OSTEOARTHRITIS ACTION ALLIANCE

Osteoarthritis

The Challenges are Opportunities for the Pharmacist

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Learn more about the symptoms of osteoarthritis at **StandUp2OA.org**

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Program Preview

Osteoarthritis (OA) is the most common form of arthritis; however, many people choose to self-medicate with over-the-counter (OTC) analgesics, for example, without obtaining any formal medical advice or diagnosis. Pain and disability caused by OA is well-described and often the focus of educational programming, but it is also important to consider other comorbidities that can be affected by the presence and severity of OA. Over two-thirds of patients with OA have at least one other chronic health condition (e.g., hypertension, depression, COPD, diabetes, obesity) complicating not only the treatment choices for OA, but also the suggested treatment recommendations for the comorbidities. Given the extensive impact of OA on physical function, healthcare costs, loss of income, and overall health, combined with its association with other comorbidities and the fact that disease-modifying therapies have not been identified, many of the challenges identified in OA can be opportunities for the pharmacist! The pharmacist, as the most accessible healthcare provider, is in an ideal position to screen patients for OA, serve as an educator and coach regarding prevention strategies, counsel patients on the safe and effective treatment options available, and triage when necessary.

The information conveyed in this continuing education program as well as the accompanying toolkit will give the pharmacist ideas and guidance on how to assume a more active role in the detection, prevention, and treatment of OA.

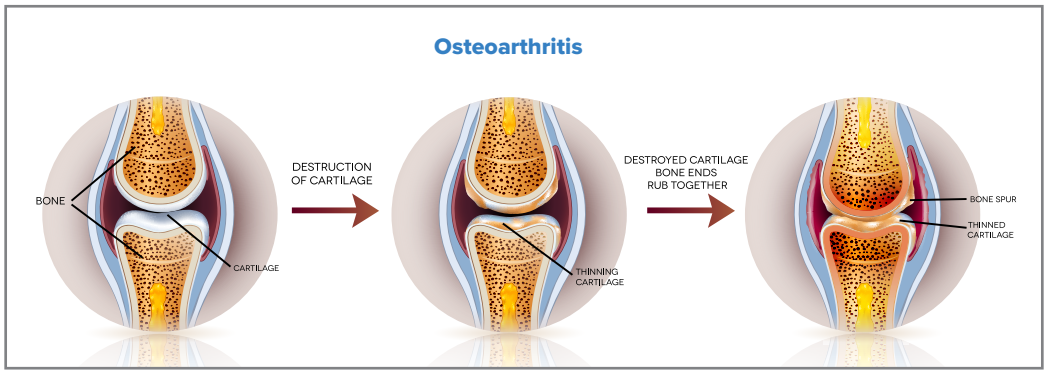
Epidemiology

Arthritis is a serious health crisis as it affects more than one in five adults.[1] Over 50 million adults in the U.S. have been formally diagnosed with arthritis; however, due to the frequent subtle onset of some forms of arthritis and the ability to self-medicate preventing a formal diagnosis, experts believe this number could approach 100 million.[1,2] In 2013, there were almost 100 million outpatient visits and nearly 6.5 million hospitalizations due to arthritis that resulted in over $300 million in direct medical costs and lost earnings.[2,3]

While there are estimated to be over 100 types of arthritis, OA is the most common form affecting over 30 million U.S. adults and accounting for one out of every four arthritis-related healthcare visits. Despite the significant individual and global impact of OA, treatment continues to be symptom-modifying at best. According to the Consumer Healthcare Products Association, U.S. consumers visit their physician three times a year but, in the same year, make almost nine times more trips to the store or pharmacy to purchase OTC products.[4] In fact, in 2017 nearly $900 million was spent on OTC external analgesics and $4.1 billion dollars spent on OTC internal analgesics. This places the pharmacist in a key position to assist patients with OA who are seeking help, including pain relief. In addition, the pharmacist is well-positioned to identify and screen patients at risk for OA, provide treatment recommendations for drug and non-drug therapies (e.g., community-based programs or weight management), advise prescribers and patients on the safe selection of all OA drug therapies, and counsel patients on the safe and proper use of the chosen drug therapy.

Pathogenesis & the Paradigm Shift

Much has been learned about the pathogenesis of OA in the last two decades; however, this research has not produced effective treatment options for preventing the onset of OA or for reversing the process once initiated. Pain in OA is likely the result of a complex interplay of factors including mechanical, inflammatory, and centralized pain pathways.[5] Osteoarthritis is frequently described in terms of its severity. In mild OA, patients have low levels of pain with well-preserved joint function and quality of life (QOL). In cases of moderate OA, patients have more persistent pain which begins to impair functionality, participation in activities, and QOL. In severe OA, patients have persistent pain which significantly impairs functionality, restricts participation in activities and significantly impairs QOL.



Osteoarthritis is a disorder within a joint that affects all joint tissues, including cartilage, synovium, extracellular matrix, and subchondral bone. Historically, OA was considered a non-inflammatory arthritis caused by "wear and tear" on the affected joint(s); however, at a molecular level, proinflammatory factors are now appreciable contributors to the process of joint degradation. Recent research has demonstrated that certain metabolic disorders could have a direct impact on bone formation and synovial inflammation.[6]

Cartilage is a frictionless, aneural, and avascular substance that covers the end of bones in a joint. Cartilage is only 2-5 mm thick and may be compressed as much as 40% when bearing a load.[5] Water is the primary component of cartilage, but it also contains collagen, proteoglycan aggregates (aggrecans), proteins, and chondrocytes. Cartilage is metabolically active and undergoes continual internal remodeling. Synovial fluid, found in the joint capsule, is a viscous liquid that aids in the lubrication and movement of a joint. Synovial fluid allows key nutrients to reach the cartilage while blocking harmful substances. Along with muscles and subchondral bone, synovial fluid is a key component to joint stress reduction or load absorption.

Age-related changes within a joint can increase the risk of developing OA due to the joint's susceptibility to injury and decreased capacity for repair.

Hyaluronic acid is a key component of both synovial fluid and cartilage. Hyaluronic acid facilitates the viscosity of the synovial fluid, acts as a shock absorber under sudden joint loading, and filters potentially damaging cells and molecules.[7]

Chondrocytes are cells found in cartilage and control the remodeling and affect the production of collagen and proteoglycans. When an injury is sustained (e.g., trauma or repeated maximal loading), proteoglycans attract water and expand. Chondrocytes, although normally dormant, begin to proliferate due to the loss of matrix. When cartilage degeneration exceeds the rate of chondrocyte remodeling, OA occurs. If OA progresses, proinflammatory mediators (e.g., cytokines and chemokines) are naturally produced as a response to joint injury which can lead to extensive matrix degradation and loss. When collagen is degraded and lost, the cartilage has limited ability to repair and chondrocytes die.

Within the joint, soft tissue damage leads to thickening of the joint capsule which can result in visible, but often minor joint swelling. Bone sclerosis and osteophyte (bone spur) formation can also result when OA is more moderate to severe.

Age-related changes within a joint can increase the risk of developing OA due to the joint's susceptibility to injury and decreased capacity for repair. Cellular and animal research are also supporting the theory that cellular senescence and mitochondrial dysfunction due to advancing age are contributors to the development of OA as well.[8]

Classification and Risk Factors

Osteoarthritis can be classified as either primary or secondary. Primary OA is idiopathic, while secondary OA is associated with a known cause such as metabolic or endocrine disorders (e.g., Paget's disease, acromegaly), joint injury or trauma, or inflammatory arthritis. For most patients, OA is linked to multiple risk factors and can be grouped into modifiable and nonmodifiable.

Risk Factors for Osteoarthritis

Non-Modifiable	Potentially Modifiable
Age	Weight
Sex	Occupation
Race	Certain sports
Gender	Future injury
History of joint trauma	Malalignment

Age is by far the most well-known risk factor for OA, but advancing age does not automatically lead to the development of OA. Furthermore, OA is occurring in younger adults at increasing rates. In 1997, the incidence of OA in people between the ages of 25 and 34 years was reported to be less than 1%, and in those over the age of 55 years, the rate was 80%.[9] In 2018, of the proportion of US adults with self-reported OA, 11.7% are aged 18-44y, 45.7% are aged 45-64y, and 42.6% are aged 65y and older.[3] It is important to note that the prevalence and incidence of OA vary depending on the definition used in the analysis, the specific joints being evaluated, and whether the diagnosis is self-made or medically confirmed.

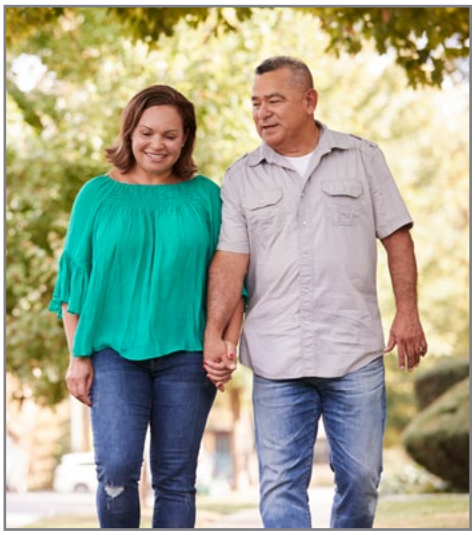
Sex and ethnicity are also risk factors; however, the frequency and severity of OA differ among the types of OA being considered. Female sex is associated with an increased risk of OA especially OA of the hand, foot, and knee. Older women are more than twice as likely to develop OA of the hand as their male counterparts.[2] The Women's Health Initiative revealed that older African-American, Native American, and non-white Hispanic women are more likely to develop OA than white women.[10, 11] African-Americans are more likely to develop symptomatic knee and hip OA compared to other races.[12] Hip OA is 33% more prevalent in older African-American men than white men.[2]

Previous traumatic injury to cartilage, ligaments, and/or meniscus also places someone at higher risk of developing OA in the affected joint(s). Someone with a history of a previously torn anterior cruciate ligament (ACL) or meniscus is 2.5 times more likely to develop knee OA and four times more likely to undergo an eventual total knee arthroplasty.[5, 12, 13] For example, among young athletes who sustain an ACL injury, 10-90% will develop OA within 10-20 years. Furthermore, surgical reconstruction and rehabilitation do not mitigate the risk of developing OA following ACL injury.[14]

Obesity is regarded as the strongest modifiable risk factor for the development of OA of the knee; moreover, it has been associated with higher rates of disability.[15, 16] Men and women who are obese have a 2.8-fold and 4.4-fold increase in developing knee OA, respectively. For each kilogram (2.2 pounds) of excess weight, the risk of developing OA increases by approximately 10%.[15] Someone with ten pounds of additional weight increases the force exerted on their knee by up to 60 pounds with each step.[17] Excess body weight is also associated with an increased risk of OA of the hand giving credence that certain metabolic changes (not just excessive weight-bearing activities) contribute to the development of OA.

Genetic influences on the risk of developing OA have been known for decades; Stecher demonstrated a strong correlation of hand OA in female twins in the early 1940's.[18] Additionally, multiple gene interactions within collagen, cartilage, and bone may also contribute to the development of OA.

Certain occupations (e.g., construction, healthcare, and farming) and high-impact, professional sports (e.g., baseball, soccer, and football) involving prolonged standing, squatting, lifting, kneeling, and repetitive motion, where the result is the application of excessive mechanical stress on a joint, raises the risk of OA. Research has clearly demonstrated the health benefits of light to moderate physical activity in reducing OA-related joint pain; however, the extent to which participation in non-contact recreational sports may increase the risk of OA has not been fully elucidated.[19] Moderate vigorous physical activity was not significantly associated with a risk of radiographic knee OA in subjects ranging in age from 45 to 83 years.[20]



Diagnosis and Clinical Presentation

Osteoarthritis is diagnosed based on patient history, physical examination, and radiographic evaluation. Based on presenting symptomology, additional scans and/or laboratory testing may be necessary. The American College of Rheumatology published classification criteria for OA of the hip, knee, and hand to assist in the identification of patients with symptomatic OA.[21-23] The joints most often affected by OA include the hands, hips, knees, lower back, and neck.

Symptoms vary based on the affected joint(s) and the severity of the condition. Typically, patients with mild OA experience localized, insidious pain in a joint (or sometimes multiple joints) that is relieved by rest, but aggravated by activity. Joint stiffness and limited range of motion are also frequent complaints. Crepitus, a crackling or grinding sound within a joint, may be audible. The affected joint distribution in mild cases of OA may be either unilateral or bilateral. On physical exam, the affected joint may appear normal; however, tenderness, pain or mild swelling may be present. Joints with OA are not usually appreciably warm, red, or largely swollen. Pain, however, is a frequent complaint.[24, 25] Although OA is not necessarily progressive, in more moderate to severe forms, the intensity of the pain can vary especially at night when activity has been high throughout the day. Muscle wasting and joint deformity may also be present.

When a patient presents with complaints of "joint pain," certain key elements should be evaluated to best direct care.

The below Table illustrates distinguishing characteristics between OA and other common forms of arthritis such as rheumatoid arthritis (RA) and gout. If a patient presents with symptoms characteristic of inflammatory arthritis, prompt referral to their primary care provider is recommended.

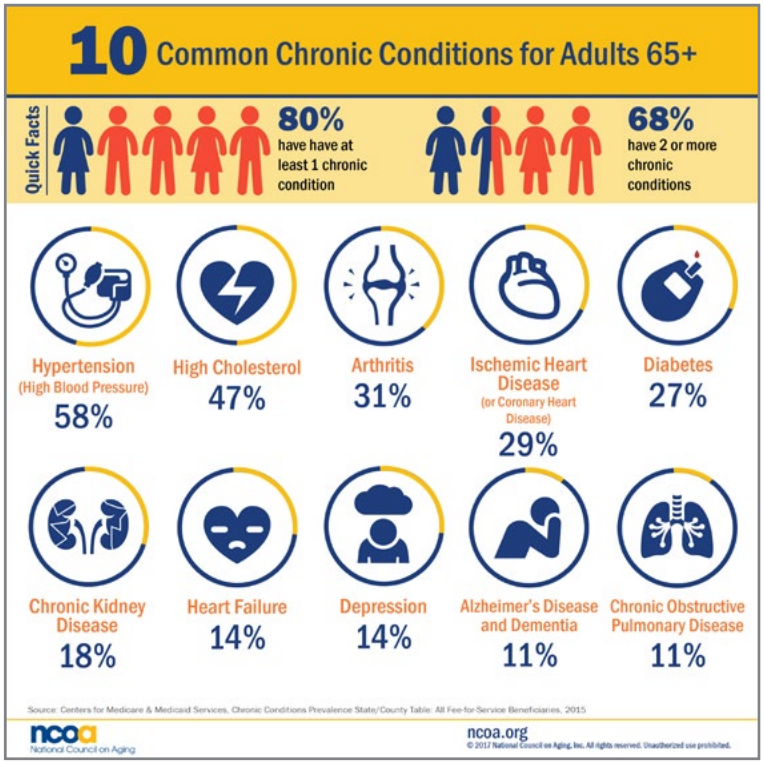
Comparison of Osteoarthritis, Rheumatoid Arthritis, and Acute Gout

Characteristic	Osteoarthritis	Rheumatoid Arthritis	Acute Gout
Visible signs of inflammation	None or very mild	Often present	Yes
Onset of Pain	Gradual (months to years)	Gradual (weeks to months)	Often sudden (frequently overnight)
Inactivity stiffness	< 30 minutes	> 30 minutes	Unpredictable
Systemic Symptoms	No	Yes	Not routinely
Initial number of affected joints	Often 1-2	2+ (bilateral, symmetrical)	1 (often the great toe)
Common joint involvement	Distal hands, basal thumb, knees, hip, spine	Feet, ankles, proximal hands, wrists, ankles, feet	Hands, wrists, elbows, knee, ankle, great toe

Comorbidities in Osteoarthritis

Recent evidence has demonstrated that a number of comorbidities often coexist in patients with OA. In 2015, Birtwhistle et al. demonstrated those with OA also had several concurrent conditions that included: hypertension (prevalence ratio [PR] 1.17, 95% confidence interval [CI] 1.15-1.18), depression (PR 1.26, 95% CI 1.22-1.3), chronic obstructive pulmonary disease (COPD) (PR 1.16, 95% CI 1.11-1.21) and epilepsy (PR 1.27, 95% CI 1.13-1.43).[26] By evaluating the National Health and Nutrition Examination Survey III data, Puenpatom et al. identified that metabolic syndrome was more prevalent in those with OA than without.[27] In fact, the metabolic pathological changes that occur in a joint with OA have been directly linked to insulin resistance, low bone density, alterations in collagen production and the impact of LDL oxidation on bone formation and development of low-grade synovial inflammation.[28] Results from a longitudinal cohort study showed that long-standing, type 2 diabetes is a predictor of severe OA (knee and hip, predominantly) independent of age and body mass index; moreover, these patients have a 2-fold increase in the rate of joint arthroplasty.[29] The rate of cardiovascular disease and mortality is higher in those with OA.[30]

According to the National Council on Aging, 80% of senior adults (> 65 years) have at least one chronic health condition, and 70% have two or more chronic conditions.[2, 31] Awareness of these possible concurrent conditions is vital when considering the best approach to the treatment of OA. Additionally, these conditions can complicate medication selection, especially with regard to analgesia, given the vulnerability of the aging population to adverse drug reactions and medication side effects. For example, a nonsteroidal anti-inflammatory drug (NSAID) may be relatively contraindicated in a patient with uncontrolled hypertension, heart failure, and/or compromised renal function. Conversely, the patient's ability to participate in exercise therapy (e.g., cardiac rehabilitation, regular physical activity) as a treatment option for cardiovascular disease, diabetes, or obesity may be limited in the presence of OA.



The Role of the Pharmacist in Managing OA

The American Pharmacists Association (APhA) Foundation convened an expert panel on OA and chronic pain to direct pharmacists' patient care services in an effort to improve people's health. Six key themes were identified by the panel of experts as a means of making a positive "IMPACT" on healthcare changes and the lives of those with OA.[32]

1. **I**mprove the climate surrounding pain management.
2. **M**aximize access to care.
3. **P**rovide support for caregivers.
4. **A**dvocate for sustainable system changes.
5. **C**ollaborate and coordinate team-based care.
6. **T**ailor the care plan to meet the needs of the individual.

IMPACT: APhA's Key Themes for Osteoarthritis & Chronic Pain

The pharmacist can **I**mprove the climate surrounding pain management, **M**aximize access to care, **P**rovide support for caregivers, **A**dvocate for sustainable system changes, **C**ollaborate and coordinate team-based care, and **T**ailor the care plan to meet the needs of the individual. The pharmacist is uniquely positioned, as the most accessible healthcare provider, to implement these themes and elevate patient care.

The targets of OA therapy are SIMPLE - manage **S**ymptoms (e.g., reduce pain and stiffness), **I**ncrease **M**obility, **P**revent disability, and maintain or improve quality of **L**if**e**. Treatment options involve both non-pharmacological and pharmacological agents, but the foundations to therapy remain targeting risk factors and increasing mobility.

Treatment Options for Osteoarthritis

Nonpharmacological	Pharmacological
Education	Acetaminophen
Physical activity	Non-steroidal anti-inflammatory drugs (NSAIDs)
Weight loss	Capsaicin
Physical therapy	Rubefacients
Occupational therapy	Duloxetine
Assistive devices (e.g., walking aids, braces)	Intra-articular corticosteroids
Thermal modalities	Intra-articular hyaluronic acid
Glucosamine / Chondroitin	Tramadol
Tai Chi	Opioids
Acupuncture	
Surgery	

The most effective means for managing the symptoms and preventing or delaying the progression of OA is through the use of nonpharmacological therapies (i.e., physical activity, weight loss).[33] All treatment guidelines strongly support the use of nonpharmacological modalities as initial therapy, but also as adjuvant treatment for OA.[33-35]

Ascertaining information, such as the number and specific joint(s) involved, degree of functional discomfort and level of impairment, weight or body mass index (BMI), and overall health status will facilitate a patient-specific treatment plan. It is also important to gauge the patient's motivation and to set small, realistic goals to enhance treatment success.

Educating patients about OA is key to optimizing management. Dispelling misconceptions (e.g., "nothing helps," "progression is inevitable," "I'm wheelchair bound"), especially regarding increasing physical activity and achieving or maintaining healthy weight, are vital to the success of symptom management. Taking the time to share effective, evidence-based treatments, including community-based programs while promoting the avoidance of advertised "cures" may be one of the best avenues to successful OA management.

Selected Resources for Osteoarthritis

CDC Recommended and Promising Programs for Arthritis	
Active Living Every Day	Visit the site
Arthritis Foundation Aquatics Program	Visit the site – English Visit the site – Spanish
Arthritis Foundation Exercise Program	Visit the site – English Visit the site – Spanish
EnhanceFitness	Visit the site
Fit and Strong	Visit the site
National Council on Aging – Engaging Veteransin Evidence-Based Programs	Visit the site
National Physical Activity Plan	Visit the site
Office of Disease Prevention & Health Promotion	Visit the site
Osteoarthritis Action Alliance	Visit the site
Self-Management Resource Center (Arthritis Self-Management Program)	Visit the site – English or Here Visit the site – Spanish
Physical Activity for Arthritis	Visit the site – English Visit the site – Spanish
Walk With Ease	Visit the site – English Visit the site – Spanish
Additional Resources for Arthritis	
Arthritis Resource Finder	Visit the site
Falls Prevention Programs	Visit the site
Tai Chi for Arthritis	Visit the site

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Asking the patient to provide their treatment goal(s) will facilitate the opportunity for the pharmacist to engage the patient in establishing a realistic treatment plan. While assessing long-term goals is important, the pharmacist is encouraged to help the patient aim for smaller, more short-term goals. The Arthritis Foundation promotes the establishment of SMART goals – those that are **S**pecific, **M**easurable, **A**ttainable, **R**elevant, and **T**ime-bound.

Exercise is one of the best treatments for OA because it can reduce pain and increase joint function, but it should be individualized. In a meta-analysis by Wallis et al, patients with severe knee OA who were waiting for a joint arthroplasty had less pain after participating in pre-operative exercise.[36] If someone hesitates at the notion of "exercise," then a suggestion to "just move" may seem more easily accomplished. Extinguishing any fear that exercise or movement will further worsen pain or increase joint damage and emphasizing that it can help reduce pain and protect the joint should be discussed. In fact, limiting the amount of "inactivity" may also help with pain reduction. Simple suggestions for increasing movement include: walking more within the home and around the outside of the house, walking to the mailbox, and choosing a parking spot away from the storefront door. Encouraging progress beyond these basic movements can be beneficial to the patient's success. In general, low-impact aerobic exercise is recommended. Water aerobics or pool therapy, for example, may be an excellent way to improve muscle strength while minimizing joint loading. Many local gyms or activity centers offer programs tailored for those with arthritis. Hand exercises, such as range of motion and stretching, may help improve hand pain related to OA.

Tai Chi is a form of exercise from ancient China that utilizes slow movements to enhance muscle strength, improve flexibility and balance. The benefits of Tai Chi in patients with OA have received mixed results in clinical research; however, some patients did report a reduction in pain and/or an improvement in function.[37] Tai Chi has also been shown to reduce the risk for falls in senior adults.[38] The Arthritis Foundation's Tai Chi Program has demonstrated improvements in pain, fatigue, stiffness, and helplessness that were sustained one-year following program participation.[39] Tai Chi can be performed individually or in a group setting.

For some patients, referral to physical therapy or occupational therapy should be considered. These disciplines can provide manual and/or exercise therapy to help improve activity, balance, and gait. These specialists should also be consulted when employing the safe and effective use of an assistive device (e.g., cane, walker). Finally, older adults or those whose balance is compromised due to arthritis may benefit from community-based falls prevention programs to improve agility and strength as a means of reducing injury risk.[40]

In the presence of excess weight, the biomechanical load on weight-bearing joints is significantly increased; thereby, disrupting joint integrity and increasing pain. A 10-pound weight loss in someone overweight can reduce the risk of knee OA by 50%.[15] In the IDEA trial (Intensive Diet and Exercise for Arthritis), subjects with knee OA who were overweight and who achieved a modest weight loss (10% of body weight) through diet and exercise, achieved a 50% reduction in pain scores.[41] Weight loss counseling is a key component to successful weight loss in patients. The CDC reports that adults with arthritis who are overweight or obese and who receive provider counseling about weight loss are four times more likely to attempt to lose weight; yet, fewer than half of those adults are actually receiving such counseling.[42] Pharmacists can engage patients in weight loss counseling with successful strategies such as motivational interviewing to better advise and assist the patient, guiding the patient to programmatic resources, and simply educating patients that even small amounts of weight loss can significantly reduce joint load and pain, but is also achievable.[43]

In OA of the knee, the use of custom-made foot orthotics may help reduce the mechanical load placed on a joint. By redistributing weight, the stress placed on the joint can be reduced, thereby, reducing pain. The application of thermal modalities (e.g., ice or heat) to the affected joint(s) may also be employed. Although the effectiveness of this modality is not consistently demonstrated in clinical research, it has been shown to provide temporary relief in some patients – especially before exercise. Acupuncture uses the insertion of slender metal needles into the skin at targeted points in the body with the aim of increasing energy flow. The insertion of the needles is thought to trigger the release of enkephalins, endorphins, and possibly cortisol which are thought to be the mechanism by which some patients experience a reduction in OA pain. The effectiveness of acupuncture in clinical research is not consistently demonstrated, but it has provided pain relief to some patients.[44]

For patients with more severe knee or hip OA, surgery (e.g., joint replacement or arthroplasty) may be the only viable option when non-operative interventions have failed. However, up to 20% of patients who undergo total joint replacement surgery report significant long-term pain despite having surgery.[45] Patients identified at higher risk of persistent pain despite having had surgery are those who have multiple joints affected with OA, significant pain preoperatively, high body mass index, co-morbidities and depression.[46]

In the presence of excess weight, the biomechanical load on weight-bearing joints is significantly increased; thereby, disrupting joint integrity and increasing pain.

When patients are scheduled for surgery, the pharmacist should instruct the patient to discuss what, if any, medications should be temporarily discontinued and the appropriate timeline for such. Post-surgery, the pharmacist should work with prescribers to ensure a smooth transition of care. This includes assuring all medications are resumed (or discontinued) appropriately, providing medication counseling on prevention (or treatment) of thromboembolic disorders, pain management, and encouraging physical activity throughout the recovery phase.

The pharmacological options for OA target the treatment of pain since no disease-modifying therapies have been developed to date.

In light of the paucity of effective treatments for the management of OA and the enormous direct-to-consumer advertising for "all natural" treatments reporting to be "safe and effective" in patients with OA, the use of complementary alternative medicines (CAM) is a billion-dollar industry. While most herbal supplements have few side effects in the majority of users, the science behind their claims is often unsubstantiated and the placebo effect cannot be discounted. Based on either inconsistent data or lack of scientific evidence, neither the American College of Rheumatology nor the American Association of Orthopedic Physicians recommends the use of herbal supplements for the treatment or prevention of OA. This includes, but is not limited to: glucosamine, chondroitin, turmeric, ginger, copper, and omega-3. Patients taking supplements with reported pain relief and no adverse effects, however, are usually not encouraged to discontinue the product.[47]

The pharmacological options for OA target the treatment of pain since no disease-modifying therapies have been developed to date. Simple OTC analgesics (e.g., acetaminophen, aspirin) as well as non-steroidal anti-inflammatory drugs (NSAIDs), narcotics, and intra-articular injections are the mainstay of OA analgesia despite their unwanted side effects and/or minimal efficacy. As research promotes the rise of evidence-based medicine and the re-evaluation of clinical treatment guidelines, it is important for the pharmacist to remember that OA treatment should be individualized, and risks and benefits of drug therapy carefully weighed.

Until the most recent treatment guidelines for OA were published by the ACR in 2012, acetaminophen (APAP) was the drug of choice (over NSAIDs) for the initial management of mild OA pain. As an agent with no anti-inflammatory activity, APAP can provide adequate pain relief in some patients without the many untoward effects of NSAIDs providing there is little to no inflammation present in the joint. The ACR conditionally recommends acetaminophen for both hip and knee OA based on clinical research.[33] Given the overall safety of APAP, it warrants consideration for the initial trial of mild OA pain unless there is a contraindication (e.g., reported allergy). While the suggested maximum dose of APAP is < 3 grams per day, the risk of hepatotoxicity is very low at doses of less than 4 grams per day. The biggest caution with the use of APAP is the risk of potential overdose when consumers do not recognize the APAP content of many OTC and prescription-based products. Pharmacists should always counsel patients on the acetaminophen content of products and advise a total dose from all sources of less than 3 to 4 grams per day.

NSAIDs are recommended for hand, knee, and hip OA especially in the presence of appreciable inflammation.[33] When taken only as needed, these drugs provide more analgesia than anti-inflammatory effects. Lower (OTC) doses of ibuprofen (< 1200 mg/day) are usually not enough to provide good anti-inflammatory activity. There is no superiority data to recommend one NSAID over another and when one NSAID does not appear to work, consideration for the use of a different NSAID should be made when inflammation is noted.

NSAIDs pose a higher risk of gastrointestinal (GI) (e.g., ulceration and bleeding), renal (e.g., acute renal failure), and cardiovascular (e.g., hypertension, heart failure, stroke, myocardial infarction) side effects than acetaminophen and caution should be used when recommending and dispensing these agents to patients. The FDA has issued a black box warning on all NSAIDs for these side effects. Senior patients are most vulnerable to the adverse effects of NSAIDs; furthermore, seniors may also experience sedation, confusion, and/or falls when taking NSAIDs. In addition to advancing age, risk factors for NSAID-induced GI toxicity include: history of a GI bleed or peptic ulcer disease, chronic alcohol use, high-dose or multiple NSAID use, and concomitant corticosteroid therapy.[5] The pharmacist should consider the risk factors for GI toxicity and consider recommending GI prophylaxis when indicated. Selective COX-2 inhibitors (e.g., celecoxib) are associated with fewer GI and bleeding side effects making them a better consideration option in some patients. Risk factors for NSAID-induced renal toxicity include: advancing age, pre-existing renal disease, hypertension, diabetes, heart failure, cirrhosis, and extra-cellular volume depletion.[5]

> *NSAIDs should be used at the lowest effective dose for the shortest time possible in an effort to minimize their side effects.*

NSAIDs pose the potential for more drug interactions than acetaminophen. NSAIDs should be avoided or used with extreme caution when medications that increase the risk for bleeding (e.g., aspirin, warfarin, low-molecular weight heparin, anticoagulants, and glucocorticoids) are used concomitantly. Concurrent use of a diuretic, angiotensin converting enzyme (ACE)-inhibitor, angiotensin receptor blockers (ARB), or direct renin inhibitor (aliskiren) should also be carefully evaluated since concurrent use can significantly increase the risk of acute renal failure. Considerations for the pharmacist when recommending or dispensing oral NSAIDs for OA are noted in the Table below

Pharmacist Checklist for Recommending Oral NSAIDs for OA

- ☐ Non-pharmacological therapies (e.g., weight loss, exercise, and education) have been implemented, but pain persists
- ☐ Patient has failed an adequate trial of scheduled acetaminophen
- ☐ Allergies have been reviewed and verified
- ☐ Patient has been assessed for their risk of GI, renal, and CV side effects (and others as indicated)
- ☐ Potential drug interactions have been evaluated
- ☐ Patient has been counseled on proper NSAID use
- ☐ Gastrointestinal prophylaxis has been considered

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Topical NSAIDs (e.g., diclofenac solution or 1% gel) are FDA-approved for the treatment of OA of the hand, hip, and knee. While they carry the same black box warning as the oral NSAIDs, given their minimal systemic absorption, they appear to be better tolerated in some patients and have fewer drug interactions. The ACR supports topical NSAID use in OA of the hand and knee, but not the hip.[33]

Topical capsaicin has demonstrated efficacy for the treatment of OA-associated pain of the hand, hip, shoulder and knee, and appears to have a relatively safe side effect profile.[48] As an extract of hot chili pepper, capsaicin inhibits substance P, a mediator for pain transmission in the central nervous system (CNS). With regular, prolonged use (four times a day for 2-3 weeks), patients reported mild to moderate pain relief – especially of the hands and knee.[49] To help improve adherence, twice-daily application may be attempted while still achieving pain relief.[50] A burning sensation is the most common side effect and patients should be cautioned to avoid contact with open skin and mucous membranes.

Trolamine salicylate, a rubefacient, is a non-prescription counterirritant that works primarily by increasing blood flow to the application site. When applied, capillaries become dilated causing a sensation of warmth and sensory nerve endings become disrupted. The evidence for the use of trolamine salicylate is minimal; however, the ACR supports its use in the treatment of hand OA.[33]

Duloxetine is a relative newcomer to the OA treatment armamentarium. The reuptake of the neurotransmitters serotonin (5-HT) and norepinephrine (NE) to which duloxetine selectively inhibits, plays a role in the attenuation of pain signals within the CNS.[51] The brain not only receives and interprets pain signals, it has the capacity to modulate those signals. Duloxetine as a centrally-acting analgesic is FDA-approved for OA of the knee. It has demonstrated a greater reduction in pain when compared to placebo.[51, 52] Although it is generally well-tolerated, frequently reported adverse effects include nausea, constipation, fatigue, diarrhea, and somnolence.[53] Duloxetine is extensively metabolized by CYP1A2 and CYP2D6; therefore, inhibitors of these enzymes (e.g., ciprofloxacin, fluoxetine, bupropion) and substrates for CYP2D6 (e.g., tramadol, codeine, tamoxifen) may interact with duloxetine.[53] Additionally, concurrent use with other serotonergic agents (e.g., tramadol, triptans, antidepressants, cyclobenzaprine, methadone, St. John's Wort, and monoamine oxidase inhibitors (MAOIs)) and medications that could affect platelet function or bleeding risk should be avoided or used with extreme caution.[53] Research has indicated that it may take four weeks before any significant OA pain relief with duloxetine may be seen; therefore, it is important for the pharmacist to include this fact in their patient counseling.[51] The most recent published treatment guidelines from the ACR only conditionally recommend duloxetine in OA of the knee in patients > 75 years of age; otherwise, they provide no recommendations for its use.[33]

Intraarticular injections are used primarily as alternative therapies to acetaminophen and NSAIDs for OA and their efficacy has been associated with a placebo effect.[54] Intraarticular corticosteroids are conditionally recommended by the ACR for the initial treatment of OA; however, due to their potential systemic and local adverse effects combined with their short duration of action (4-6 weeks) and lack of consistent efficacy, they are most often used as second line agents or when local inflammation within a particular joint is appreciated. Published treatment guidelines for OA do not currently support the use of intraarticular hyaluronic acid derivatives, or viscosupplementation, due to inconsistent results and variable response.[55]

Tramadol and opioid narcotics should be reserved for patients who fail or who are not candidates for first-line therapies. When used, tramadol and opioids are frequently "add-on" therapy to acetaminophen or NSAIDs. Tramadol has an affinity for the mu-opioid receptor, but also inhibits norepinephrine and serotonin. This unique mechanism lends to its efficacy as an analgesic, but also gives rise to the potential for drug interactions with other serotonergic medications; similar to the drug interactions with duloxetine). Tramadol and opioids are frequently associated with nausea, vomiting, constipation, sedation, and respiratory depression. When used in older patients, falls and altered mental status may also occur. It is important to note that tramadol can lower seizure threshold and should be used cautiously in patients with a history of epilepsy or other seizure disorder, or in anyone prescribed other medications that can lower seizure threshold (e.g., bupropion, antipsychotics). Despite the potential to provide strong analgesia, many patients report only modest improvements in pain with tramadol and opiates and the effects are usually short-term resulting in the need for multiple daily dosing.

Despite the availability of many potential drug treatment options for OA, evidence supporting superior efficacy and/or sustained relief is lacking; furthermore, untoward side effects can be a real detriment. These challenges, however, can become opportunities for the pharmacist. Whether it is screening for OA, making recommendations on treatment considerations, or counseling patients on the use of available treatment options, the pharmacist is strategically placed to engage patients and serve as a vital resource.

Clinical research has demonstrated the positive roles a pharmacist can play in caring for patients with OA.[55-57] Dr. Jason Kielly and colleagues examined the role the pharmacist can have in OA and concluded that they have "the resources, the skills, and the opportunity to become leaders in OA care and improve the lives of those affected by the condition."[59]

Future Treatment Options

Ongoing research continues to explore innovative treatment options for osteoarthritis. Tanezumab, a monoclonal antibody that inhibitors nerve growth factors, is currently in Phase 3 trials. According to the manufacturers, Pfzier and Eli Lilly, two subcutaneous doses of tanezumab given eight weeks apart provided statistical improvements in pain, function, and reported self-assessment of OA when compared with placebo.[60, 61]

The following case scenarios are examples of real patients and illustrate how the pharmacist can be a leader in providing care to patients with OA.

CASE VIGNETTE 1

Betty, a 65-year-old Caucasian woman with obesity who is a regular patient at your pharmacy asks for your advice regarding ibuprofen or glucosamine with chondroitin to help with "arthritis pain" in both her hands. She is currently employed as a seamstress. Based on her medication profile she is currently being treated for hypertension and type 2 diabetes mellitus.

Betty's risk factors for OA include her gender, age, weight, and occupation. Both hands appear normal (e.g., no deformities and no visible signs of inflammation); however, Betty reports stiffness and pain (lasting for ~15-20 minutes) when she first wakes up and after resting for prolonged periods. She has not missed any days from work, but admits the pain is significantly worse compared to a year ago. When asked, Betty states she is looking for pain relief and fears the arthritis "will spread" to her other joints.

- What SMART goals can be established for Betty?
- Which risk factors should be targeted?
- What community-based programs should be considered?
- What drug therapy poses the least risk for Betty?

In accordance with the Arthritis Foundation, the pharmacist and Betty should work to establish SMART goals. Specific and Measurable goals, as stated by Betty, are to have reduced pain and to prevent OA from affecting other joints. Based on her risk factors, other specific goals would be weight loss and avoidance of prolonged periods of inactivity. These goals are Attainable and Relevant, but it is important for the pharmacist to ascertain Betty's motivation to achieve these goals. Providing Betty with education about OA and explaining that it does not "spread" is a good place to start. It is important, however, to identify Betty's risk factors and explain the importance of self-directed care. While weight loss may not appear relevant to hand OA and could be daunting for a patient who is morbidly obese, education on the importance of weight loss, even a modest 5-10 pounds, can significantly improve mobility and function as well as reduce pain and may even help prevent OA in other joints such as her knees. The pharmacist can serve as Betty's coach by encouraging healthy eating habits as well as hand exercises. One simple suggestion to increase mobility is that while Betty is watching TV, for example, she opens and closes her hands 5-10 times when a commercial is played. Advice on joint protection strategies is also warranted. For example, use two hands when lifting a pot off the stove or when pushing open a door. Referral to an occupational therapist may also be considered for evaluation of splinting and the use of other assistive devices. The pharmacist should advise Betty to consider community-based activity programs designed specifically for patients with arthritis and provide resources (e.g., educational handouts or weblinks) to facilitate her active participation in such programs. The

Centers for Disease Control (CDC) and other organizations (e.g., American Physical Therapy Association and the American Pharmacists Association) advocate the Arthritis Foundation's aquatic and exercise programs, as well as programs such as EnhanceFitness and Walk With Ease.

As for selecting a medication to help with pain, given Betty's age as well as her history of hypertension and diabetes, an NSAID should be avoided as first-line therapy. Neither glucosamine nor chondroitin will treat her acute pain and the benefit of these agents in OA is unsubstantiated. Alternatively, APAP (< 4 grams per day) may be a safe and effective treatment option for Betty. While taking APAP, Betty should be counseled to avoid other APAP-containing products (e.g., cough and cold remedies or any product claiming to be "aspirin free"). It is also important that her goals be time-bound. Establishing with Betty a specific time for follow-up and reflection on what has been attempted and what has worked (or not) should be established. The use of APAP and initiation of range of motion exercises should produce some benefit within a few days; however, weight loss will take several weeks. Consideration for follow-up can be as simple as discussing outcomes with Betty at her next medication refill request.

CASE VIGNETTE 2

Mary is a 54-year-old woman who comes into the pharmacy asking for a product she saw advertised on late-night television to help with arthritis pain. Upon questioning, she has bilateral ankle pain; moreover, both ankles appear swollen, erythematous, and are warm to the touch. Mary reports that the pain and swelling started approximately three weeks ago. The pain persists despite resting and keeping her feet elevated. She also complains of a reduced appetite and feeling more fatigued. She takes no medications except for a daily multivitamin.

- What is your assessment of Mary's presentation?
- What instructions do you provide to her?

Mary's symptoms are not consistent with OA; therefore, self-management should not be implemented. She should be counseled to seek prompt medical attention from her primary care provider. The pharmacist should also follow-up to ensure that Mary seeks the proper medical attention.

CASE VIGNETTE 3

John and his wife come into the pharmacy to get his prescriptions filled following his hospital discharge. John is a 70-year-old African-American man who is slightly overweight and has dyslipidemia and hypertension. He recently suffered a right cerebral vascular accident (CVA) due to atrial fibrillation that resulted in mild left hemiparesis. Prior to his stroke, he was prescribed a statin, ACE-inhibitor, diuretic, and calcium channel blocker. In addition to all those medications, John has a new prescription for a novel oral anticoagulant (NOAC) for secondary stroke prevention and an NSAID.

Given the significance of the drug interaction between the NSAID and NOAC, your discussion with the patient and his wife reveals that just before discharge the physical therapist felt that John's OA in his right knee was limiting his mobility. He was given several doses of acetaminophen, but it did not provide much pain relief. John indicated that the pain was worse at the start of therapy than at the end.

- What is the assessment and plan for John?
- What SMART goals should be established?
- What community resources should be recommended?
- What should the pharmacist monitor and evaluate regarding John's care?

In this common scenario, the pharmacist can quickly detect the potential drug-drug interaction and intervene, but the pharmacist can also educate the patient and his wife on non-pharmacological treatment modalities that may provide better, more sustained, pain relief. SMART goals specific to John's case include weight reduction and increased activity with limited periods of inactivity. Sustained periods of rest between therapy sessions will worsen OA pain; therefore, prompting simple activity (e.g., every 20-30 minutes) may reduce OA pain and stiffness. Advising him to discuss specific exercises with the physical therapist targeting the OA in his knee is also encouraged. These exercises can be done at home. While an oral NSAID may provide additional pain relief, John's age, co-morbidities, and concomitant drug therapy makes an oral NSAID relatively contraindicated and the prescriber should be contacted. Since a trial of acetaminophen was not helpful, consideration could be given to using a topical NSAID. While these drugs carry the same black box warnings as oral NSAIDs, research has shown that the drug interactions with the NOAC, ACE-inhibitor, and diuretic are reduced; thereby, reducing the risk of bleeding and acute renal failure.

The pharmacist could help in the coordination of care by advising continued therapy with physical therapy or cardiac rehabilitation as well as provide coaching on simple ways to increase activity around the home. John is at risk for falls; therefore, promotion of safety is paramount. Periodic reassessment should also take place to evaluate his current non-drug and drug therapy regimens for the desired outcome(s).

Conclusion

Osteoarthritis is indisputably a health crisis. While advancements in the understanding of the pathogenesis have been made, effective treatment strategies provide only temporary symptomatic relief at best and require patient self-management to complement clinical care. The pharmacist is perfectly positioned to be a key leader and coach in educating the public and health care team in the detection, prevention, and treatment of OA. Screening patients for OA is a simple, but highly effective intervention. In a Canadian study, a brief screening questionnaire given by community pharmacists identified >80% of patients with knee pain who had undiagnosed OA. Within six months of receiving diagnosis, through medical intervention, a statistically significant number of these patients reported improvements in their pain, function, and daily activity scores.[56] A simple screening tool not only helped in the diagnosis, but gave the pharmacist an opportunity to provide education on the prevention and treatment options for arthritis, review medications and make recommendations in accordance with current OA guidelines, as well as refer patients who may benefit from the services of allied health professionals (e.g., dietician, physical therapist, occupational therapist) and from engagement in self-management strategies.

Knowledge of community-based arthritis programs can be a real asset to patients seeking pain relief and social support. Recognizing concomitant health conditions that can be impacted by OA and vice versa is another critical factor to safe and effective OA treatment. The Osteoarthritis Action Alliance (OAAA) has developed a Pharmacist Toolkit to facilitate the detection, management, and prevention of OA (add reference here). This toolkit recognizes that successful OA management requires a partnership among pharmacists and patients to facilitate multimodal care strategies and long-term success. Contents include educational information for pharmacists to expand their knowledge of OA and confidence in recognizing and managing patients with OA. The toolkit also contains recommendations for pharmacists to refer patients to clinical care and/or self-management. Finally, the toolkit contains resources that can better enable the pharmacist to guide and support patients' engagement in community-based and self-directed programs for physical activity, weight management, falls prevention, and chronic disease self-management. With evidence-based education and actionable tools and resources, pharmacists and their patients can feel empowered to engage in proactive care for osteoarthritis.

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