.