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Author Disclosures: Brittany Hoffmann-Eubanks and the *DSN* editorial and continuing education staff do not have any actual or potential conflicts of interest in relation to this lesson.

Universal program number: 0401-0000-16-207-H01-T

CE Broker tracking number: 20-558317

Activity type: Knowledge-based

Initial release date: Dec. 21, 2016

Planned expiration date: Dec. 21, 2019

This program is worth 1.5 contact hours (0.15 CEUs).

Target Audience

Pharmacy technicians in community-based practice.

Program Goal

To provide the community pharmacy technician with a review of osteoarthritis and rheumatoid arthritis to assist patients.

Learning Objectives

Upon completion of this program, the technician should be able to:

1. Describe the prevalence of osteoarthritis and rheumatoid arthritis in the U.S. population;
2. Compare and contrast the clinical presentation and diagnosis of osteoarthritis and rheumatoid arthritis;
3. Recognize current treatment options for osteoarthritis management; and
4. Recognize current treatment options for rheumatoid arthritis management.

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A technicians' guide to osteoarthritis and rheumatoid arthritis in adults

INTRODUCTION

It is estimated that 52.5 million adults, or approximately 1-in-5 U.S. adults, has clinically diagnosed arthritis.¹ Arthritis is a general term that includes more than 100 different rheumatic diseases and conditions. Arthritis is a disease that commonly is thought to target the elderly; however, it affects individuals of all ages. Risk of arthritis increases with age; however, two-thirds of people with arthritis actually are younger than 65 years of age.¹⁻² Arthritis is more common in women than men (29% versus 19%, respectively) and includes all racial and ethnic groups. The number of adults with arthritis is expected to increase to 78 million by the year 2040.² Arthritis is more common in patients with other conditions, such as heart disease, diabetes, high blood pressure and obesity (see Figure 1).¹⁻² For example, about 49% of adults with heart disease and 47% of adults have arthritis. Patients who have comorbid conditions along with arthritis experience more complicated disease-state management that often results in lower quality of life.

Arthritis is the most common cause of disability among U.S. adults.¹⁻⁴ Approximately 22.7 million U.S. adults report limitations in their activities due to arthritis.³ For example, 6 million adults report an inability to walk a quarter mile, 14 million report limitations in bending or kneeling and 8 million have difficulty climbing stairs. In addition to the physical limitations, patients also report less socialization with friends and family as a result of their mobility concerns.

As mentioned above, arthritis is a large general term that includes

more than 100 different rheumatic diseases. This lesson will focus on two of the most common rheumatic conditions — osteoarthritis, or OA, and rheumatoid arthritis, or RA.

Pharmacy technicians often are the first point of contact for patients arriving in the pharmacy. This presents a unique opportunity to assist in identifying patients who may need additional care. Patients who need additional care can be referred to the pharmacist for consultation and aid to be sure that they receive proper care and treatment.

EPIDEMIOLOGY

Osteoarthritis

Osteoarthritis is the most prevalent joint disease in the United States, affecting approximately 27 million Americans.⁴⁻⁷ Overall, OA affects 13.9% of U.S. adults ages 25 years and older, and 33.6% of those ages 65 years and older.⁴ Further prevalence data can be broken down based upon the definition of OA, specific joints involved and characteristics of the patient population (see Table 1). Osteoarthritis is a progressive disorder that often develops over years in patients whose symptoms may remain stable for long periods during this time.⁷ Osteoarthritis can occur in any joint of the body; however, most commonly it is found in the small joints of the hands, knees, spine, hips or feet. After 50 years of age, women become more likely than men to be affected by OA.⁴

Rheumatoid arthritis

Rheumatoid arthritis is the most common systemic inflammatory autoimmune disease in the United States.⁸⁻⁹ The most recent prevalence

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data in the United States comes from the Rochester Epidemiology Project in Minnesota.¹⁰ From 1995 to 2007, 41 per 100,000 people were diagnosed with RA yearly. Incidence rose with age — 8.7 per 100,000 of people ages 18 years to 34 years, and 54 per 100,000 of people ages 85 and older.¹⁰ Data also showed a peak from ages 65 years to 74 years, with 89 per 100,000 people of all estimated ages adjusted to the 2000 U.S. population.¹⁰ Another study from the Minnesota data estimated a lifetime risk for RA at 4% for women and 3% for men.¹¹ It is important to note that due to the demographics of the population area containing Minnesotan adults, the data cannot be generalized beyond Caucasians. Globally, rheumatoid arthritis affects about 1% of the population.¹² Rheumatoid arthritis has a significant impact on a patient's ability to perform activities of daily living, such as work and home activities; also, it increases mortality.¹³⁻¹⁵ Approximately one-third of patients are work-disabled within two years of disease onset, and approximately 50% are work-disabled after 10 years.¹² In 1997, RA accounted for 22% of all deaths due to arthritis and other rheumatic conditions in the United States.⁸ Notably, as a result of CV risk factors and RA disease-related risk factors, cardiovascular mortality appears to be 1.5-fold higher in patients with RA compared with the general population.¹² Rheumatoid arthritis is a complicated exchange between chance, genes and the environment.¹⁶ Twin studies, for example, have revealed a strong genetic disposition for RA with concordance rates of 15% to 30% in monozygotic twins and 5% in dizygotic twins.^{12,16-17} The concordance rates among twins can only be applied in the context of prevalence of disease related to heritability. Data from another study suggested that 50% to 60% of disease among twins is related to the environmental and genetic sharing that takes place among twins.¹⁸ There is a well-documented association between RA susceptibility and differences in human leukocyte antigen, or HLA-DRB1 alleles, particularly among those positive for certain autoantibodies, such as rheumatoid factor, or RF, and anti-citrullinated protein antibody, or ACPA.^{12,16-17}

ETIOLOGY AND PATHOLOGY

Osteoarthritis

Osteoarthritis commonly is referred to as a “wear-and-tear” disorder of the joints, focusing on the loss of cartilage; however, now it is widely accepted that the disease process involves the entire joint.¹⁹ In addition to loss of cartilage, there is remodeling of subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles and, in some cases, synovial inflammation.²⁰ It has been suggested that

Table 1

Average annual prevalence of osteoarthritis in the ambulatory healthcare system in the United States from 2001 to 2005

OSTEOARTHRITIS CLASSIFICATION	AUTHOR	AGE IN YEARS	MILLIONS AFFECTED	GENDER AFFECTED IN MILLIONS
Knee	Dillon et al 1994	≥ 60	37.4	42.1 female; 31.2 male
	Leyland et al 2012	≥ 60	47.8	-
	Felson et al 1987	≥ 45	19.2	19.3 female; 18.6 male
	Jordan et al 2007	≥ 45	37.4	42.1 female; 31.2 male
	Felson et al 1987	≥ 26	4.9	4.9 female; 4.6 male
Hip	Jordan et al 2009	≥ 45	28	25.9 female; 25.4 male
Symptomatic radiographic OA in the hand (per 100)	Zhang et al 2002	≥ 26	6.8	9.2 female; 3.8 male
	Dillon et al 2007	≥ 60	8 overall	-
Radiographic knee OA (per 100)	Dillon et al 1994	≥ 60	12.1	10 female; 13.6 male
	Felson et al 1987	≥ 45	6.7	7.2 female; 5.9 male
	Jordan et al 2007	≥ 45	16.7	18.7 female; 13.5 male
	Felson et al 1987	≥ 26	4.9	4.9 female; 4.6 male
Radiographic hip OA (per 100)	Felson et al 1987	≥ 45	8.7	9.3 female; 9.2 male

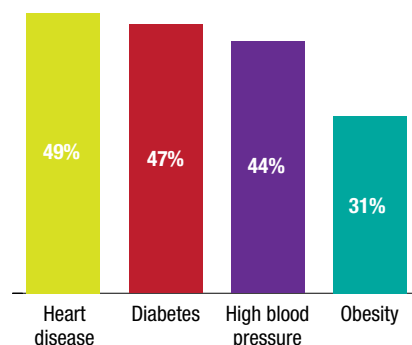
Information from resource 4: Centers for Disease Control and Prevention. Arthritis: Osteoarthritis (OA). Available from: <http://www.cdc.gov/arthritis/basics/osteoarthritis.htm>. Accessed 17 July 2016. OA=osteoarthritis

these changes may occur due to an imbalance between the breakdown and repair of joint tissue.¹⁹⁻²⁰ Osteoarthritis is categorized into two major classes— primary (idiopathic) OA, in which there is no identifiable cause, and secondary OA, which is associated with a known etiologic cause. Development of OA is a complex multifactorial process that includes both modifiable and nonmodifiable risk factors (see Table 2).

Obesity

Obesity is one of the most important preventable risk factors for the development of OA.⁵⁻⁶ In early analysis, questions arose as to whether obesity preceded osteoarthritis development and was indeed confirmed with a greater risk found in women compared with men.⁵ More recently, a 2010 meta-analysis showed that those who were obese or overweight had a 2.96 higher risk of knee OA compared with those of normal weight (95% CI 2.56 to 3.43).²¹ Additionally, from the same meta-analysis, those in the “overweight” body mass index, or BMI, category had double the risk of developing incident knee OA compared with the population with normal weight. Risk of incident knee OA increases with increasing BMI,

FIGURE 1: PREVALENCE OF OTHER CHRONIC CONDITIONS IN ADULTS WITH ARTHRITIS



Adapted from resource 1: Centers for Disease Control and Prevention. “At a Glance 2015: Arthritis.” Available from: <http://www.cdc.gov/chronicdisease/resources/publications/aag/arthritis.htm>. Accessed 17 July 2016.

regardless of knee alignment.²² The Framingham study showed that women who lost about 5 kg had a 50% reduction in risk of developing symptomatic knee OA, and was confirmed in a more recent meta-analysis.^{6,22,23} Weight loss also has shown to decrease pain and disability in patients with

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already-established incident knee OA.²³⁻²⁴

Age

Age is one of the strongest risk factors for OA of all joints.^{5-6,22,25} The exact mechanism is not known but may be a consequence of cumulative exposure to biomechanical stresses and biological changes making the joint and surrounding tissues less resilient.²² It is important to note that while OA occurs from a combination of factors, including excessive mechanical stress, it is not a guaranteed outcome of aging.²⁶ For example, an individual who is more susceptible to OA due to modifiable and nonmodifiable risk factors may not actually experience OA until an injury occurs.

Gender

The female sex is associated with higher prevalence and greater severity of disease.^{6,22,27} An observed increase in OA in women during menopause has led to speculation that decreasing estrogen levels may have a role. However, observational studies and clinical trials have resulted in conflicting evidence.²⁸⁻³⁰ For example, in the Heart and Estrogen/Progestin Replacement Study, a randomized controlled trial of older postmenopausal women with heart disease, there was no significant difference found in the prevalence of knee pain or disability between the treatment groups (estrogen replacement and placebo).^{6,22,29} In contrast, the Women's Health Initiative showed a borderline significance in women using estrogen replacement therapy who were less likely to require total knee or hip arthroplasty, but this association was not seen with estrogen plus progestin compared with placebo.^{6,22,30}

Genetics

Several studies have shown an inheritable component to OA (~40% to 65%) with strongest evidence for hand and hip OA compared with knee OA.^{6,22,31-33} There have been three loci — GDF5, 7q22 and MCF2L — that have been linked to OA at genome-wide significance levels.^{22,34-36} An additional study identified five new susceptibility loci for OA-implicating chromosomes three, six, nine and 12.^{22,37} Pain severity related to OA also is an area of study in which a cohort study found an association with the COMT gene and pain sensitivity in hip OA. Other genes also have been studied, such as TRPV1 and PACE 4 gene Pcsk6, which were associated with knee pain in two meta-analyses.^{22,38-39}

Occupation/injury

Occupations that require repetitive use of joints have been associated with increased risk of OA. A 2011 meta-analysis showed a

Table 2
Risk factors for the development of osteoarthritis in adults

OA RISK FACTOR CATEGORY	OA-SPECIFIC RISK FACTORS	
Non-modifiable	Age	Increases with age
	Gender	Women > men
	Race/ethnicity	Varies among racial/ethnic groups
	Genetics	Strong genetic role
Modifiable	Diet	Area for future study
	Obesity	No. 1 risk factor
	Injury/surgery	Knee has strongest risk
	Occupation/sports	Repetitive use of joints increases risk
Other factors	Estrogen deficiency	Complex role of estrogen
	High bone-density	Inverse relationship observed between OA and osteoporosis
	Vitamins C, D and E	Conflicting supplementation evidence
	C-reactive protein	Appear to correlate with pain and stiffness

Information from resources 5,6,7

PATIENT SCENARIO 1

SP is a 78-year-old female who presents to the pharmacy with her daughter to drop off a prescription refill for Ramipril 5 mg daily. The patient explains that she has been having a lot of leg pain when walking, and that the pain often “comes and goes.” Upon further discussion, the technician learns that the patient reports the pain as “achy” when sitting and “sharp” when walking. The technician notes that the patient has a prescription for gabapentin 300 mg on file, but the patient states that the pain feels different than her nerve pain. The technician reviews the patient's profile and notes that the patient does not have any medications typically used to treat pain. What is the appropriate next step for the pharmacy technician?

Discussion

The patient can benefit from further consultation with the pharmacist. At a minimum, the technician should be an advocate for the patient and alert the pharmacist for the needed discussion. The technician can be of greater value by advising the patient of the importance of meeting with the pharmacist and by properly preparing the pharmacist by passing along the additional details that the patient shared when dropping off the prescription. This will improve the efficiency of the discussion and avoid having the patient need to repeat key details.

In the absence of other medical information, the patient may be suffering from osteoarthritis. The pharmacist can use the description of the symptoms during the assessment to make a non-pharmacologic recommendation as appropriate. The pharmacist also may recommend a pharmacologic intervention if appropriate, or recommend that patient be seen by a primary care physician for further evaluation. Thus, by communicating the information learned when the patient first arrived, the technician can assist in helping the patient receive proper care to minimize the patient's pain.

1.6-fold increase in risk of knee OA related to occupational activities with the most risk related to activities other than standing.⁴⁰ There have been numerous studies that have shown knee injuries are a strong risk factor for OA. Further, two meta-analyses found a four-fold increased risk of developing OA when a knee injury occurred.⁴¹⁻⁴²

Rheumatoid arthritis

Rheumatoid arthritis is a common systemic inflammatory autoimmune disease where the exact etiologic cause is unknown. More recently, RA has been regarded as a

clinical syndrome with several disease subsets that involve multiple inflammatory cascades that converge into a final pathway leading to characteristic RA damage.⁴³ It is postulated that RA results from two potential blows — an environmental trigger and genetic susceptibility.^{12,44} The first physiologic structure affected by rheumatoid arthritis is the synovium (synovial joint membrane that lines joint capsules and creates synovial fluid for the hands and feet).¹² Such additional inflammatory changes and influx of inflammatory mediators as T-cells and cytokines lead to cartilage and bone de-

struction and potentially may lead to systemic involvement of multiple organs and tissues.^{12,16,45} There are several risk factors associated with the development of RA.

Genetics

Genetic factors account for 50% of risk associated with RA development.^{17,43} There are more than 30 genetic regions that have been associated with RA with no major pathogenic insights at this time, excluding HLA and PTPN22.⁴³

Female sex

RA is three times more frequent in women than men, and highest among women older than 65 years of age.⁴³ Pregnancy often has been shown to cause remission of RA.⁵⁴ Recent data also suggests that postpartum women are less likely to be diagnosed with RA when compared with their nulliparous counterparts.⁴⁶ In addition, breastfeeding decreases the risk of RA in women who have breastfed for at least 24 months.⁴⁷

Environmental

Smoking increases the risk of RA by two-fold, especially in ACPA-positive disease; the gastrointestinal microbiome also has been shown to be involved in autoantibody production (bacteria dependent).^{12,43,48} Such infectious triggers as Epstein-Barr virus, parvovirus, mycoplasma and proteus have been studied and reviewed, but data largely has been disappointing.¹⁷ Other risk factors that may play a role but in which strong evidence is lacking include alcohol and coffee intake, oral contraceptive use and vitamin D status.⁴³

The above-mentioned gene and environment interactions result in the loss of self-tolerance driving the influx of inflammatory mediators and the characteristic destructive processes seen in rheumatoid arthritis. It is important to consider the roles of the adaptive and humoral immune system components in the pathogenesis of RA to understand current and future treatment options for RA.

CLINICAL PRESENTATION AND DIAGNOSIS

Osteoarthritis presentation

OA most commonly presents in patients over the age of 50 years and has an insidious onset over many months to years.⁷ Since the primary symptoms of OA are joint pain, stiffness and limitation of movement, pain is usually the first symptom that leads patients to seek out their primary care physician, or PCP.^{7, 10-11} Pain generally is characterized by patients as deep and aching, and the stiffness or pain usually resolves in less than 30 minutes, unlike rheumatoid arthritis. OA pain may be weather related and can result in severe limitations of activities of

PATIENT SCENARIO 2

KP is a 63-year-old male who presents to the pharmacy to pick up his Meloxicam 15 mg. The technician notices that the patient is struggling to open his wallet and has very swollen fingers. The technician engages the patient in conversation about his hands. The patient states that he has had a lot of stiffness in his fingers, especially by his “knuckles,” and that it is very painful and persistent. The patient goes on to tell the technician that he has tried acetaminophen for multiple weeks now and today saw his doctor, who wants him to try the Meloxicam. The patient states he was diagnosed with rheumatoid arthritis a few months ago but it seems to be getting worse. The technician pulls up the patient’s profile of current medications.

Acetaminophen: 500 mg, two tablets every eight hours as needed for pain
Last two fills: 30, and 30 days ago
Methotrexate 2.5 mg, four tablets weekly
Last two fills: 38 days, 40 days ago
Folic Acid: 1 mg, one tablet by mouth daily (except on day of methotrexate administration)
Last two fills: 45, 35 days ago

What is the most likely cause of the patient’s continued swelling and pain?

Discussion

In the absence of other health information, the patient appears to be nonadherent with the disease modifying anti-rheumatic drug therapy methotrexate. Methotrexate is a recommended first-line medication for all patients after diagnosis, regardless of their disease activity level. The technician should alert the pharmacist about the lack of adherence, providing the opportunity for the pharmacist to consult and counsel the patient on the importance of the chronic medication for the treatment of their rheumatoid arthritis.

daily living. OA pain typically affects one to a few joints at a time, develops over a long period of time, is increased by joint use and impact, and can worsen after rest (gelling), with variable intensity throughout the day and week.⁴⁹ In advanced disease, pain may be consistent even during periods of rest. Moreover, patients who seek out their PCP also report difficulty or limitations in activities of daily living, such as walking, climbing stairs and completing household chores.⁷ In addition to pain, physical manifestations of OA that can be observed are crepitus with movement (grating sound or sensation produced by friction between bone and cartilage), joint-line tenderness, bony swelling, deformity (late disease), joint-space narrowing and presence of osteophytes.⁴⁹

Osteoarthritis diagnosis

Patients with OA are evaluated based upon their history, physical examination, radiographic findings and the extent of joint involvement. Joints most commonly affected are the hands, knees, hips and spine, but nearly any joint can be involved (see Table 3).⁵⁰⁻⁵⁵

OA commonly is asymmetric, effecting one joint severely, such as the hip, with practically normal function of the other. OA primarily is a clinical diagnosis that can be made by healthcare providers based upon a history and physical examination.^{7,49-50} Laboratory tests and radiographic examinations are not routinely required for diag-

nosis if presentation is typical with respect to signs and symptoms based upon the following criteria:⁴⁹

- Persistent usage-related joint pain in one or a few joints;
- Age \geq 45 years; and
- Only brief morning stiffness (\leq 30 minutes).

Clinicians may feel confident of an OA diagnosis in the presence of other risk factors mentioned above (i.e., obesity and age). However, clinical judgment should be exercised, along with appropriate imaging and laboratory assessments, if patients present with atypical signs and symptoms (e.g., pain for 45 minutes or longer, and significant joint inflammation), weight loss, or are ages 45 years or younger and absent any major joint trauma.⁴⁹ Laboratory testing may be conducted in some cases to rule out other diseases, such as rheumatoid arthritis (e.g., ACPA or RF) and gout (uric acid).⁷ Additionally, such markers of inflammation as erythrocyte sedimentation rate, or ESR, and C-reactive protein, or CRP, generally are within normal limits in patients with OA, synovial fluid lacks crystals and white blood cell counts are less than 1500 cells/ μ L.^{7,50}

False-positive results may be possible; therefore, it is important for healthcare providers to consider the purpose of the test and the potential for unnecessary confusion due to results in patients who have a low probability of gout or autoimmune arthritis.⁷

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Rheumatoid arthritis presentation

The hallmark characteristics of RA include presence of pannus (synovial *hyperplasia*), cartilage damage and bony erosion.^{12,16-17,52} Approximately 80% of patients are affected with these hallmark issues within one year of diagnosis.¹² Patients typically present with pain and stiffness in multiple joints. The most common areas involved in the body are the wrists, proximal interphalangeal joints and metacarpophalangeal joints.⁵³ Morning stiffness that lasts longer than one hour is a defining characteristic of RA. Patients often present with visible “boggy” swelling or subtler synovial hyperplasia that can be palpated upon examination.⁵³ Patients also may complain of such systemic symptoms as fatigue, weight loss and low-grade fever with active disease. RA also is associated with several systemic complications that for the purpose of this lesson will not be discussed in detail but have been reviewed elsewhere.¹² It appears that prolonged inflammatory mediators due to the loss of tolerance contributes to the extra-articular involvement. Further, extra-articular involvement appears to increase mortality with men being affected higher than women.^{12,54} As discussed earlier in this lesson, the majority of deaths in patients with RA seem to be related to cardiovascular disease that isn’t otherwise explained by traditional risk factors (e.g., hypertension, diabetes and dyslipidemia).^{12,16,55}

Rheumatoid arthritis diagnosis

The diagnosis of RA primarily is based upon physical examination findings.^{12,16,53} In 2010, the American College of Rheumatology, or ACR, and the European League Against Rheumatism, or EULAR, worked collaboratively to update the current RA classification criteria (see Table 4).⁵⁶ The purpose of the new 2010 criteria was to address the gap of the 1987 ACR classification criteria, which poorly identified patients with early arthritis that may develop into RA.^{12,43,53,56} Patients who are identified earlier in the disease process have been shown to have better outcomes, specifically with respect to erosive joint damage and extra-articular disease that may be prevented or delayed with proper therapeutic treatment.⁴³ The new criteria are intended to be used to identify clinical trial patients, differentiate patients with synovitis and determine the group at highest risk for developing persistent or erosive RA.^{12,56} In addition, the ACR/EULAR criteria authors also developed an algorithm for practitioners to classify definite RA.⁵⁶

Diagnostic tests also may aide in the diagnosis of RA due to the common presence of such autoantibodies as rheumatoid factor, or RF, and anti-citrullinated protein antibody, or ACPA.⁵³ ACPA is more specific to

Table 3
Signs, symptoms and examination findings of osteoarthritis

JOINT	SIGNS AND SYMPTOMS	JOINT EXAMINATION FINDINGS	RADIOLOGIC EVALUATION
Knee	Pain with climbing stairs Genu varum (“bow-legged”) Transient joint effusion	Deformity Local tenderness Bony proliferation Occasional synovitis Limited motion	Early mild OA: • Radiographic changes often absent Progressive OA: • Joint space narrowing • Subchondral bone sclerosis • Marginal osteophytes Late OA: • Abnormal alignment of joints • Effusions
Hip	Groin pain with weight-bearing exercises Stiffness after activity Limited joint movement		
Hand	Pain with movement Crepitus with movement Limited movement		
Feet	Typically involves the first metatarsophalangeal joint (big toe) Additional joints also may be affected		

Adapted from resources 52 and 59

RA and, when present, may be prognostic for increased joint disease and lower remission rates.^{43,53} Approximately 50% to 80% of patients with RA have RF, ACPA or both.⁴³ Additionally, CRP and ESR, both of which are inflammatory markers, have been added to the new ACR/EULAR classification criteria since they are frequently elevated in RA patients and useful for disease activity and therapeutic monitoring.^{53,56} Additional tests that may be ordered are a complete blood cell count with differential, assessment of renal and hepatic function, assessment of hepatitis C, hepatitis B and tuberculosis prior to treatment.

TREATMENT AND MANAGEMENT: OA

In 2012, the ACR published updated guidelines for the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip and knee.⁵⁷ Goals of therapy are to:

1. Educate the patient, family members and caregivers;
2. Relieve pain and stiffness;
3. Maintain or improve joint mobility;
4. Limit functional impairment; and
5. Maintain or improve quality of life.⁵⁷⁻⁵⁹

Treatment of OA generally consists of four intervention categories:

1. Nonpharmacologic;
2. Pharmacologic;
3. Complementary and alternative; and
4. Surgical.

Patients with OA should receive some form of intervention from the nonpharmacologic and pharmacologic categories.⁵⁰ Surgical interventions should be reserved as a last line for patients who fail pharmacologic therapy and suffer from intractable pain and loss of function.⁵⁰

Nonpharmacologic interventions: OA

All patients with OA should receive patient education about the disease process, treatment and prognosis. Patient educa-

tion is a crucial component of the treatment process in that often patients see OA as a normal part of the aging process, in which little or nothing can be done to alleviate symptoms or the progression of the disease. This presents a great opportunity for the technician to call attention to the need to discuss a patient’s overall condition with the pharmacist. The 2012 ACR and British guidelines encourage an exercise regimen that can consist of aquatic, aerobic and/or resistance land-based activities.^{57,60} The ACR guidelines do not recommend one form of exercise over another; instead, the patient’s preference and physical ability should be used to guide the decision process. Weight loss also should be recommended when possible, particularly if the patient is overweight or obese.^{7,50} Recent randomized control trials have shown that weight loss as small as 4% can reduce pain, improve physical function and even have positive effects on cartilage structure.^{7,61-63} The pharmacist may be able to help the patient with referrals to an occupational or physical therapist to help tailor exercise regimens, assess muscle strength and stability and recommend such joint-protection modalities as canes, walkers and braces. Other alternative treatment modalities with scant evidence and small effect size include insoles, lasers, transcutaneous electrical nerve stimulation, ultrasound, electrotherapy and acupuncture.^{7,64-68} Heat and ice are additional options that have been shown to be effective, and appropriate counseling should take place to ensure patients avoid burns from heat or frostbite from cold therapies.^{7,69}

Pharmacologic therapy

Acetaminophen

Traditionally, acetaminophen has been the mainstay of mild osteoarthritis treatment. It is an inexpensive agent, generally considered safe and is effective.⁵⁰ A 2006 Co-

chran review determined that acetaminophen was more effective than placebo, equal to NSAIDs and had fewer gastrointestinal side effects.^{50,70} In contrast, a 2016 network meta-analysis concluded that there was no role for single-agent paracetamol (acetaminophen) for the treatment of patients with osteoarthritis, regardless of dose.⁷¹ The authors state that even though paracetamol has been on the market for more than 50 years, the efficacy of the drug has never been properly established or quantified in chronic disease and thus is most likely not as useful as once believed.⁷¹ Since this meta-analysis was published in May 2016 and the most recent 2012 ACR OA guidelines still support the use of acetaminophen as a first-line agent, it is very likely that practitioners may still recommend its use due to the safety profile, long-term experience with the drug and low cost.

Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

In knee and hip OA, the 2012 ACR OA guidelines include NSAIDs as an alternative first-line therapy to acetaminophen in patients who do not respond, or who have contraindications to the use of acetaminophen.⁵⁷ Additionally, patients who have had an upper GI bleed in the past (>1 year) should use selective cyclooxygenase 2, or COX-2, inhibitors or a nonselective NSAID in combination with a proton-pump inhibitor, or PPI. Patients who have had an upper bleed within the last year should start with a selective COX-2 inhibitor with a PPI. In chronic management of patients with knee and hip OA, a PPI should be considered for all patients to reduce the risk of developing GI events. Patients who are using less than 325 mg of low-dose aspirin — in whom an oral NSAID is recommended — a nonselective NSAID, other than ibuprofen, should be initiated. NSAIDs should not be used in patients with stage IV and V chronic kidney disease, and should be used conservatively based on an individual patient basis in stage III. NSAIDs should not be used in patients with contraindications to these agents, and caution should be used with the known risk of gastrointestinal adverse effects and cardiovascular events, especially in patients who are ages 75 years or older.

In July 2015, the Food and Drug Administration strengthened their warning of heart attack and stroke risk for NSAIDs.⁷² In 2005, a boxed warning was added to NSAID prescription drug labels for heart attack and stroke risk. Recent data reviewed by the FDA suggests that past cardiovascular history is not necessary for patients to be at risk of an event that could lead to death.⁷³⁻⁷⁵ Previous thought also included that patients would be at increased risk with long-term NSAID use. However, the new FDA warning now

states that risk of heart attack or stroke can occur early in the first few weeks, with risk increasing with longer use and higher doses.⁷³ In addition, it also was understood that the risk among NSAIDs as a total class was similar or no different; however, recent data the FDA reviewed suggests that some NSAIDs may have greater risk than others, requiring future research to determine relative risk.⁷³ If any patients who are using NSAIDs complain of chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body, or slurred speech, they will need to seek immediate medical attention.⁷³

Topical NSAIDs

Topical NSAIDs are preferred agents for knee OA as an alternative to acetaminophen in patients who are ages 75 years or older due to limited absorption and low GI risk.⁵⁷

Intraarticular corticosteroid injections

Intraarticular corticosteroid injections are recommended in knee and hip OA as an alternative first-line agent when patients have failed acetaminophen and NSAIDs.⁵⁷ Intraarticular corticosteroids are considered safe and well tolerated, and frequency should be limited to no more than every three months due to risk of systemic side effects.^{50,76} Patients can expect the effects of the corticosteroid injection to provide short-term relief lasting approximately four to eight weeks.⁵⁰

Tramadol

Tramadol is recommended as an alternative first-line agent in patients for hand, hip and knee OA who have failed treatment or contraindications are present for acetaminophen, NSAIDs and intraarticular injections.⁵⁷ Additionally, tramadol can be combined for improved pain control with acetaminophen or NSAIDs. Patients should be counseled on the risk of such common adverse events as drowsiness, dizziness and constipation. Patients also should be instructed to avoid operating heavy machinery or driving while using tramadol.

Topical capsaicin

Topical capsaicin may be considered as a first-line alternative agent in hand OA by the 2012 ACR OA guidelines.⁵⁷ The guidelines do not recommend in the use of hip or knee OA. Clinical evidence is limited to small studies that showed a small improvement in pain, but capsaicin is an acceptable alternative for patients who cannot use oral NSAIDs due to the low risk of side effects (i.e., skin irritation or burning).⁷⁶⁻⁷⁷

Opioid analgesics

The 2012 ACR OA guidelines reserve opi-

oid analgesics as a last line of therapy in patients who have not responded adequately to first-line agents or in those with intractable pain who are unwilling to undergo — or are not candidates for — total joint arthroplasty.⁵⁷ The authors further suggest that practitioners should follow the recommendations of the American Pain Society/American Academy of Pain Medicine for chronic management of non-cancer pain.⁷⁸

Duloxetine

Duloxetine is recommended as adjunctive therapy in patients with OA who have had a partial response to acetaminophen or NSAIDs.^{57,76 79-80} Patients who suffer from neuropathic pain and/or depression may make duloxetine a preferred second-line agent. Common side effects associated with duloxetine are nausea, vomiting, constipation and nominal blood-pressure increases.

Complementary and alternative medicine: OA

Effectiveness of acupuncture for OA was reviewed in a meta-analysis where a short-term benefit was observed but considered clinically irrelevant by the authors.^{50,81} Glucosamine and chondroitin are not conditionally recommended by the authors of the 2012 ACR OA guidelines.⁵⁷ The authors cite heterogeneity in effect size, lack of efficacy and lack of prescription quality preparations in their decision. Their decision also was based on multiple studies and meta-analyses that affirm the lack of efficacy for glucosamine and chondroitin.⁸²⁻⁸⁶ In spite of this evidence, both nonprescription agents are still widely used by the public within the United States as nutritional supplements. In contrast, a 2015 Cochrane review of chondroitin in osteoarthritis concluded that chondroitin, alone or in combination with glucosamine, was better than placebo in improving pain in patients with OA in short-term studies.⁸⁷ The authors recommended further studies to explore the role of chondroitin in the treatment of osteoarthritis.

TREATMENT AND MANAGEMENT: RA

In the past, RA treatment primarily consisted of symptom- and pain-control utilizing NSAIDs.⁸⁸ However, NSAIDs have lost their first-line treatment due to concerns of limited efficacy, inability to prevent long-term bone/cartilage damage and gastrointestinal and cardiovascular side effects.^{43,89-90} Instead, management with NSAIDs for pain and inflammation should utilize short-acting agents for the shortest period of time combined with proton-pump inhibitors to minimize risk.^{43,53} Additionally, a 2011 Cochrane review found that NSAIDs, when used at inflammatory arthritis doses — excluding inflammatory doses of aspirin — can be safely combined with methotrexate,

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or MTX.⁹¹ Furthermore, in the last decade there have been significant developments in the treatment of RA, increasing options for pharmacologic intervention and making disease remission a realistic goal.⁹² Remission is defined by the 2015 ACR RA panel as “a tender joint count, swollen joint count, C-reactive protein level (mg/dL) and patient global assessment of ≤ 1 each or a simplified disease activity score, or DAS, of ≤ 3.3 .”⁹ The 2015 ACR RA guidelines stratify treatment into early RA, which has a disease duration shorter than six months; established RA, which has a disease duration longer than six months; or meet 1987 ACR RA criteria.⁹ Further, the ACR panel identifying early RA as its own separate treatment category is directly related to evidence that suggests a delay in treatment is a prognostic factor for poor treatment response.^{89,92-94} Disease modifying anti-rheumatic drugs, or DMARDs, are the mainstay of treatment, and current traditional DMARDs and biologics available for RA treatments in the United States are reviewed in Table 5. In January 2016, the ACR published updated guidelines for the treatment of rheumatoid arthritis, citing the rapid availability of new evidence, new treatment modalities, advancement of guideline methodologies and the need to broaden its 2012 recommendations.^{9,88} The new ACR RA guidelines focused on six key areas:

1. Use of traditional DMARDs, biologic DMARDs (biologics) and tofacitinib;
2. Use of glucocorticoids;
3. Use of biologics and DMARDs in high-risk populations;
4. Use of vaccines in patients starting/receiving DMARDs or biologics;
5. Screening for tuberculosis, or TB, with respect to biologics or tofacitinib; and
6. Laboratory monitoring for traditional DMARDs.

Pharmacologic treatment: RA

Current goals of therapy include:

- Attaining low-disease activity, or LDA;
- Prevention of joint damage and deformity;
- Improved quality of life;
- Control of long-term complications (e.g., extra-articular disease); and
- Remission.^{54,88-89}

When treating women of child-bearing age, extra precautions are needed as treatments can have harmful effects on conception and pregnancy.^{43,53}

Traditional DMARDs

There are four traditional DMARDs that are recommended by the 2015 ACR RA guidelines for the treatment of RA:

1. Methotrexate;
2. Leflunomide, or LEF;

Table 4

Drug category and treatment options per the 2015 ACR RA guidelines

RA DRUG CATEGORY	DRUG TREATMENT OPTIONS
DMARD monotherapy*	Typically MTX, but also may be SSZ, HCQ or LEF
Double DMARD therapy	MTX + SSZ, MTX + HCQ, SSZ + HCQ or combinations with LEF
Triple DMARD therapy	MTX + SSZ + HCQ
TNF biologics	Adalimumab, certolizumab pegol, etanercept, golimumab or infliximab
Non-TNF biologics**	Abatacept, rituximab or tocilizumab (excluding anakinra)
Low-dose glucocorticoid	≤ 10 mg/day of prednisone (or equivalent)
High-dose glucocorticoid	>10 mg/day of prednisone (or equivalent)
Short-term glucocorticoid	<3 months of treatment

*Azathioprine, cyclosporine, minocycline, and gold, were considered but not included in 2015 ACR RA guidelines due to their infrequent use in RA and/or lack of new data since 2012

**Anakinra was considered but not included in the 2015 ACR RA guidelines due to its infrequent use in RA and/or lack of new data since 2012

MTX: methotrexate, SSZ: sulfasalazine, HCQ: hydroxychloroquine, LEF: leflunomide, TNF: tumor necrosis factor
Adapted from resource 9: Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*. 2016 Jan;68(1):1-25

3. Sulfasalazine, or SSZ; and
4. Hydroxychloroquine, or HCQ.⁹

MTX remains the preferred first-line agent and should be initiated as soon as the disease is diagnosed.⁹ If MTX is contraindicated or not tolerated, LEF, SSZ or HCQ also can be considered as alternative therapy. If disease activity — as measured by one of the six validated indices recommended by the ACR RA panel — is moderate or high after DMARD monotherapy, combination (double or triple) DMARD therapy may be considered (see Table 4). Additionally, a TNF inhibitor plus or minus MTX, or a non-TNF inhibitor plus or minus MTX, may be considered. If a patient has failed either DMARD monotherapy or biologic therapy (plus or minus MTX) with moderate to high disease activity, the patient should then be treated based upon the established RA guidelines. It is important to note that throughout the early and established RA guidelines, patients also may use short-term glucocorticoids (≤ 10 mg/day of prednisone or equivalent). Glucocorticoids have been shown to reduce synovitis in the short-term and decrease joint damage long-term.^{43,95} However, the risk versus benefit does not support routine use due to such adverse effects as infection and osteoporosis. Thus, they are typically used for less than three months for disease flare-ups and to allow other slow-acting therapies, such as DMARDs, to take effect. Intra-articular glucocorticoids also have been shown to be effective for local treatment of specific active joints.^{43,96}

DMARD biologics

Biologic agents include monoclonal antibodies and recombinant receptors to block cytokines that promote the inflammatory cascade (see Table 6).⁵³ TNF inhibitors are

first-line among biologic therapy (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) followed by non-TNF inhibitors abatacept, rituximab and tocilizumab.⁴³ The biologic agents have been well-studied, and their efficacy has been established.^{43,97-103} Biological agents are recommended in patients who have moderate or high disease activity who are already on DMARD monotherapy. Combination with MTX is preferred due to superior combination efficacy over biologic monotherapy.⁹ Adverse effects include reactions and infections at infusion and injection sites.⁴³ TNF inhibitors pose serious risks for the development of tuberculosis. Patients will need a chest radiography or skin test before starting treatment. The PCP also will rule out hepatitis B and C before prescribing treatment with biologics. Infection is the main risk due to suppression of the immune system. Risk includes bacterial infections (i.e., sepsis, abscesses) fungal infections (i.e., candidiasis) and viral infections (i.e., herpes zoster).⁴³ Additionally, cancer risk, especially lymphoma, has been researched, and observed risk is increased in severe RA.¹⁰⁴

Tofacitinib

Tofacitinib is a targeted synthetic DMARD that was approved for the treatment of RA by the FDA in November 2012. It is a novel drug that inhibits janus kinase, or JAK, an intracellular enzyme that regulates cytokine-receptor mediated functions on the cellular membrane.⁹² The 2015 ACR RA panel has a conditional recommendation in early RA to use TNF inhibitor monotherapy over tofacitinib monotherapy, and TNF inhibitor plus or minus MTX over tofacitinib plus or minus MTX, due to low quality of evidence, long-term safety concerns need-

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Table 5
Comparison of available disease modifying anti-rheumatic drugs for the treatment of rheumatoid arthritis

MEDICATION CLASS	MEDICATION	PHARMACOLOGY	DOSE AND ROUTE	DOSE	ADVERSE EFFECTS
Traditional DMARDs	Auranofin*	Gold salt; unknown mechanism	Oral	3 mg to 6 mg daily or 3 mg twice daily	Diarrhea Hypersensitivity reactions
	Azathioprine*	Antiproliferative to T- and B-cells	Oral	50 mg to 200 mg daily	Hepatotoxicity Myelotoxicity GI toxicity
	Cyclosporine*	Calcineurin inhibitor decreases IL-2	Oral	2.5 mg/kg to 5 mg/kg per day	Nephrotoxicity Hypertension Hirsutism
	Hydroxychloroquine	Interferes with antigen processing an immune function	Oral	200 mg to 400 mg daily	Rare ocular toxicity (retinopathy)
	Leflunomide	Antimetabolite	Oral	10 mg to 20 mg daily	Hepatotoxicity Myelotoxicity Hypertension Teratogenesis
	Methotrexate	Antimetabolite	Oral or Sub-Q	7.5 mg to 25 mg weekly	Hepatotoxicity Myelotoxicity Hair loss Teratogenesis
	Sodium aurothiomalate	Gold salt with unknown mechanism	IM	50 mg weekly	Hypersensitivity reactions Nephritis Fibrosing alveolitis
	Sulfasalazine	Anti-inflammatory/antimicrobial	Oral	1000 mg to 1500 mg twice daily	Hepatotoxicity Myelotoxicity Hypersensitivity reactions Anemia in G6DP deficiency
Biologic TNF inhibitors	Adalimumab	Human mab	Sub-Q	40 mg every two weeks	Injection-site reactions Opportunistic infections TB
	Certolizumab pegol	Pegylated Fab fragment from humanized mab	Sub-Q	200 mg every two weeks or 400 mg monthly	Injection site reactions opportunistic infections TB
	Etanercept	Recombinant TNF receptor (p75) dimerized on IG frame	Sub-Q	50 mg weekly or 25 mg twice weekly	Injection-site reactions Opportunistic infections TB
	Golimumab	Human mab	Sub-Q	50 mg or 100 mg every four weeks	Injection-site reactions Opportunistic infections TB
	Infliximab	Chimeric mab	IV	3 mg/kg (weeks zero, two and six) then 3 mg/kg to 10 mg/kg every four to eight weeks	Infusion reactions Opportunistic infections TB
Non-TNF biologics	Abatacept	Recombinant CTLA4 molecule dimerized on IG frame; Blocks T-cell costimulation and Th17 cell response/IL-6	IV then Sub-Q (can give Sub-Q without loading dose)	8 mg/kg to 10 mg/kg at weeks zero, two and four then monthly or 500 mg to 1000 mg IV loading dose then 125 mg Sub-Q within a day, then once weekly	Infusion reactions Opportunistic infections
	Anakinra**	Recombinant IL-1 receptor antagonist	Sub-Q	100 mg daily	Injection-site reactions Opportunistic infections Neutropenia
	Rituximab	Chimeric mab to CD20 for B-cell depletion	IV	1000 mg in two infusions, two weeks apart, repeating every four to eight months	Infusion reactions Opportunistic infections
	Tocilizumab	Humanized mab, IL-6 receptor blockade	IV	8 mg/kg every four weeks	Infusion reactions Opportunistic infections Elevated cholesterol
	Tofacitinib	Cytokine inhibitor	Oral	5 mg twice daily	Serious infections Malignancy Elevated cholesterol Neutropenia

*Not included in the 2015 ACR RA Guidelines due to infrequent use in RA and/or lack of data since 2012

**Not included in the 2015 ACR RA guidelines due to infrequent use in RA and/or lack of data since 2012

Mab = GI= gastrointestinal, Sub-Q = subcutaneous, IV= intravenous, mab= monoclonal antibody

Information from resources 12 and 54

ing further study and shorter experience using tofacitinib.⁹ In established RA, tofacitinib is again conditionally recommended

as a last-line agent for the same reasons cited in early RA.⁹ A 2016 Cochrane review concluded that TNF-inhibitors were superior

to anakinra and tofacitinib in patients with incomplete response to methotrexate or other traditional DMARDs.¹⁰⁶ The au-

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thors cite that there are very few head-to-head, randomized control trials of biologic agents in patients with RA, and that further research is needed to evaluate the role of tofacitinib and its long-term safety. The safety of tofacitinib also is a FDA concern, as a Risk Evaluation and Mitigation Strategy, or REMS, document was issued in 2015 that highlighted concerns for serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts, hemoglobin and increases in lipid panel parameters associated with tofacitinib.¹⁰⁶

CONCLUSION

In conclusion, there are millions of adult patients within the United States who suffer from arthritis. Two of the most common forms of arthritis — osteoarthritis and rheumatoid arthritis — can present with similar risk factors and clinical presentation. In order for patients to receive the proper treatment, patients should be thoroughly evaluated, and additional tests should be conducted as necessary to aid in diagnosis. Early diagnosis has been shown to improve outcomes in both disease states, and treatment guidelines have updated accordingly with aggressive new strategies aiming to reduce erosive joint damage and advanced disease. Research in both disease states must be continued to further the development of novel drug treatment options to meet goals of therapy and improve patient's quality of life. Technicians

PRACTICE POINTS: OSTEOARTHRITIS

- Osteoarthritis is the most prevalent joint disease in the United States, affecting approximately 27 million Americans.⁴⁻⁷
- Osteoarthritis commonly is referred to as a “wear-and-tear” disorder of the joints, focusing on the loss of cartilage; however, now it is widely accepted that the disease process involves the entire joint.¹⁹
- Obesity is one of the most important preventable risk factors for the development of OA.⁵⁻⁶
- It is important to note that while OA occurs from a combination of factors, including excessive mechanical stress, it is not a guaranteed outcome of aging.²⁶
- Pain generally is characterized by patients as deep and aching, and the stiffness or pain usually resolves in less than 30 minutes.
- All patients with OA should receive patient education about the disease process, treatment and prognosis.

PRACTICE POINTS: RHEUMATOID ARTHRITIS

- Rheumatoid arthritis is the most common systemic inflammatory autoimmune disease in the United States.⁸⁻⁹
- More recently, RA has been regarded as a clinical syndrome with several disease subsets that involve multiple inflammatory cascades that converge into a final pathway leading to characteristic RA damage.⁴³
- Genetic factors account for 50% of risk associated with RA development.^{17,43}
- Gene and environmental interactions result in the loss of self-tolerance, driving the influx of inflammatory mediators and the characteristic destructive processes seen in rheumatoid arthritis.
- Morning stiffness that lasts longer than one hour is a defining characteristic of RA.
- NSAIDs have lost their first-line treatment due to concerns of limited efficacy, inability to prevent long-term bone/cartilage damage, and gastrointestinal and cardiovascular side effects.^{43,89-90}

in the community pharmacy can assist pharmacists in identifying patients who may not be adherent to their medications or requiring additional information from the pharmacist.

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Learning Assessment

Successful completion of “A technicians’ guide to osteoarthritis and rheumatoid arthritis in adults” (0401-0000-16-207-H01-T) is worth 1.5 contact hours of credit. To submit answers, visit our website at www.DrugStoreNewsCE.com. Please note: Assessment questions submitted online will appear in random order.

- The risk of arthritis increases with age. Two-thirds of people with arthritis actually are younger than which of the following ages?**
 - 45 years of age
 - 55 years of age
 - 65 years of age
 - 75 years of age
- Men are more likely to be affected by osteoarthritis than women after the age of 50 years.**
 - True
 - False
- What percentage of patients are work disabled within between two years and five years of being diagnosed with RA?**
 - 30% (two years); 50% (five years)
 - 40% (two years); 60% (five years)
 - 50% (two years); 70% (five years)
 - 60% (two years); 80% (five years)
- Obesity is the most important preventable risk factor for the development of osteoarthritis.**
 - True
 - False
- Which risk factor for the development of RA accounts for approximately 50% of risk?**
 - Age
 - Genetics
 - Environment
 - Gender
- Although pain in advanced disease can occur during rest, the deep, aching stiffness that is associated with osteoarthritis usually resolves in 30 minutes or less.**
 - True
 - False
- Which of the following is not a hallmark characteristic of rheumatoid arthritis?**
 - Bony erosions
 - Cartilage damage
 - Crepitus
 - Synovial hyperplasia
- Patients who are identified earlier in the RA disease process have not been found to have improved outcomes with respect to erosive joint damage and extra-articular disease.**
 - True
 - False
- Which two treatment categories should patients with osteoarthritis receive?**
 - Complementary/alternative and non-pharmacologic
 - Non-pharmacologic and surgical
 - Pharmacologic and surgical
 - Non-pharmacologic and pharmacologic
 - Complementary/alternative and pharmacologic
- In 2015, the Food and Drug Administration strengthened the warning for NSAIDs on OTC and prescription labels due to the risk of which of the following conditions?**
 - Heart attack and stroke
 - Heart attack and GI risk
 - Stroke and GI risk
 - None of the above
- Glucosamine and chondroitin are effective options for the reduction of pain in patients with osteoarthritis.**
 - True
 - False
- NSAIDs lost their first-line treatment status due to limited efficacy, inability to prevent long-term bone/cartilage damage and adverse effects.**
 - True
 - False
- Which of the following traditional DMARDs is the preferred first-line agent in patients with RA, regardless of disease activity level, and should be initiated as soon as the patient is diagnosed?**
 - Hydroxychloroquine
 - Leflunomide
 - Methotrexate
 - Sulfasalazine
- Pre-treatment screening is required in all patients in whom a TNF inhibitor is initiated to rule out which of the following conditions?**
 - Candidiasis
 - Herpes zoster
 - Sarcoidosis
 - Tuberculosis
- Which of the following is the novel biologic agent approved by the FDA in 2012 for the oral treatment of rheumatoid arthritis?**
 - Anakinra
 - Etanercept
 - Rituximab
 - Tofacitinib