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THERAPY IN PRACTICE

Pharmacological Treatment in the Management of Glenohumeral Osteoarthritis

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Abstract

Glenohumeral osteoarthritis (GH-OA) is a common cause of shoulder pain and is characterized by articular cartilage thinning, glenoid bone loss and deformity, osteophytosis, and other associated changes. The prevalence is estimated to be between 85 and 94% in men and women over the age of 80 years. A diagnosis of GH-OA is established based on clinical history, physical examination, and radiographic assessments. Non-pharmacological treatment options may serve as adjuvants to other therapies and should be incorporated for a more holistic approach to management. Pharmacological treatments include oral agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids and antidepressants. The National Institute for Health and Care Excellence (NICE) UK guidelines recommend NSAIDS as the first-line drugs for OA; topical forms of some of these agents can also be used. However, clinical evidence is largely lacking for its use in GH-OA, although patients with other types of OA, especially the knee and hip, are using these products in efforts to relieve joint pain. Intra-articular injections such as platelet-rich plasma, cortisone, and hyaluronic acid are usually used to control symptoms in moderate to advanced arthritis or in non-surgical candidates. Other non-surgical treatment options include suprascapular nerve block and radiofrequency ablation, and these options have been studied on different levels of evidence. Furthermore, all these treatments have their own indications, contraindications, and adverse effects profiles. Surgical treatment of GH-OA is reserved for patients who do not respond to conservative management or who suffer from debilitating symptoms that severely impair their quality of life.
Level of Evidence IV, review article

1 Introduction

Musculoskeletal problems account for 131 million medical visits in the US alone each year, costing more than $200 billion [1]. One of the leading causes of joint pain involves osteoarthritis (OA), which impacts over 300 million individuals worldwide [2]. Glenohumeral OA (GH-OA) is a common cause of shoulder pain and is characterized by several pathologic changes that result in pain and functional impairment to varying degrees.

GH-OA is the one of the most common shoulder pathologies in the elderly population and is estimated to impact up to 20% of those aged ≥ 60 years [3, 4]. Furthermore, the incidence of GH-OA increases with age, with a prevalence rate of 85% and 94% in men and women over the age of 80 years, respectively [5].

Patient symptoms and disease severity are the predominant factors when determining treatment modalities. The treatment options for GH-OA range from simple lifestyle modifications, physiotherapy, pain medications, and injections to surgical interventions such as arthroscopic debridement or total shoulder replacement. This review aims to provide an evidence-based summary of the available non-surgical treatment options of GH-OA while also

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Key Points

Glenohumeral osteoarthritis (GH-OA) results in significant pain and limitations.

Several biomechanical and biochemical factors play a role in the development and progression of GH-OA. Age is one of the strongest contributing factors linked to the development of primary GH-OA, particularly after the age of 60 years.

The treatment options for GH-OA range from simple lifestyle modifications, physiotherapy, pain medications, injections to surgical interventions such as arthroscopic debridement, or total shoulder replacement.

Non-pharmacological treatment modalities can be used in patients with GH-OA before resorting to pharmaceutical and surgical options, particularly if symptoms are mild and the condition well tolerated.

highlighting gaps in the current knowledge base to provide directions for future studies.

2 Pathogenesis and Risk Factors

Several biomechanical and biochemical factors play a role in the development and progression of GH-OA, which can be generally categorized into primary and secondary OA, with the former representing about 90% of cases [6]. Age is one of the strongest contributing factors linked to the development of primary GH-OA, particularly after the age of 60 years [7]. OA associated with aging results from an age-related increase in cartilage catabolism. It has been proposed that chondrocyte anabolic activity decreases with age and that could tip the balance towards an increased catabolic activity that plays a key role in the increased susceptibility to OA [8].

Additionally, the incidence of GH-OA is also associated with female sex. Epidemiologic studies have found that woman have a sevenfold increased prevalence of shoulder OA than men of the same age [9]; however, the differences among males and females in the development of OA have not been well studied but may include anatomic differences, previous trauma, and genetic and hormonal differences [8].

Obesity represents one of the most important risk factors for the incidence and development of OA, not only in weight-bearing joints but also in the GH joint. A study evaluating the relationship between obesity and GH-OA in 596,874 individuals who were age- and sex-matched found the incidence of GH-OA to be greater in individuals with a BMI $\geq$ 30 [10], who were also more likely to undergo total shoulder arthroplasty (TSA) and other surgical interventions for their condition. This has been linked to proinflammatory cytokines (CKs) that lead to subsequent articular damage in obese individuals [10].

Research suggests the contribution of genetics in OA is estimated to be between 40 and 80%, however although genetics and bone density are known risk factors for other forms of OA, such as knee and hip joint OA, a clear definitive link to shoulder OA has not yet been established [11]. The initiation and progression of OA may be associated with quantitative and qualitative changes in key genes that trigger a cascade of changes, leading to disorders in several signalling pathways [12].

In contrast, patients who are younger than 60 years of age mostly present with secondary GH-OA [13]. Secondary OA might be a consequence of GH dislocations and subluxations through osteochondral fractures and subchondral bone injury [13]. Atraumatic avascular necrosis (AVN) can also lead to secondary OA. Many risk factors have been associated with AVN of the humeral head, such as the use of systemic corticosteroids, radiation, chemotherapy, alcohol misuse, diseases of the haematopoietic system, and treatment with antineoplastic drugs such as altretamine, bendamustine, busulfan, and carboplatin [14].

3 Clinical Assessment

The diagnosis of GH-OA is established based on clinical history, physical examination, and radiographic assessments (Fig. 1). A detailed history and thorough physical examination are the first steps in establishing a primary diagnosis of OA.

Patients with GH-OA usually present with gradual onset, over months or years, of anterior shoulder and upper arm pain, mild morning and inactivity stiffness, and restricted movement [15]. However, patients with a history of trauma or systemic inflammatory disease may have an earlier onset of disease with accelerated development. Initially, the pain of GH-OA is predominantly activity-related and most severely affecting motion in abduction/elevation and external rotation, but can eventually progress to affect all movements. Night pain and persistent discomfort at rest may also occur [15]. In most patients, the site of maximum pain is usually referred to the outer aspect of the upper arm close to the deltoid insertion, but pain may be experienced over a wide and diffuse area, including the whole deltoid contour down the radial aspect of the forearm to the elbow (rarely, even to the wrist) [15]. The pain is often eased by rubbing or squeezing

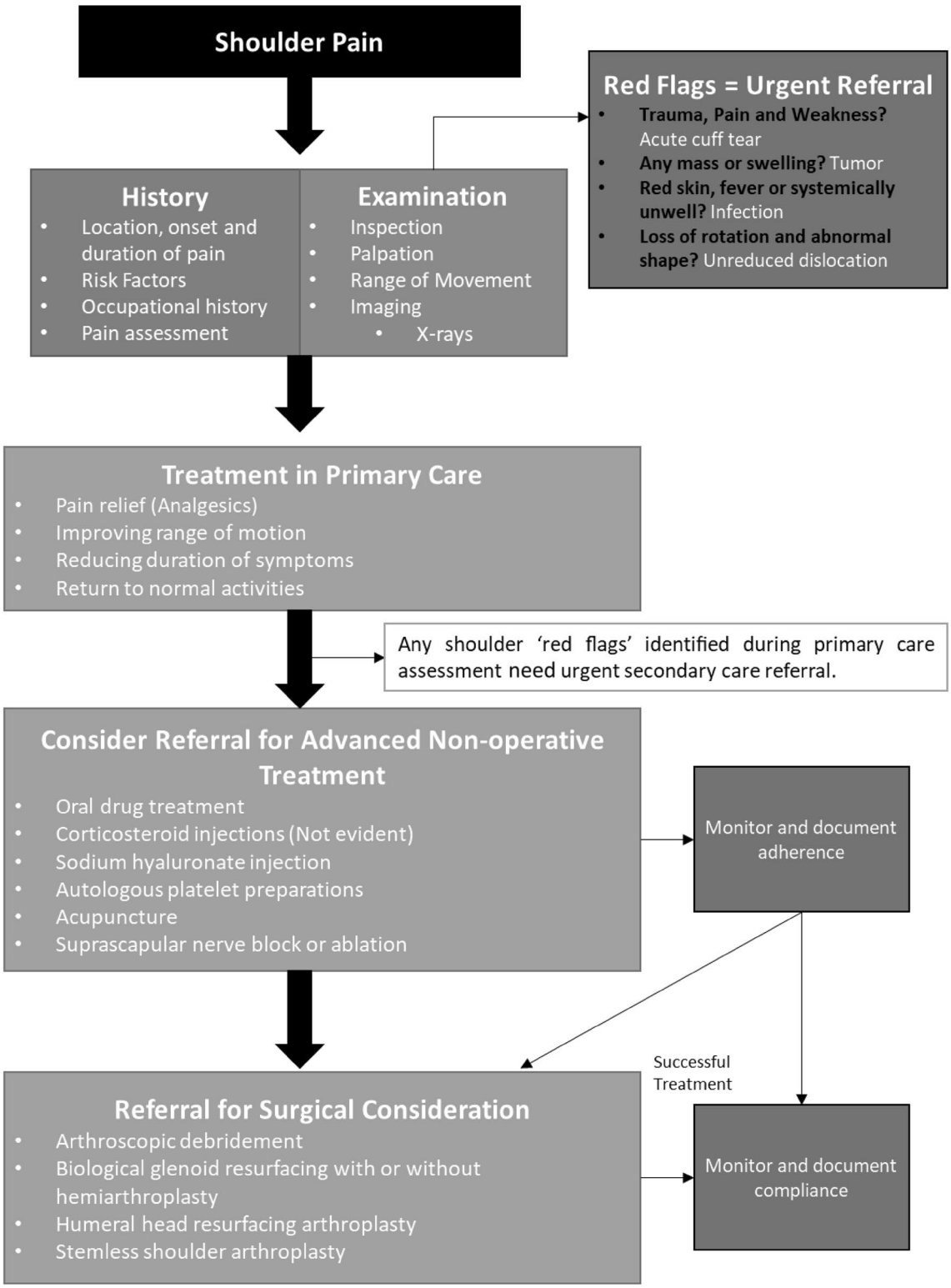

Fig. 1 Suggested diagnosis and treatment guidelines for glenohumeral osteoarthritis

the site of maximum discomfort (a characteristic of distally referred, rather than locally originated, pain) [15].

A physical examination for GH-OA should be focused on excluding etiologies such as rotator cuff pathology, shoulder bursitis, and acromioclavicular pathology, among others. In

addition, a thorough neck and neurovascular examination are indicated, especially in patients with neck pain and pain radiating down the arm, which suggests cervical spine pathology.

Physical examination might reveal glenohumeral anterior joint line tenderness with a coarse crepitus that can be felt over the anterior joint line. Weakness is a frequent finding and often wasting of the deltoid (causing sharper bony angulation or 'squaring' of the shoulder) and/or rotator cuff muscles is also seen. Other causes of shoulder pain include bursitis, biceps tendinopathy, or rotator cuff illness. Finally, red flags, such as fever, night sweat, and unintentional weight loss, include suspected malignancies and acute infections, which should be addressed in an emergency setting [16].

4 Radiological Assessment

Radiographic evaluation remains the cornerstone to confirm a diagnosis of GH-OA [17]. A proper radiographic evaluation should include three shoulder x-ray projections (AP glenoid view [Grashey view], Y lateral view, and axillary view). There is not always a correlation between the intensity of symptoms and the severity of the radiological findings. Glenohumeral joint space narrowing and posterior glenoid erosion are telltale radiographic features of shoulder OA. Additional common findings include the presence of an inferior humeral head osteophyte and subchondral sclerosis, historically identified as a 'goat's beard' [18].

Although computed tomography (CT) or magnetic resonance imaging (MRI) scans are not required and have limited value for a diagnosis of GH-OA [19], CT can identify articular abnormalities whereas MRI detects soft-tissue pathology and minor alterations in articular cartilage and subchondral edema. Nevertheless, advanced imaging is recommended when patients do not respond to non-operative management in preparation for surgical planning [19].

5 Management Principles

The main goals in the treatment of GH-OA are to control pain and restore function. Treatment options can range from conservative to invasive options such as surgery. Due to the relatively moderate benefits, ideally a combination of therapeutic approaches should be utilized to maximize efficacy and minimize adverse effects [2].

6 Non-Pharmacological Treatment

Non-pharmacological treatment modalities can be used in patients with GH-OA before resorting to pharmaceutical and surgical options, particularly if symptoms are mild and the condition well tolerated. Non-pharmacological treatment options may also serve as adjuvants to other therapies and should be incorporated for a more holistic approach to management.

Weight loss and activity modifications are usually the first steps in managing GH-OA. Patients should follow a dietary plan targeting a BMI of < 30, which has been shown to reduce pain and the incidence of surgical interventions [20]. Furthermore, occupations requiring repetitive overhead movement patterns, heavy lifting, and forceful work should be avoided, or at least reduced, as they have been shown to increase the incidence and progression of GH-OA [21]. Workplace adaptations or modified duties should be considered when possible.

Physical activity is another important non-pharmacological intervention. Certain exercises, particularly aerobic and strength-based, have proved effective in managing shoulder arthritis and should be incorporated as part of the management plan [22]. Typical rehabilitation programmes include a gentle range of motion (ROM) and isometric strengthening of the rotator cuff and scapulothoracic musculature [23].

It is important to start with these treatment interventions in early disease stages as non-pharmacological treatment options for GH-OA are most effective if started before the development of atrophy or joint contracture, and customized to the specific needs of patients [24].

Other physical therapy options such as shoulder massage, joint mobilization, joint manipulation, phonophoresis, iontophoresis, laser acupuncture, and electrical stimulation have been described. However, despite patients reporting modest improvements, due to the lack of quantitative/qualitative studies on the subject recommendations for these forms of physical therapy as a treatment modality for shoulder OA cannot be made at this moment based on current evidence [25].

7 Pharmacological Treatment

7.1 Oral Medications

7.1.1 Acetaminophen

Historically, acetaminophen is regarded as the first-line drug for most forms of OA [26]. It has been proven to be well tolerated and effective, in maximum dosages of 4 g daily, for managing pain and alleviating symptoms in GH-OA [27]. However, although it has a relatively safe profile, the dose needs to be adjusted and monitored in the elderly population, as discussed in Sect. 10 (Management Considerations for Patients with Comorbidities).

7.1.2 Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have also been shown to be effective in treating shoulder pain, with up to 67% of patients reporting improvement [28, 29]. NSAIDs may be administered topically or orally depending on the dose required, tolerance, and relative risk-reward ratios. Furthermore, although cyclooxygenase (COX)-1 and COX-2 inhibitors have been proven to be equally efficacious, COX-2 inhibitors are often preferred due to a relatively better safety profile, particularly in older patients and patients with comorbidities such as cardiovascular, gastrointestinal, or renal diseases [30]. A previously published systematic review observed that there was moderate quality evidence to support the use of NSAIDS for shoulder pain [31], and this is further supported by recent randomized trials indicating that NSAIDs, namely celecoxib, are more effective than both acetaminophen and placebo for pain relief in OA [32]. The National Institute for Health and Care Excellence (NICE) UK guidelines recommend NSAIDS as the first-line drugs for OA [33].

7.1.3 Antidepressants

Serotonin (5-HT) and norepinephrine have been implicated in the underlying pathophysiology of chronic pain [34]. 5-HT or norepinephrine receptor modulators are commonly used in managing chronic pain and include tricyclic antidepressants (nortriptyline) and serotonin-norepinephrine reuptake inhibitors (SNRIs; duloxetine). Existing guidelines recommend the use of duloxetine in chronic pain related to OA, including from the shoulder [35]. The antidepressants have been shown to be effective for relieving pain, especially when it is associated with depression. On the other hand, there has been a lack of evidence to prove that selective serotonin reuptake inhibitors (SSRIs) are effective [36].

In one randomised controlled trial (RCT), duloxetine was studied in 512 patients, with the primary outcome, pain severity, being measured by visual analogue scale (VAS). Duloxetine was associated with significant improvements in shoulder pain ($p = 0.021$) at week 9 [37]. Other RCTs found that duloxetine 80 mg once daily reduced symptoms significantly compared with placebo in patients with chronic pain ($p < 0.001$) [38]. However, a limited number of studies have been conducted to determine SNRI efficacy in GH-OA [39]. Despite this, in patients with absolute contraindications to NSAID therapy, such as NSAID hypersensitivity or salicylate hypersensitivity, duloxetine remains a viable option.

7.1.4 Oral Corticosteroids

Several trials have shown oral glucocorticoids to effectively manage the symptoms of OA in general [40–42]; however, owing to the lack of clinical trials evaluating the effectiveness of oral glucocorticoids in the management of shoulder OA specifically and its wide list of known adverse effects, the American Academy of Orthopaedic Surgeons (AAOS) does not recommend their use [43].

7.1.5 Opioids

Although opiate-based analgesia can provide pain relief, evidence regarding opioid use is poor [43]. As such, the most recent guidelines recommend that opioids are not indicated for OA. There are concerns regarding the safety and effectiveness of opioid medication taken orally [43]. A meta-analysis showed that NSAIDs and opioids provided similar pain relief for patients with OA, with no statistically significant difference among the drug classes under consideration (NSAIDs, less-potent opioids, potent opioids; $p = 0.22$) [44]. However, for short-term use, opioids may be considered in patients with debilitating symptoms not responding to other pharmaceutical options.

7.1.6 Nutritional Supplements

Although frequently used, nutritional supplements such as glucosamine, chondroitin, vitamin D, diacerein, avocado soybean unsaponifiables (ASUs), and fish oil cannot be recommended due to a lack of clear evidence demonstrating a clinically significant benefit from these supplements [45]. Other supplements of interest that may have small effects on symptoms include curcumin (the active ingredient of turmeric) and *Boswellia serrata,* but the data for these supplements are also limited [46].

7.2 Topical Agents

Topical NSAIDs are applied in the form of a gel, cream, spray, or plaster to the skin, where they penetrate the skin and enter tissues or joints and reduce the inflammation processes in the area. Topical NSAID drug levels in the blood are significantly less compared with their oral counterparts [47]. Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in OA in studies lasting 6–12 weeks. With topical diclofenac and ketoprofen, the number needed to treat for clinical success in six and four trials (2353 and 2573 participants, respectively) was 9.8 (95% confidence interval [CI] 7.1–16) and 6.9 (95% CI 5.4–9.3) [moderate quality evidence], respectively [48].

Topical capsaicin, a transient receptor vanilloid-1 receptor antagonist, has been extensively studied in the treatment of OA of the hand and knee, with promising results and a good safety profile. Nonetheless, it is yet to be evaluated in the treatment of shoulder OA [49].

Moreover, no RCTs directly compared topical NSAIDs with capsaicin. A recent network meta-analysis comprised 28 RCTs (7372 participants), of which 17 RCTs (3174 participants) compared the efficacy of topical NSAIDs with topical capsaicin for pain relief in OA [50]. No significant differences were observed in pain relief between topical NSAIDs and capsaicin (overall: effect size [ES] 0.04, 95% CI − 0.26 to 0.33; as licensed: ES − 0.09, 95% CI − 0.34 to 0.16).

Furthermore, medical use of topical cannabis is an emerging topic of interest in the field of orthopedics [51]. Although clinical evidence is largely lacking for its use in GH-OA, patients with other types of OA, especially the knee and hip, are using this product in efforts to relieve joint pain [52, 53].

7.2.1 Intra-Articular Injections

Intra-articular injections remain one of the most used non-operative treatment modalities in the management of OA. Corticosteroids (typically methylprednisolone or triamcinolone) are the most common.

Corticosteroid injections are often used in clinical practice for patients with shoulder pain of all etiologies. Nonetheless, there is no specific evidence to support the long-term use of corticosteroid injections in the management of GH-OA [54]. Furthermore, a recent radiological study suggested that intra-articular corticosteroid injections may adversely affect hyaline cartilage and may accelerate OA progression [55].

For these reasons, the AAOS does not recommend the use of intra-articular corticosteroid injections in GH-OA, even though they have proven to be effective in other similar conditions [29]. Moreover, a recent systematic review and meta-analysis observed that corticosteroids may not have additional benefits beyond local anesthetic agents used as part of the injection [56]. Considering that, given the short-term (4 weeks) effect of corticosteroid injections, they may be useful as a diagnostic aid when GH-OA presents with concomitant pathologies or for managing an acute exacerbation of pain as a result of inflammation within the joint. Nevertheless, this needs to be evaluated further in clinical trials before a recommendation is made [16]. Thus, if corticosteroid injections are used, some authors advocate that it should be limited to no more than three injections in a single joint unless there are special circumstances [57].

These injections are not without adverse effects. Adverse effects such as transient hypothalamic-pituitary-adrenal axis suppression in addition to increased episodes of hyperglycaemia and raised ophthalmic pressures in diabetic patients have been reported following corticosteroid injections [54].

As for intra-articular sodium hyaluronate/hyaluronic acid, a randomized controlled trial has demonstrated a decrease in short-term pain scores and overall functional improvements in patients diagnosed with GH-OA when administered intra-articular sodium hyaluronate/hyaluronic acid [58]. The outcomes of hyaluronic acid injections for GH-OA were studied in a systematic review and meta-analysis that showed a reduction in VAS pain score at 3 months of 26.2 mm (95% CI 22.0–30.3 mm; $I^2 = 31\%$) and at 6 months of 29.5 mm (95% CI 25.5–33.4 mm; $I^2 = 19\%$) [59]. The included studies reported an improvement in functional outcomes. Similar clinical improvements were reported in the intervention and control groups, suggesting that these improvements may not be directly related to HA.

Platelet-rich products are increasingly being used to treat symptoms of GH-OA due to a study that demonstrated their efficacy for knee OA [61, 62]; however, there is no evidence to support the use of platelet-rich products in the management of GH-OA specifically, although platelet-rich plasma (PRP) preparations have been shown to be efficacious in relieving pain and improving joint function in other shoulder pathologies [63]. To our knowledge, peer-reviewed studies on PRP for GH-OA are limited [6], however there are studies documenting excellent results in the knee. According to the meta-analysis by Han et al., PRP injections were more effective in reducing pain than hyaluronic acid injections in patients with knee OA at 6 and 12 months of follow-up, with use of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and the VAS pain score. In addition, the PRP group exhibited better functional improvement, as shown by the WOMAC function score at 3, 6, and 12 months [64].

Lastly, the use of orthobiologics is an area of recent interest due to the availability of new promising products addressing OA, including mesenchymal stromal cells (MSCs) and bone marrow aspirate concentrate (BMAC) [65]. However, evidence regarding the use of the orthobiologic injection to treat GH-OA is scarce [6, 66].

Septic arthritis in patients receiving intra-articular injections was also reported as a possible complication [60].

8 Suprascapular Nerve Block and Radiofrequency Ablation

Theoretically, suprascapular nerve block or ablation should relieve pain and improve symptoms in patients with shoulder OA. Accordingly, several studies have demonstrated the benefit of using suprascapular nerve block in several shoulder pathologies, including GH-OA [67]; however, the benefit is only short-term and there are concerns regarding the potential risk associated with the procedure [67]. In the hope of prolonging relief by targeting the nerves to the shoulder

joint, radiofrequency procedures have been considered [68], however existing evidence is mixed and of low quality [69].

9 Surgical Treatment

Surgical treatment of GH-OA is reserved for patients who do not respond to conservative management or who suffer from debilitating symptoms that severely impair their quality of life. TSA is the recommended treatment in most patients with GH-OA with a competent rotator cuff, especially the elderly [70]. Patient satisfaction and recovery have been overwhelmingly positive with TSA [71]. Studies have not only reported improvements in pain but also in active and passive ROM of the shoulder joint [72]. Despite concerns about the longevity of the prosthesis used during TSA, prosthetic survival was 93% and 87% after 10 and 15 years, respectively [73].

Other surgical treatment options such as hemiarthroplasty have been shown to be inferior to TSA in the management of GH-OA in terms of pain relief, ROM, and longevity [74].

Minimally invasive surgical options, particularly arthroscopic procedures, have demonstrated high patient satisfaction rates [75]; however, other studies have reported poor results in the long term, with patient satisfaction reducing considerably after a 1-year follow-up period [76]. Thus, for the reasons detailed above, both the AAOS and the NICE recommend TSA as the surgical treatment of choice in patients with GH-OA [29].

10 Management Considerations for Patients with Comorbidities

Comorbidities in patients with any form of OA are frequent and thus directly impact the pharmacological treatment options. A meta-analysis of 42 studies placed the prevalence of comorbidities in patients with OA at 67%, compared with 56% in the general population [77]. The most prevalent comorbidities were hypertension (50%), cardiovascular disease (35%), peptic ulcer disease (16%), and diabetes (14%).

NSAIDs should be used with caution in GH-OA patients with additional comorbidities. When possible, NSAIDs should be used for the shortest period, owing to decreasing efficacy and increasing incidence of adverse effects with prolonged use [78].

NSAIDs, specifically COX-2 inhibitors, have been shown to raise blood pressure and thus should be used sparingly in patients with poorly controlled hypertension [79]. In such instances, the use of acetaminophen should be preferred. Owing to their minimal effect on blood pressure, intra-articular glucocorticoid injections are also safe to use in patients with hypertension [80].

Given the established link between NSAID use and the incidence of peptic ulcer disease, NSAIDs are contraindicated in GH-OA patients with active peptic ulcer disease [81]; however, NSAIDs may be used sparingly, with COX-2 inhibitors preferred, in patients with a history of peptic ulcer disease or those deemed to be at risk for it.

Oral pharmacological agents, other than NSAIDs, are considered well tolerated in diabetic patients with GH-OA. Furthermore, although intra-articular glucocorticoid injections pose a theoretical risk for hyperglycaemia, the elevation in blood glucose levels is only transient and thus intra-articular corticosteroid injections can also be safely used in these patients [82].

Dose adjustments for all oral pharmacological agents are especially important in older patients (aged $\geq$ 50 years). The metabolism of acetaminophen in older patients is highly variable and may be reduced in frail older patients due to a decreased volume of distribution and intrinsic conjugative activity of the liver. Thus, older adults may be at increased risk of hepatotoxicity and the maximum daily dose should likely be reduced to between 2 and 3 g/day [83]. Furthermore, opioid use in older adults is associated with an increased risk of cognitive impairment and injuries, in addition to an increased risk of cardiovascular events, pneumonia, and mortality [84].

11 Limitations

Although evidence pertaining to the surgical management of GH-OA is plentiful, the same is not true for non-surgical management options. Limited high-quality studies have been carried out in patients with GH-OA to evaluate the efficacy of pharmaceutical treatment options in this specific group. Studies that do exist are short-term studies with a small sample size. It is for this reason that practice guidelines for the management of GH-OA are limited and, in many cases, extrapolate information obtained from the treatment of OA in other joints. Thus, further research comparing the treatment effects in GH-OA can serve as an area of interest in the foreseeable future.

12 Summary of Practice Guidelines

Practice guidelines for the pharmacological and non-pharmacological management of GH-OA are limited, however the AAOS and NICE have published such guidelines. Figure 1 presents a brief flow chart for the diagnosis and treatment of GH-OA. We also discuss detailed treatment

Table 1 Clinical practice guidelines for treating glenohumeral osteoarthritis

Intervention	American Academy of Orthopaedic Surgeons	National Institute for Health and Care Excellence
Physical therapy	Uncertain	Recommend
Acetaminophen	Uncertain	Recommend (prefer topical over oral)
NSAIDs	Uncertain	Recommend (prefer topical over oral)
Opioids	Not recommended	Not recommended
Vitamin supplementation	Not recommended	Optional
Oral corticosteroids	Not recommended	Not recommended
Injectable corticosteroids	Uncertain	Beneficial in some instances
Injectable viscosupplementation	Optional	Not recommended
Arthroscopic treatment	Uncertain	Beneficial in some instances
Open debridement	Uncertain	Beneficial in some instances
Interposition arthroplasty	Uncertain	Beneficial in some instances
Hemiarthroplasty/total shoulder arthroplasty	Optional	Recommend

NSAIDs non-steroidal anti-inflammatory drugs

protocols in this review alongside various clinical practice guidelines (Table 1).

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Code availability Not applicable.

Ethics approval This review did not require ethics approval.

Consent to participate Not applicable.

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