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What Do We Know about Pharmacologic Management of Osteoarthritis-Related Pain?

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Abstract

Background—Pain is a common and debilitating symptom associated with osteoarthritis (OA) among adults, particularly in older adults.

Objective—To review efficacy and safety data regarding commonly employed pharmacologic treatments for OA to include oral (e.g., acetaminophen), topical (e.g., lidocaine) and intra-articular (e.g., steroid) interventions.

Methods—We searched the Medline, PubMed, CINAHL, and Cochrane Review databases to identify English-language articles that presented efficacy (e.g., pain, stiffness, function) or safety (e.g., frequency and type of specific adverse events) data. Two authors independently abstracted information from the retained studies/reviews.

Results—To date, most studies have focused on adults with knee OA and reported data on short-term outcomes only. Treatment efficacy varies by analgesic class, with smallest effect sizes observed for acetaminophen and largest effect sizes for opioids and viscosupplementation. Treatment-related adverse event rates vary widely, with acetaminophen and topical agents having the best safety profiles, while opioids and oral NSAIDs have the worst profiles. Few investigations enrolled older individuals (e.g., those 75 years and up), those from diverse race/ethnicity groups or reported results stratified by other potentially important predictors including age and gender.

Conclusions—Available evidence indicates that most current pharmacologic agents provide mild-to-moderate pain relief; some analgesics (e.g., topical agents and acetaminophen) have substantially better safety profiles than others (e.g., oral NSAIDs and opioids). The long-term safety and efficacy of these agents and their effects in diverse subpopulations of adults (particularly older adults) with OA remain to be determined.

Keywords

Analgesia; osteoarthritis; pain

INTRODUCTION

Osteoarthritis (OA) constitutes a significant public health problem.^{1,2} Approximately 50 million adults in the U.S. have arthritis (with OA being the most common), including half of all individuals over the age of 65.¹ The prevalence of OA is greater among women than men, increases with age, and affects all race/ethnicity groups.³ Because there are currently

no disease-modifying therapies, treatment is directed at managing OA-related symptoms (e.g., pain and joint swelling), with a goal of minimizing functional impairment and preserving quality of life. Nonpharmacologic treatments in the form of patient education, exercise, weight loss, and physical therapy can provide substantial benefit,⁴ but are underutilized.⁵ Pharmacologic interventions constitute the most commonly prescribed therapy by healthcare providers⁶ and commonly employed treatment by patients with OA.⁷ Joint replacement is routinely considered for individuals with severe symptomatic disease who have failed to respond to customary therapies. Although joint replacement surgery can be very effective,⁸ many adults (particularly older minorities) forego surgery which limits the reach of this intervention.⁹

This article synthesizes current knowledge regarding the pharmacologic management of OA-related pain among adults, with a particular focus on older adults, i.e., those ages 65 and above. A focus on older adults is appropriate for several reasons. First, the consequences of inadequately treated pain are particularly significant in this age group, including poor self-rated health and decreased cognition and mobility.^{10,11} Pain is by far the most frequently cited symptom causing activity of daily living disability in later life and can threaten an older persons' ability to remain independent in the community.¹² Older adults have the highest rates of chronic analgesic use of any age group and are the most susceptible to adverse effects of analgesic treatment.¹³ Finally, the co-occurrence of other chronic conditions, multiple sites and causes of pain, high prevalence of polypharmacy, and older adults' concerns about analgesic medications, e.g., fear of side effects and addiction, as well as a lack of age-relevant studies to guide decision making challenge even seasoned clinicians when attempting to manage OA-related pain using analgesics in older adults.¹³

METHODS

Medline, PubMed, and the Cumulative Index to Nursing and Allied Health Literature databases (01/95-06/11) as well as the Cochrane Reviews were searched to identify relevant articles for review. The following search terms were selected based on the first author's experience managing pain in older patients with OA: Acetaminophen, non-steroidal anti-inflammatory agents, opioid, intra-articular injections, corticosteroid, hyaluronic acid, capsaicin, lidocaine, glucosamine, and chondroitin. These terms were linked with osteoarthritis, degenerative joint disease, randomized controlled trials, systematic review and meta-analysis. Identified abstracts were reviewed in detail by two investigators (MCR, RS) who independently abstracted information (e.g., estimates of treatment effect and safety data) from all relevant articles. Discrepancies in the abstraction process were resolved by discussion. Effect sizes (to include standardized mean differences) are presented and allow for comparison across analgesic classes. An effect size less than 0.2 is thought to be negligible, 0.20-0.49 is small, 0.50-0.79 is moderate, while an effect size of 0.80 or above is considered to be large.

RESULTS

Characteristics of Retained Studies

With few exceptions, studies examined analgesic safety and efficacy over brief periods of time (12 weeks or less). Most investigations were sponsored by pharmaceutical companies, and older age was often an exclusion criterion for study entry. Investigations enrolled patients with osteoarthritis of the knee or hip for the most part and frequently excluded individuals with other comorbidities. Few studies enrolled individuals from diverse race/ethnicity groups or reported results stratified by other potentially important predictors including age and gender.

The following sections summarize efficacy and safety data with respect to oral, topical, and intra-articular interventions and synthesize recommendations regarding their use from various clinical practice guidelines.

Oral Treatments

Acetaminophen—Acetaminophen is one of the most commonly employed analgesics for the treatment of OA.¹¹ Its mechanism of action remains unclear but is thought to be a weak inhibitor of cyclooxygenase isoenzymes. In a recent meta-analysis of seven randomized controlled trials (RCTs) comparing acetaminophen (up to 4 grams daily) to placebo, acetaminophen was found to be modestly effective in reducing pain; standardized mean difference (SMD) = -0.13 ; 95% CI -0.22 to -0.04 .¹⁴ In 10 RCTs that compared acetaminophen to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen was less effective at reducing pain or improving function.¹⁴ While the overall safety profile of the medication is excellent,¹¹ acetaminophen toxicity remains the leading cause of acute liver failure in the U.S.¹⁵ Unintentional overdose is the leading cause of acetaminophen-induced hepatotoxicity; the vast majority of persons experiencing this outcome report having taken acetaminophen to treat their pain.¹⁵ In addition, a large population-based retrospective cohort study found that concomitant use of NSAIDs and acetaminophen increased risk for hospitalization due to gastrointestinal events when compared with individuals using acetaminophen alone or an NSAID alone.¹⁶ An important limitation of this study, however, was an inability to account for over-the-counter analgesic use. These (and other) data led the Food and Drug Administration (FDA) to recommend that maximum amounts of acetaminophen in prescription acetaminophen combination products be limited to 325 milligrams and implement public awareness campaigns about the problem in an effort to reduce the risk of liver injury.¹⁷

Despite its modest impact on pain, acetaminophen is recommended as first-line therapy for the treatment of mild-to-moderate pain given its low cost and overall safety profile.¹¹

Non-steroidal anti-inflammatory drugs (NSAIDs)—NSAIDs continue to be one of the most commonly prescribed and consumed analgesic agents (as over-the-counter products). Over 111 million NSAID prescriptions are written annually in the U.S.,¹⁸ while approximately 70% of older adults report taking an NSAID at least once a week.¹⁹ A meta-analysis of 27 RCTs examining the efficacy of oral NSAIDs reported an effect size (es) of 0.29, 95% CI 0.22–0.35 for pain reduction.²⁰ While oral NSAIDs are considered more effective pain relievers than acetaminophen, this class of medications has significant limitations in the form of cardiovascular, renal, and gastrointestinal toxicity. Use of selective or non-selective NSAIDs is associated with increased risk for myocardial infarction, stroke and mortality.²¹ It is estimated that over 100,000 hospitalizations occur annually on account of NSAID-induced gastrointestinal and renal toxicity and that approximately 20% of all congestive heart failure admissions can be attributed to NSAID use.^{22–24} In light of these data, the American Geriatric Society's clinical practice guidelines on the pharmacologic management of pain recommends use of oral NSAIDs sparingly and only "with extreme caution."¹¹

Opioids—Opioids are strong pain relievers that are typically initiated only when other analgesic medications (and nonpharmacologic interventions) have been tried and failed. Papaleontiou et al. recently examined the effects of opioid use among older adults. In this meta-analysis of 40 treatment studies, most investigations examined outcomes among older adults with OA of the hip or knee.²⁵ Positive effect sizes were demonstrated for reductions in pain (es = -0.56 , $p < 0.001$) and physical disability (es = -0.43 , $p < 0.001$), but not for improvement in quality of life (es = 0.19, $p = 0.171$).²⁵ Common adverse events included

constipation, nausea, and dizziness, prompting opioid discontinuation in about 25% of cases. Furthermore, Solomon and colleagues used Medicare claims data to examine the safety of selective and nonselective NSAIDs versus opioids for non-malignant pain.²⁶ Subjects receiving selective NSAIDs or opioids were at increased risk for adverse cardiovascular outcomes relative to nonselective NSAID users. NSAID and coxib users had similar fracture risk, while opioid use was associated with significantly increased fracture risk, adverse events requiring hospitalization, and all-cause mortality.²⁶

Opioid use for OA-related pain remains controversial, principally due to concerns about the potential for analgesic misuse/abuse and patient harm.²⁷ Given concerns about an expanding evidence base demonstrating NSAID-related toxicity, one recently published guideline for managing persistent pain recommends that clinicians consider opioid therapy for individuals who fail acetaminophen therapy and continue to experience moderate-to-severe pain or pain-related functional impairment despite non-opioid therapy.¹¹

Glucosamine and Chondroitin—Glucosamine is a major building block of proteoglycans, which is a key component of cartilage, whereas chondroitin is purported to protect cartilage by providing joint lubrication and compressive resistance.^{28–30} Both products require prescriptions in Europe, but are sold as over-the-counter formulations in the U.S. A recent Cochrane Review reported no benefit from glucosamine use (in terms of pain reduction or improvement in function) after analyzing data from the most rigorously conducted randomized controlled trials.²⁸ However, positive effects in the form of pain reduction and improvement in function were found in studies that were not as rigorously conducted and in trials that employed one particular type of glucosamine preparation (Rotta).²⁸ In studies lasting longer than 12 months, there is some evidence that long-term use of glucosamine can reduce joint space loss, but the clinical significance of this finding remains unclear.²⁹ In a recent meta-analysis examining the effects of chondroitin, positive treatment effects were found in small trials with reduced methodologic quality.³⁰ When examining outcomes of three large-scale, well conducted RCTs, beneficial effects were not found. Both glucosamine and chondroitin appear to be safe for use.^{28–30} Because neither supplement is considered to be a medication, production is not regulated in this country so product quality and cost can vary widely.

Topical Treatments

Nonsteroidals—Given the established risks associated with oral NSAIDs,^{21–24} increasing attention has focused on development and testing of topical NSAIDs as a means of mitigating NSAID-related risk. Two topical NSAIDs have been approved for use by the FDA (both are diclofenac preparations), while a number of trials are currently testing other topical NSAID formulations.³¹ In one meta-analysis of 13 RCTs, topical NSAIDs were found to be superior to placebo in relieving osteoarthritis-related pain for up to 2 weeks, but treatment effects did not persist beyond 2 weeks.³² Topical NSAIDs were less effective than oral NSAIDs. Baraf and colleagues conducted a post-hoc analysis using data from 3 RCTs.³³ This study found that topical diclofenac was superior to placebo (i.e., an inert gel preparation) in both younger and older (65 and above) patients with knee osteoarthritis. Relative to placebo, pain scores were reduced, on average, by 1 point (scale range = 20 points), whereas function scores improved, on average, by 3 points (range = 0–68). With respect to safety, topical (vs. oral) preparations appear to be safer overall.^{31–33} However, one systematic review found that approximately 20% of subjects receiving a topical NSAID reported a systemic adverse event.³⁴

Lidocaine—Lidocaine is an FDA approved drug for the treatment of neuropathic pain and is thought to provide analgesic effects by blocking sodium channels in sensory nerves.

Several small studies have been conducted in individuals with OA.^{35–37} In one post-hoc analysis of data from an RCT comparing lidocaine patch 5% versus celecoxib for the treatment of OA-related knee pain, both medications were equally effective in reducing pain (approximate 30% reduction from baseline levels) and improving physical function (approximate 35% improvement from baseline levels). The patch appears to be well tolerated.³⁵ However, cost issues may limit its use.

Capsaicin—Capsaicin is the active component of chili peppers. Mason et al. identified 3 RCTs that examined treatment effects in individuals with musculoskeletal pain and reported that 38% of participants receiving active treatment reported an improvement of 50% or greater in terms of pain relief relative to 25% of participants receiving placebo.³⁸ In a recent RCT, Kosuwon et al.³⁹ found that 0.0125% capsaicin gel was effective (relative to placebo) in treating mild-to-moderate pain associated with knee OA. Roughly half of all patients reported experiencing local adverse events in the form of burning, stinging and erythema, but discontinuation rates were low.³⁹

Intra-Articular Treatments

Corticosteroids—Steroid joint injection has been a commonly practiced intervention for the past five decades.⁴⁰ In a Cochrane meta-analysis, intra-articular injection of steroids (relative to placebo) was found to be effective for reducing pain measured on a 0–100 mm scale, with a weighted mean difference of –21.91 points (95% CI –29.93 to –13.89) at 1 to 2 weeks. This effect did not persist at the 4 week follow-up.⁴⁰ No improvements in self-reported physical function was observed. When compared with hyaluronan/hylan (HA) products, steroids were found to produce similar short-term results (out to 4 weeks) but HA products were superior in terms of pain relief and improvement in function beyond 4 weeks.⁴⁰ Most steroid injection related adverse events were rated as mild or moderate. Overall, steroid injections were deemed safe but provide only short-term benefits.⁴⁰ The question of how frequently patients can receive steroid joint injections remains unknown.

Hyaluronan/Hylan (HA) derivatives—Hyaluronan and Hylan (also referred to as viscosupplements) are thought to work by improving the elastoviscous properties of joint synovial fluid, which progressively diminish over time in the setting of OA. A Cochrane review⁴¹ synthesized results from 63 trials examining outcomes in persons with knee OA. This meta-analysis found that when compared to placebo, viscosupplementation provides moderate-to-large treatment effects for pain and function, with maximal benefit detected between 5 and 13 weeks after joint injection.⁴¹ No major safety issues were identified.⁴¹

DISCUSSION

Among adults with OA, available evidence indicates that most current pharmacologic agents provide mild-to-moderate pain relief. Modest analgesic effects have been observed for acetaminophen, while the largest effects have been reported for opioids and viscosupplementation. Topical agents and acetaminophen have superior safety profiles when compared with other analgesic interventions, including oral NSAIDs and opioids.

This review highlights several knowledge gaps regarding the pharmacologic management of OA. First, the long-term safety and effectiveness of commonly prescribed analgesic agents remain to be determined among adults with OA-related pain. Second, safety and efficacy data for minority populations as well as older populations (those 75 years of age and older) is particularly lacking. There is an urgent need to address these gaps, given established disparities in the management of OA-related pain as a function of race/ethnicity⁴² and advancing age.²⁵ Finally, the uncertainty regarding long-term benefits and safety of existing

pharmacologic interventions for OA also provides strong support for efforts to develop and test disease modifying OA drugs (DMOADs). Initiatives are underway examining various therapies that may alter disease progression, including growth factors, cytokine manipulation, and gene therapy.^{43,44}

This study has several implications for nursing practice. Because analgesic medications can lead to adverse events if taken in large quantities (e.g., acetaminophen) or even in small quantities (e.g., opioids), it is imperative that careful analgesic medication histories, side effect assessments, and analgesic education be part of routine practice. Nurses can improve the quality of care delivered to patients with OA and other arthritis-related disorders by 1) taking comprehensive analgesic medication histories to include inquiring about all over-the-counter (OTC) analgesic use and the specific ways in which both prescribed and OTC analgesics are consumed; 2) assessing for side effects, particularly among patients who have been newly started on an analgesic medication (e.g., constipation in patients started on an opioid); 3) eliciting patients' attitudes, beliefs, and barriers (e.g., cost, stigma, fear of addiction) regarding analgesic medication use; because certain attitudes, beliefs and barriers contribute to undertreatment of pain;²⁷ and finally 4) educating patients with OA (and caregivers when appropriate) about the risks and benefits of specific analgesic agents and ways in which medication safety can be improved. Medication safety training interventions are available,^{45–47} can be feasibly employed in nursing practice, and could help to improve the quality of care and outcomes of care for millions of individuals with OA.

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