Non-surgical treatment of osteoarthritis-related pain in the elderly

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Abstract Osteoarthritis (OA), the third most common diagnosis in the elderly [1], causes significant pain leading to disability and decreased quality of life in subjects 65 years and older [2]. Traditionally, clinicians have relied heavily on the use of non-steroidal anti-inflammatory drugs (NSAIDs) to treat the pain of OA, as numerous studies have proven these agents to be effective. The cardiovascular, gastrointestinal, renal and hepatic toxicities of NSAIDs have limited their use, particularly in the elderly. Acetaminophen has been recommended as initial therapy due to relative safety. Several other topical, oral and intra-articular agents are available today, with use limited by efficacy and side effect profiles. Many non-pharmacologic approaches are available but underused, and may be attractive choices to avoid poly-pharmacy in older patients. We will attempt to

highlight the evidence behind available non-surgical therapies for OA while paying specific attention to issues in geriatric patients.

Keywords Osteoarthritis · Arthritis · Pain management · Elderly · Treatment · Safety · Toxicity · Efficacy · Rheumatology

Introduction

Osteoarthritis (OA) is the leading cause of functional decline and morbidity in the elderly [3], disabling approximately 10% of Americans greater than 60 years of age, with an economic impact of more than \$60 billion per year [4]. Recent advances in understanding of the osteoarthritic disease process have led us to appreciate that pain can be generated by neurovascularized tissues within and around the joint, namely the synovium, capsule, ligaments, muscle [5] and subchondral bone [6]. The mechanisms generating pain are at-least two-fold: (a) inflammatory pain triggered locally within synovium and soft tissues, and (b) neuropathic mechanisms involving both locally and centrally mediated pain pathways [7••]. Clinically, we rely heavily on NSAIDs and intra-articular (IA) corticosteroids to treat OA pain, but several other oral, intra-articular and topical agents are available. In the elderly particularly, non-pharmacologic options like exercise, weight loss, physical therapy (PT), bracing and orthotics should be considered first to minimize medication adverse effects (AE). Furthermore, depression and anxiety commonly accompany chronic pain and must be addressed as they impact functional decline [8]. In this review, we will discuss both non-pharmacological and pharmacological options available for management of OA with attention to issues specific to older adults.

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Non-pharmacologic interventions

Conservative measures play an important role in management of OA-related pain and disability, particularly in the geriatric population due to increased risk of co-morbidities, medication toxicity, and poly-pharmacy. The American College of Rheumatology (ACR) recommendations for the management of OA [9] begin with conservative strategies such as self-management programs (e.g., Arthritis Foundation Self-Management Program), social support, weight loss, and appropriate footwear. Following are some commonly used conservative strategies:

Orthotics and footwear

Both the ACR [9] and the Osteoarthritis Arthritis Research Society International (OARSI) [10••] recommend use of lateral-wedged (LW) insoles for OA. These insoles have been studied specifically in management of knee OA with varus deformity. LW orthotics decrease the degree of varus misalignment at the knee by causing ankle pronation, thereby decreasing medial joint load associated with OA progression [11]. Two randomized controlled trials (RCTs) demonstrated that use of LW orthotics can decrease patient consumption of oral analgesics in medial knee OA at 6 months [12] and 2 years [13]. No improvement in function or pain was noted. The long-term effects of these insoles are currently unknown, and there is concern regarding their use in patients with foot problems [14] and severe knee OA [15]. Favorable responses have been demonstrated in patients who are less obese [16], and have less severe disease [16, 17]. Since an insole is a simple and inexpensive measure, we recommend that LW insoles are an option in ambulating elderly who need to decrease NSAID consumption. A podiatric evaluation should be obtained prior to use.

Elevated joint load is associated with severity and progression of knee OA. Bare foot walking reduces joint loads at the hip and knee [18]. Shakoor and colleagues showed that common shoes such as clogs and stability shoes lead to increased joint loads compared with bare foot walking [19•]. A specially designed flat, flexible shoe which mimics bare foot walking reduced joint load on the knee by 12% compared to a control walking shoe [20]. Educating elderly patients about selection of footwear, promoting flat and flexible low heel shoes may help in reducing joint loads. Whether reduction of joint loads by footwear translates to less pain or reduced progression of OA has yet to be definitively demonstrated, and again foot issues need to be taken into consideration.

Knee bracing (conservative realignment)

Various types of external bracing devices are available commercially: rest braces, knee sleeves, un-loading knee

braces as well as patellar taping and bracing. Rest braces are made of stiff composite material designed for joint immobilization; given the risk of muscle weakness their use for knee OA is not recommended, and in the elderly could compound already existing frailty. Other options are discussed below.

Simple neoprene knee sleeves have been demonstrated to decrease pain and perhaps improve function in patients with medial knee OA [21]. Varus malalignment of the knee has been implicated as a contributing factor to knee OA progression [22], and valgus unloading knee braces may reduce medial knee loading in varus deformity, and improve pain and function [23]. Stability and balance are of particular importance in elderly patients at greater risk for falls, and unloading braces can stabilize the joint and improve balance [24]. However, a systematic review of available studies in 2006, consisting of only two small observational studies, suggested that these braces have limited efficacy in knee OA [25, 26]. Non-compliance secondary to skin irritation and bulkiness limit use [25]. Though further studies are needed, the use of unloading braces is an option when noticeable varus malalignment at the knee exists, and may be particularly attractive when improvement in balance and prevention of falls may be a therapeutic goal.

Another attractive conservative option is patellar taping. This is done by applying adhesive, rigid, tape to position the patella, while patellar bracing can be done with an external device. Both methods have been suggested for use in OA affecting the patellofemoral knee compartment. A systematic review [27••] assessing patellar taping in knee pain concluded that medially directed force on patella produces significant reduction in pain, though only 3 studies in this review included older adults. As taping can cause skin irritation and is difficult to self-apply, researchers recently evaluated patellofemoral bracing as an alternative to taping in a randomized controlled crossover trial [28••]. This well-designed study evaluated 80 patients but did not demonstrate a significant beneficial effect of patellar bracing on pain or function. Whether the specific brace utilized actually had its desired effect on patellar alignment and tracking was not evaluated. Clearly more work is needed, but as taping is inexpensive and relatively harmless, it can be employed in older adults with patellofemoral OA, patellar malalignment and anterior knee pain.

Physical therapy and exercise

Prolonged inactivity can result in deconditioned muscles and periarticular stiffness contributing to worsening symptoms of OA [29]. Targeted PT to improve muscle function and aerobic exercise can lessen knee OA symptoms [30]. A longitudinal cohort study including 2000 knees suggested better knee extensor strength predicted lower incidence of

symptomatic knee OA [31]. A 12 week RCT of a PT-based quadriceps strengthening program was aimed at reducing joint load, a factor predictive of OA progression [32], in patients with medial knee OA. This program resulted in increased muscle strength but failed to reduce joint load [33]. Similarly, hip abductor strength training via a home exercise program did not affect knee or hip joint loads but decreased symptom scores [34]. A supervised hip abductor strengthening program has similarly been shown to reduce pain and improve function in knee OA [35]. Although the reported differential effects of muscle strengthening approaches on pain and joint load may at first be surprising, is important to note that symptomatology in OA is quite complex, involving multiple mechanisms. The available studies may either be too small to identify a minor effect of these interventions on joint loads, or the effect of exercise on symptoms may be related to additional factors other than joint load. A recent systematic review of 12 RCT [36•] concluded that exercise therapy plus manual joint mobilization was superior to either strength training or exercise therapy alone in medial knee OA, though all three modalities improved pain and physical function. Thus, PT has become a mainstay of symptomatic OA treatment and rehabilitative efforts, given its safety and impact on pain and function.

PT takes on additional importance in elderly patients with multiple co-morbidities contributing to disability and requiring rehabilitation. The FAST trial (Fitness arthritis and Seniors Trial) demonstrated that debilitated adults >60 years of age with knee OA had modest improvements in pain, function and disability when enrolled in either resistance or aerobic exercise programs [37]. Exercise improves well-being and preserves function and therefore is highly recommended in older adults that can comply safely.

Pharmacologic therapies

Oral analgesics

Acetaminophen

Acetaminophen (Tylenol®, Paracetamol® and Panadol®) has both analgesic and anti-pyretic actions [38]. Acetaminophen, up to 4 g per day, is the first medication recommended by ACR [9], OARSI [10••] and EULAR (European League Against Rheumatism) [39] guidelines for treatment of mild to moderate OA. A systematic review evaluating 15 RCTs assessing acetaminophen in hip or knee OA pain [40] concluded that though beneficial over placebo, acetaminophen was inferior to NSAID for pain control and reduction of stiffness and swelling. However, acetaminophen has a better safety profile in most studies than NSAIDs. Recently there has been controversy regard-

ing cardiovascular (CV) [41], gastrointestinal (GI) [42•] and renal [43] toxicities of acetaminophen, with chronic use of more than 3 g per day associated with similar side effects as NSAIDs. In addition, the combination of acetaminophen and NSAIDs may compound the risk of GI toxicity [44]. We suggest care be used to ensure patients, particularly older adults, do not exceed safe daily dosages, and use of proton pump inhibitor (PPI) should be encouraged especially with doses greater than 3 g/day or with combination therapy of acetaminophen and NSAID [42•].

NSAIDs

NSAIDs treat inflammatory pain, and also reduce swelling and joint stiffness. A systematic review of 27 RCTs confirmed the superiority of NSAID to acetaminophen for pain relief in OA [44]. In large RCTs, selective COX-2 inhibitors (i.e. celecoxib or Celebrex®) appear to produce pain relief similar to non-selective NSAIDs (i.e. ibuprofen, naprosyn, diclofenac) but conventional NSAIDs are associated with higher GI toxicity including ulceration, perforation and bleeding [45, 46]. In the largest population based cohort study of patients over 65 years, GI toxicity and hospitalization was twice as high in patients receiving non-selective NSAIDs compared to either celecoxib, or non-selective NSAIDs in combination with a PPI [42•]. In patients over 75 years of age, PPI usage even with celecoxib reduced hospitalization secondary to GI toxicity by 30% [47].

In addition to well-documented GI, renal and hepatic toxicities, increasing awareness of CV risks of NSAIDs has made many physicians and patients more guarded in their use, particularly in the geriatric population. A meta-analysis of observational studies on a variety of NSAIDs concluded celecoxib had the least CV toxicity among the selective COX-2 inhibitors, while Naproxen, Ibuprofen and Piroxicam conferred lesser CV risk than diclofenac among non-selective agents [45]. Despite side effects, NSAIDs still remain an option in patients with OA-related pain due to their proven efficacy. The high rate of co-morbidities in the elderly complicates their use. The decision to use NSAIDs must be a joint decision between the physician and patient, after discussion of the risks, and with a prospective plan for monitoring side effects and controlling blood pressure.

Tramadol

Tramadol is a weak, atypical opioid analgesic, though it does not have as much abuse potential as other narcotics [48] and is not regulated as a controlled substance making it more attractive to most patients and practitioners. A meta-analysis examining the effects of tramadol on OA pain was published in early 2007 [49]; eleven RCTs including 1019

patients who received tramadol or tramadol/acetaminophen in comparison with placebo or active control (either acetaminophen, diclofenac, or other weak narcotic) were included. The mean difference in pain scores favored treatment with tramadol, but the effect was small (RR 1.34, 95% CI 1.13–1.58). Compared with placebo, tramadol was more effective, but the magnitude of pain relief was similar to acetaminophen. A RCT done in geriatric patients showed improvement in pain and sleep related outcomes [50]; side effects included constipation (27.5%), nausea (23.4%) and dizziness (22.7%). Dizziness is a much more significant issue in the elderly due to the risk of falls. In addition, tramadol can decrease seizure threshold [51] when titrated or withdrawn quickly. Slow-titration of this medication may decrease side effects and improve tolerability in older adults.

Opiates

Narcotic analgesics are often used in treating pain in OA patients, but concerns about dependency and toxicities are particularly worrisome in the elderly. A recent systematic review of non-tramadol opioids (including morphine, codeine, oxycodone, and oxymorphone and transdermal fentanyl) included 10 trials and 2268 participants [52•]. Opioids had a small benefit in pain and function over placebo, though serious AE and dropouts were greater with opioids. No differences between types or doses of opioids were observed. A meta-analysis of 41 RCTs of over 6000 patients with non-cancer related pain concluded that strong opioids like morphine and oxycodone were superior to acetaminophen and naproxen for pain relief but not for functional outcomes [53]. 80% of patients included had OA, back pain or rheumatoid arthritis. Use of these agents in combination with standard therapy may allow for decreased dosages, but small benefits may be outweighed by high AE rates limiting their use particularly in older adults.

Duloxetine

In November 2010 the FDA approved duloxetine hydrochloride (Cymbalta™), a serotonin and norepinephrine reuptake inhibitor (SNRI), for the treatment of chronic musculoskeletal pain conditions including OA and chronic low back pain. This agent, first used to treat major depressive disorder, is also in clinical use for treatment of fibromyalgia. In 2009 results from a small (25 patient) single-blind pilot study suggested this agent might be useful in patients with pain from OA [54]. Along with supportive data from a rat model of OA [55], this prompted a 13-week, placebo-controlled RCT of duloxetine (60 to 120 mg daily) for pain control in OA of the knee [56•]. In this study of 256 patients, duloxetine effected significant improvements

in pain and physical function scores compared to placebo. 65.3% of duloxetine treated patients had greater than 30% reduction in pain from baseline to 13 weeks, compared with 44.1% of placebo treated patients. In a recent pooled analysis of 52 placebo-controlled trials (including 17,822 patients) for various indications [57], the most commonly reported side effects of duloxetine were nausea (23%), dry mouth (12.6%), headache (12%) and constipation (10%).

Topical/transdermal agents

Topical and transdermal agents used as adjunctive therapy theoretically reduce the incidence of systemic side effects, making them attractive in geriatric populations. Following are three commonly used agents.

Capsaicin

ACR [9], OARSI [10••] and EULAR [39] guidelines all recommend Capsaicin for management of pain in OA. Topical Capsaicin is available over-the-counter in two different strengths (0.025% and 0.075%). It has a slow onset of action and can cause local burning which may reduce compliance. In older adults, particular attention to skin integrity and application technique must be taken to avoid irritation.

Topical NSAIDs

Topical NSAIDs are recommended by OARSI [10••] and EULAR [39] guidelines for management of hand and knee OA. Two meta-analyses covering 14 placebo-controlled RCTs demonstrated efficacy of topical NSAIDs with duration of effect from two to four weeks. In this analysis, heterogeneity of the products studied, variable efficacy endpoints, and lack of adequate published studies in large numbers of patients made it difficult to conclude whether these agents remain efficacious beyond 4 weeks of treatment [58, 59]. In the United States, the FDA approved topical Diclofenac sodium 1% (Voltaren gel® and Pennsaid®) for OA pain management in 2007. A recent double blinded 8 week RCT [60•] demonstrated decrease in pain score by 42–45% in patients >40 years old with primary hand OA treated with diclofenac sodium 1% gel compared to placebo. AEs were similar to placebo in terms of GI and CV events. Another RCT compared topical diclofenec to oral diclofenec, as well as topical and oral placebos in patients with OA (mean age 61 years) [61]. This study demonstrated equivalent efficacy of topical and oral diclofenec, with a potential decrease in GI toxicity compared with oral therapy, making it an attractive choice in older adults. Whether there is also a decreased long-term CV risk with topical compared to oral diclofenec has yet to be determined. When applied topically,

diclofenac plasma concentration is 158 times less than with oral administration (voltaren gel package insert); local irritation occurs in 4% of the patients [60•].

Transdermal lidocaine patches

Although there are no RCTs testing efficacy, 5% lidocaine transdermal patches (Lidoderm™) are often used by clinicians to control pain in OA. Two open-label trials support their use, reporting reduction in knee pain in OA patients after two-weeks [62, 63]. AE are minimal; most common is local skin irritation. Dizziness and headaches have been reported with over-dosage and patients and caregivers must be advised to apply patches only for 12 continuous hours within every 24 h period (alternate 12 h on with 12 h off).

Intra-articular agents (IA)

In addition to oral agents, IA agents including corticosteroids and hyaluronic acid derivatives (HA) have been used to treat pain flares in individual joints. In addition, intra-articular blockade of IL-1 is currently under study.

Corticosteroids

IA steroid injections have been used extensively to treat OA pain, with knee OA being the most common indication. ACR [9], EULAR [39] and OARSI [10••] guidelines all recommend their use. Current treatment protocols limit corticosteroid injections to 3 to 4 injections per year, due to the theoretical risk of hastening cartilage damage. A systematic review of 28 RCTs [64] concluded that there was a significant reduction in pain one week post injection which was maximal at 2–3 weeks post-injection (RR 3.11, 95% CI 1.61–6.01). Beyond three weeks, there was no significant benefit, but longer-term effects were only evaluated by a few small studies. No improvement in function was observed at any time point. More recent studies have demonstrated potential benefit in other joints affected by OA including the hip [65]. Given the rapid action, relative safety, and low-cost of these agents, they remain useful in treatment of episodic moderate to severe OA-related pain in specific joints.

Hyaluronic Acid (HA)

There are numerous HA products and derivatives approved by the FDA for knee pain including Synvisc™ Genzyme Corp, Cambridge, Massachusetts, Hyalgan™ (Sanofi-Syhelabo Inc, New York, New York), Orthovisc™ (Anika Therapeutics Inc, Woburn, Massachusetts), Supartz™ (Seikagaku Corp, Tokyo, Japan), and Euflexxa™ (Ferring Pharmaceuticals Inc, Suffern,

New York). ACR guidelines recommend them as an option in patients at risk for GI side effects from NSAIDs [9]. This is appealing in the elderly, and may be useful in those with monoarticular large joint disease. These agents are usually administered as a series of 3–5 weekly injections, but recent data suggests a single 6 ml injection of the agent hylan-GF 20(Synvisc™) may be effective as well [66]. There is great heterogeneity in existing trials of these agents, making strong conclusions as to their efficacy difficult, with many studies of small size and varying quality [67, 68]. A systematic review assessing the efficacy of HA analyzed 76 blinded RCTs evaluating multiple HA agents. The review concluded that efficacy of these agents is comparable to NSAIDs, and was longer lasting (with peak effects seen at 5–13 weeks) than IA corticosteroids [69]. In practice, it appears that these agents may be effective in a subset of patients, although we currently have no means to identify patients who will respond. One retrospective study of 336 patients with knee OA found that patients with radiologically mild to moderate disease and those with no effusion responded better [70]. Other factors that have been reported to predict better response to treatment were age greater than 60 years and lower baseline functional capacity[71]. HA use for joints such as shoulder [72], hip [73] and first carpometacarpal joint [74] have been reported recently. The most common AE is a transient injection site reaction with mild redness, warmth and swelling in 20–30%. A “pseudo-septic” arthritis has been reported in some patients treated with the agent Hylan G–F 20 (Synvisc™) [75, 76]. These generally respond to corticosteroid injection after ruling out infection. In older adults these agents are options to try, particularly in patients with a single or few large symptomatic joints and those too frail for surgery.

Alternative agents/nutraceuticals

There are a number of nutritional and herbal supplements that are anecdotally reported to decrease arthritis pain and increase mobility. These include ginger extracts, methylsulfonylmethane, MSM s-adenosylmethionine (SAM-e), and ASU (Avocado-Soybean Unsaponifiables) [77]. Most of these supplements are unregulated, may have unclear AE and have not been studied in an appropriately randomized and controlled fashion to assess efficacy. An exception is glucosamine and chondroitin [78, 79] which is discussed below.

Glucosamine/chondroitin Glucosamine and chondroitin are available in many different formulations. As they are unregulated, the actual content of glucosamine and chondroitin in various commercial products was found to

vary from 0% to 115% of the labeled amount [80, 81]. In a systematic review of 15 placebo RCT, glucosamine sulphate (GS) preparation were minimally effective for pain relief, and no improvement in physical function or stiffness was noted [82]. The Glucosamine/Chondroitin Arthritis Trial (GAIT) was a double blinded, placebo controlled trial which found that glucosamine/chondroitin was not effective for OA pain [83•]. This trial included more than 1500 patients with knee OA and compared glucosamine hydrochloride (GH), chondroitin sulfate, the combination, and celecoxib. Neither glucosamine nor chondroitin, alone or in combination, demonstrated efficacy by the primary outcome of reduction in pain score by

20% at week 24. These results are in contrast to the GUIDE (glucosamine sulfate Unum In die Efficacy) Trial [79] that compared glucosamine sulfate (GS), acetaminophen and placebo, and demonstrated that GS was better than placebo for pain relief. Whether Glucosamine and/or chondroitin are effective in reducing joint damage from OA is controversial, with divergent results from numerous small studies, and considerable publication bias in this area [81]. In addition, these agent can be quite costly, although they appear to be safe so many patients are willing to try these nutraceuticals.

Table 1 Agents used in the non-surgical management of osteoarthritis

Non Pharmacological Measures (source recommendation in parentheses):
1) Patient Education (ACR ^a , OARSI ^b , EULAR ^c)
2) Self Management Programs e.g. Arthritis Foundation Self Management Program (ACR, OARSI)
3) Reduction of excess body weight (ACR, OARSI, EULAR)
4) Physical and Occupational Therapy (ACR)
5) Aerobic, Water-based and Muscle Strengthening Exercise (ACR, OARSI, EULAR)
6) Orthotics: Lateral wedged insoles (ACR, OARSI, EULAR)
7) Appropriate footwear (ACR)
8) Conservative Realignment/Joint Protection
9) Knee braces (ACR, OARSI)
10) Neoprene Knee sleeves (OARSI)
11) Patellar taping (ACR)
12) Assistive devices for activities of daily living when indicated (ACR) - of particular importance in the elderly
Pharmacological Measures:
1) Oral Agents
- Acetaminophen (ACR, OARSI, EULAR)
- selective COX-2 NSAIDs
- non-selective NSAIDs
- Tramadol
- Duloxetine
- Opioids
- Glucosamine/Chondroitin supplements
2) Topical agents
- Capsaicin (ACR, EULAR, OARSI)
- NSAIDs (OARSI, EULAR)
- Lidocaine patches
- Opioids (effective, but use limited by side effects)
3) Intra-articular Agents
- Corticosteroids (ACR, EULAR, OARSI)
- Hyaluronic acid

^a American College of Rheumatology [9]; ^b Osteoarthritis Research Society International [10••] and ^c European League Against Rheumatism [37] recommendations for management of OA

Table 2 Recommendations for OA treatment with specific consideration of elderly patients

- Non-pharmacologic interventions should be maximized early. Consider non-pharmacological measures (specifically weight loss, exercise, physical/occupational therapy, braces, orthotics) as initial therapy, or in combination with pharmacotherapy to minimize medication usage and side effects.
- Ensure access to proper eye glasses, hearing aids and assistive devices for activities of daily living when indicated (e.g. canes, walkers, high toilet seats, toilet bars, bath benches etc).
- Consider frequent screening for and treatment of concurrent depression and anxiety.
- Take all measures to prevent falls as they are both a cause (due to repeated joint injury) and effect of osteoarthritis and add to morbidity and functional decline.
- Consider all important elements of the past medical history and potential drug interactions when starting drug therapy. Polypharmacy is a significant issue in the elderly and must be considered prior to starting therapy.
- Among available oral agents, consider acetaminophen first whenever possible due to existing co-morbidities and higher susceptibility to side effects of other medications. Realize that acetaminophen, particularly at maximum doses given chronically, is not without potential toxicities which may be similar to NSAIDs. Doses greater than 3 grams per day should be used with caution in the elderly.
- Ensure or maximize medication compliance prior to starting drugs with potentially hazardous side effects.
- Consider adding Tramadol or duloxetine for breakthrough pain before starting stronger opioids, though nausea and dizziness may limit use. To limit side effects, slowly taper dose of these agents.
- NSAIDs (selective or non-selective agents) can be considered in low-risk patients and those who are refractory to other agents. Concomitant use of a PPI to confer GI protection should always be considered.
- Opioids should be used only when necessary, when other modalities (non-pharmacological and other pharmacological agents) have failed to control symptoms, and should be dosed with caution and monitored closely for side effects and over-dosage.
- Trans-dermal lidocaine and Intra-articular agents can be considered, especially in mono or oligoarticular OA to minimize the use of oral agents with greater risk of systemic side effects.
- Topical NSAIDs can also be effective adjuncts due to demonstrated efficacy and potentially fewer side effects compared with systemic NSAIDs.

The future of OA therapy

Both the pharmacologic and non-pharmacologic strategies discussed in this review have been demonstrated to different degrees to improve pain, and in some cases function, but no modalities have yet been shown to significantly modify the disease course. Although this remains an important goal, given the protracted course of OA and the contribution of OA-related pain to morbidity, symptom control is still an important focus of clinical management. Two pharmacologic strategies under investigation for OA treatment include blockade of Interleukin-1 (IL-1) and inhibition of nerve growth factor (NGF). Lower levels of IL-1 have been associated with decreased risk of developing OA[84]. A 12 week multicenter, RCT comparing IL-1 antagonist given intra-articularly failed to show significant improvement in pain scores compared with placebo [85•]. However, this early study employed a single injection of a very short acting agent, so the utility of longer-acting agents is still under study. Another novel therapy being investigated for pain management in OA is NGF inhibition. NGF is elevated in chronic pain conditions including OA, and decreased NGF serum levels are associated with diminished pain sensation [86]. Tanezumab®, a humanized anti-NGF monoclonal antibody, was tested in a RCT of 450 surgical candidates with knee OA refractory to non-opiate pain medications. It demonstrated significant reduction in pain compared to placebo (45–62% reduction vs. 22% respectively; $p<0.001$) [87••]. This trial has been discontinued due to an increase in the need for total hip replacement in the Tanezumab arm for unclear reasons. But at the very least these studies have identified that treatment aimed at this particular target is effective in reducing pain from OA.

Conclusions

The focus of this review was nonsurgical treatment of pain in elderly OA patients, and the specific modalities and approaches discussed are presented in Table 1. However, it is important to realize that many factors affecting the geriatric population contribute to OA-related pain, functional decline and progression [88•]. Therefore, the approach to management of OA pain in the elderly should take into consideration all of these factors. Our specific recommendations are presented in Table 2. The importance of recognizing when assistive devices such as canes and walkers are needed cannot be overstressed. OA-related instability can be due to the direct consequence of arthritic changes at the joint, accompanying neuropathic changes, or pain-related behavioral and gait changes. This OA-related instability will be exacerbated by generalized

frailty in elderly patients and must be considered when evaluating safety and risk of falls. When targeting pain, non-pharmacologic approaches should always be incorporated in management strategies when possible [9]. Pharmacologic agents should complement these conservative approaches. Use of topical and intra-articular agents to decrease dependence on oral agents may minimize systemic toxicity. Furthermore, medical treatment of pain may improve compliance with physical and exercise therapy in many patients.

In the end-stage patient with significant cartilage loss and uncontrolled pain, total joint replacement remains the most effective intervention. But there are a significant number of elderly patients who are high-risk candidates for this definitive intervention due to medical co-morbidities. In those patients, it is imperative to maximize functional capacity through the use of assistive devices. Both conservative and pharmacologic approaches to pain management are essential considerations for these patients as OA related pain and dysfunction may amplify disability caused by other co-morbidities. Hopefully, investigations into the multiple mechanisms leading to joint destruction and pain at different stages of disease will yield more effective therapies in the near future.

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- Of importance
- Of major importance

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