Asia Pacific Journal of Pain 36(1): 9-13, Mar. 2026
DOI:10.29760/APJP.202603_36(1).0002
Review Article

How Osteoarthritis Will Be Treated Tomorrow: Between Current Treatments and Therapeutic Innovations

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We are currently facing a therapeutic impasse in front of osteoarthritis, but it is the most common reason for rheumatological consultation. However, we have a wide range of medications available, both in terms of administration methods and therapeutic classes. At the forefront of the list are the undefeatable nonsteroidal anti-inflammatory drugs in their oral and/or topical forms and local delayed-release corticosteroid infiltrations. In this case, why is it so difficult to find an osteoarthritis treatment? Our objective was to make a review synthesized into a final algorithm to explain the complexity of pain, to list what provides relief today and tomorrow, and to stick to the essentials while maintaining a healthy mind and body. Recent work suggests that the pain of aging cartilage is "mixed" and composed of a magma of three components: nociceptive, neuropathic, and nociplastic. For this purpose, nerve growth factor inhibitors and promising stem cell therapies have emerged and led the way toward optimal management of osteoarthritis pain. Ultimately, should we not admit that progressive damage to chondral tissue is inevitable in itself and that it constitutes a natural consequence of aging? While waiting for an innovative medication, the key to sustainable treatment will always lie in eating as healthily as possible and maintaining a healthy weight.

Keywords: *innovation, osteoarthritis, pain, treatment*

Introduction

Osteoarthritis is a chronic degenerative disease that damages cartilage and adjacent tissues, and pain is defined as an unpleasant sensory or emotional experience [1]. Its pathophysiology is intertwined from the simple, almost daily painful stimulus to the middle of the peripheral fibers, all coordinated by a central command. Osteoarthritis is thought to be a combination of the three types of pain [2]. Many therapies exist, with a wide and diverse range available on the market, including tablets, creams and gels, injections, and others rich in nuances, ranging from phytocare to collagen and chondroitin, as well as curcumin [3]. Some are effective, and others are no better than a placebo. In this review, we will list the different treatments available for osteoarthritis and provide advice and practical solutions to help patients live with this disease.

A Pathophysiology Linked to Therapeutic Implication

The mechanism that generates osteoarthritis pain can be nociceptive, neuropathic, or nociplastic. Treatment is considered appropriate when the patho-

Received: 26 July 2025; Received in revised form: 1 September 2025; Accepted: 30 September 2025.
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physiological mechanisms are correctly understood, and the triggering site is clearly identified [4].

Nociceptive Pain

The role of nociceptive pain has always been recognized in osteoarthritis. This is a protective pain of the body: Following an external stimulus, the body will transmit the message to the spinal cord via a nerve, using two different pathways to convey it to the brain's three-level matrix system: Information-Perception-Modulation [5].

Neuropathic Pain

Neuropathic pain is due to a dysfunction of the injured brain system. The sensation will be quite "annoying" but not entirely "painful". It will vary depending on the system's somatotopy. It is caused by damage to the sensory pathways (calcium channelopathies) of the central or peripheral nervous system [6]. The patient will experience a perception of sharp, stabbing pain, cold, burning, electric shock, or tingling. Some authors [7] have suggested that nerve endings may become embedded within the cartilage.

Nociplastic Pain

Nociplastic pain originates from the central nervous system, generating a mixed sensation in different parts of the body [8]. It is chronic and difficult to systematize, usually affecting a "complaining" individual.

Therefore, given that pain is complex and combines several brain areas. The treatment prowess will consist of a global medication acting on these three components.

What About Current Treatments?

Several remedies have been proposed to slow or even eliminate osteoarthritis pain, namely pharmacological and non-pharmacological treatments.

Non-Pharmacological Treatment

The non-pharmacological approach is often recommended as a first-line treatment: reducing excess weight and adopting a healthy diet remain the primary means of managing osteoarthritis. Rehabilitation, on the other hand, aims to maintain joint mobility and muscle strength, as well as optimize movement patterns to limit joint stress and preserve joint health. Acupuncture, mesotherapy, hypnosis, yoga, or Tai Chi [9] are all disciplines that can improve patient outcomes. Electrical neurostimulation by a transcutaneous electrical nerve stimulator has also been shown to be beneficial [10]. Shock devices can also provide pain relief.

Drug Treatment

Recommendations from international learned societies [11] recommend the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) for knee and hip osteoarthritis, particularly so-called non-selective NSAIDs such as ibuprofen, preferably combined with a proton pump inhibitor or a selective COX-2 (cyclooxygenase-2) inhibitor [12,13]. However, NSAIDs have numerous drug interactions and are not without adverse effects, particularly in patients with comorbidities [14]. The dogma is to use a low dose for a short period of time. Extended-release pharmaceutical substances should be preferred in elderly patients [15]. Paracetamol, whether codeine-based or not, is commonly used for osteoarthritis pain, but its efficacy remains uncertain, and there is no improvement compared to a placebo [16]. Tramadol and other strong opioids are not recommended due to a lack of evidence [17]. Duloxetine, or a serotonin-noradrenaline reuptake inhibitor, is a potent pain modulator in the central nervous system. It is preferred in patients with diffuse nociplastic pain and/or altered mood [18]. Topical NSAIDs, comparable to oral NSAIDs in terms of efficacy, will be recommended as a first-line treatment; they remain effective in knee osteoarthritis [19]. As for capsaicin, it is particularly recommended by the American College of Rheumatology due to the risk of local adverse effects [20,21]. Cannabinoids have demonstrated a modest effect and are not currently recommended. As for infiltrations, any intra-articular procedure on a patient in chronic pain systematically produces a "placebo effect", even an infiltration with physiological serum. Indications: According to evidence-based medicine, only cortisone injections have shown a benefit on pain, unlike hyaluronic acid or PRP (platelet-rich plasma) injections. Their only drawback is that they must be renewed regularly [22].

Disciplines and Leisure Activities

Regular physical activity is beneficial for joint cartilage and general health [23]. However, certain

sports can contribute to the onset and progression of chondropathy due to the high mechanical loads and repeated microtraumas imposed on the joints [24], such as football, gymnastics, or running [25]. Medical imaging plays a key role in distinguishing simple chondropathy from advanced osteoarthritis. Nevertheless, continued supervised and adapted physical exercise is often beneficial.

Why Not Biotherapy and Nerve Growth Factor (NGF) Inhibitors?

A major innovation of the last five years has been the advent of NGF inhibitor monoclonal antibodies to combat the pain-mediating protein, which raised enormous hope well before their commercialization. Even the FDA (Federal Drug Administration) granted them the privilege of a "Fast Track" evaluation (priority evaluation process) in 2017. NGF is mainly involved in the regulation of growth, maintenance, proliferation, and survival of certain target neurons [26]. Once fixed on the TrkA receptors [27], it essentially amplifies nociceptive pain by increasing the synthesis of substance P or calcitonin gene-related peptide [28]. The first study published in 2010 in the *New England Journal of Medicine* showed very convincing results [29]. They were tested in knee or hip osteoarthritis in cases where usual analgesics had failed, and the significant difference was very relevant compared to placebo. However, the dosage used in the trial was three times higher than recommended. Unfortunately, a meta-analysis taking into account phase 3 trials has questioned the promising results of this active immunotherapy.

Therapeutic Impasse or Triple-Action Synergy

Ultimately, would not the ideal futuristic treatment be one that acts on the generator of all three types of pain? While awaiting this feat, it would be wise to adopt a balanced lifestyle consisting of relaxing activities such as balneotherapy and spa treatments, and to combat excess weight.

Therapeutic Innovations and Perspectives

No medication currently cures osteoarthritis or halts its progression [30]. The use of new approaches, such as regenerative treatments (stem cells, biomaterials), is still experimental, suggesting pain relief but with a lack of evidence for cartilage repair and truly regenerative tissue. These therapies involve mesenchymal stem cells from bone marrow, fat, or umbilical cords, which reduce chondral inflammation [31], or 3D printing using bioextrusion, which opens up promising prospects for osteoarthritis by creating patient-specific models to improve bioinks for tissue engineering and to optimize processes for bone-cartilage interface regeneration [32].

Meditation and Cognitive Rest

Prevention remains a crucial lever. Early identification of individual and environmental risk factors, longitudinal monitoring of patients in consultation, and adaptation of regular physical activity are all avenues to explore to limit the worsening of this disease. Taking time for yourself and relaxing by practicing a hobby or an activity that provides a break from daily, professional, and social stress is also important and could contribute to osteoarthritis pain management.

Conclusion and Perspectives

We have a range of treatments for osteoarthritis, combined in recent years with a plethora of alternative therapies developed from dietary supplements based on collagen, coenzyme Q10 (a mitochondrial energy producer), proteoglycans [33], curcumin [34], or medicinal plants such as phytotherapy provided by slow-acting anti-arthritic drugs [35]. These products are very expensive, not reimbursed, and have not provided any real clinical efficacy. At the end of this review, we propose a synthesis algorithm to follow in practical consultation (Figure 1).

Conflict of Interest

None.

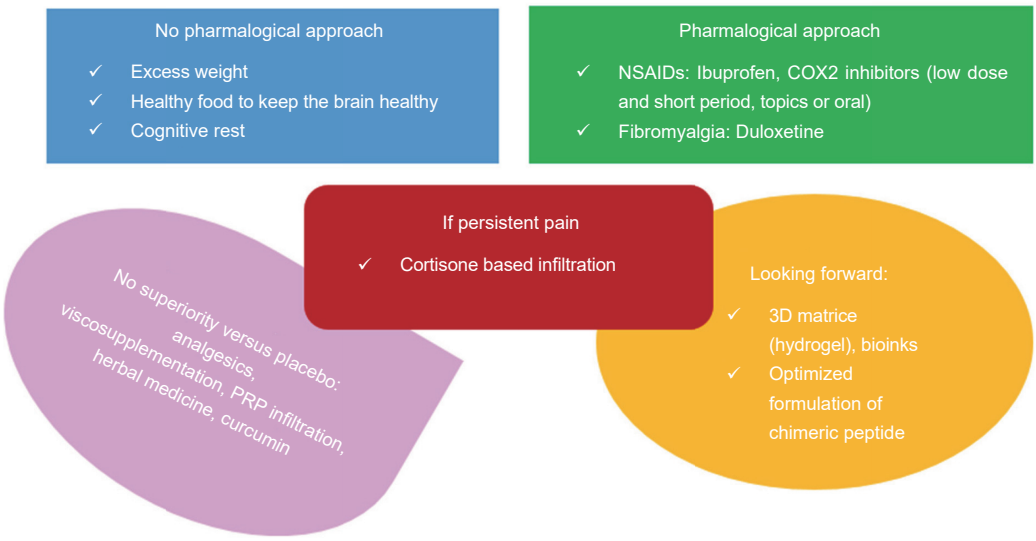

Figure 1. Practical algorithm for the management of osteoarthritis pain

Nothing prevents us from continuing to hope for the use of stem cells. In the meantime, we should focus on promoting well-being in our lives by adopting a healthy lifestyle, including a balanced diet, maintaining an appropriate body weight, and engaging in regular physical activity.

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