Pharmacist Guide to Patients' Frequently Asked Questions

As Developed From

State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age

Presented by:
The U.S. Department of Health and Human Services Office on Women's Health

In cooperation with

American Academy of Nurse Practitioners

Co-sponsored by the American Pharmacists Association (APhA) Improving medication use. Advancing patient care. and SynerMed® Communications

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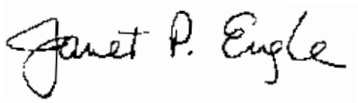
Dear Colleague,

Pain is highly prevalent in the general population and is often managed by self-medication. Selecting appropriate pain relief is not easy for most consumers, as they are bombarded with advertising, faced with shelves full of products targeting various symptoms, and far too often fail to read the product labels. Many consumers are unaware of the differences between over-the-counter (OTC) analgesics and assume that if a prescription is not needed, the medication must be safe and effective.

As a pharmacist, I understand what an important role the pharmacist plays in ensuring that consumers select appropriate OTC medications for their pain. The enclosed Pharmacist Guide to OTC analgesia was developed from presentations and discussions about the management of mild-to-moderate pain that took place at a recent educational program presented by the US Department of Health and Human Services Office on Women's Health. The guide is organized in 3 sections: (1) a brief overview of OTC analgesics, (2) a case-based discussion of OTC analgesic use in common pain conditions, and (3) a case-based discussion of analgesic use in special populations. Enclosed within the guide are patient education leaflets (3 one-sided sheets) that can be copied and distributed in order to teach consumers about properly managing their mild-to-moderate pain. This guide was designed to provide pharmacists with relevant information needed to assist consumers in OTC analgesic selection, including current data regarding the safety and efficacy of available agents, as well as strategies to identify patients at greatest risk for experiencing adverse gastrointestinal, renal, hepatic, or cardiovascular effects.

I encourage you to take advantage of this continuing pharmacy education activity co-sponsored by the American Pharmacists Association and SynerMed® Communications and supported by an educational grant from McNeil Consumer & Specialty Pharmaceuticals. By providing consumers with proactive consultation, we can better ensure safe outcomes while effectively treating their pain.



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INTENDED AUDIENCE
Pharmacists

LEARNING OBJECTIVES
Upon completion of this activity, pharmacists should be able to:

- Educate patients on the safe use of OTC pain medications
- Identify the various issues related to common medical conditions associated with mild-to-moderate pain
- Recognize the impact of common pain conditions and special patient populations in making safe therapeutic recommendations for mild-to-moderate pain
- Explain the risks and benefits of commonly used analgesics in the management of mild-to-moderate pain
- Assess the potential for adverse effects and drug-to-drug interactions with concomitant use of OTC analgesics

ACCREDITATION INFORMATION

The American Pharmacists Association and SynerMed® Communications have co-sponsored to provide continuing pharmacy education credit for the "State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age – Pharmacist Guide to Patients' Frequently Asked Questions."

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The participant should, in order, read the monograph, answer the 15-question, multiple-choice posttest, and complete the Registration/Evaluation form. To receive credit for successful completion, please mail your completed answer sheet to: American Pharmacists Association, Education Services, Lockbox #4472, P.O. Box 85080, Richmond, VA 23285-4472.

You also can go to **www.pharmacist.com** and take your test online for instant credit. A Statement of Credit will be awarded for a passing grade of 70% or better. Pharmacists who complete this exercise successfully before May 31, 2007 can receive credit.

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DISCLAIMER
State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age, as published in this *Pharmacist Guide to Patients' Frequently Asked Questions* monograph, is a certified continuing pharmacy education activity providing an in-depth, expert review and analysis of recent scientific advances and clinical controversies in the management of mild-to-moderate pain. The views presented are those of the faculty and/or contributing editors and not necessarily those of the producer, commercial supporter, the US Department of Health and Human Services Office on Women's Health, or the American Pharmacists Association. Some information presented in this monograph may be off label. Before recommending any product discussed in this publication, pharmacists should consult the full prescribing information.

State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age was a roundtable discussion presented by the US Department of Health and Human Services Office on Women's Health, under the auspices of the University of Colorado School of Medicine, and in cooperation with the American Pharmacists Association, the American Geriatrics Society, and the American Academy of Nurse Practitioners.

This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, healthcare professionals and other individuals should review and consider other publications and materials about the subject and not rely solely upon the information contained within this publication.

Section 1: OTC Analgesia for Mild-to-Moderate Pain

Section 1: OTC Analgesia for Mild-to-Moderate Pain

Every day, pharmacists are faced with the increasingly complex challenge of helping patients choose appropriate over-the-counter (OTC) medications to treat a variety of conditions. Patients must select from a wide array of products—more than 100,000 products with approximately 1000 active ingredients are marketed in the United States.[1] Optimal product selection is not only dependent on medication properties and indications, but also on patient characteristics such as age, concomitant conditions, and current medications.

Analgesics are among the most commonly utilized OTC medications. Approximately $3 billion per year is spent on OTC analgesics.[2] In 2001, several analgesics appeared in the top-25 sales list, including acetaminophen (Tylenol®), acetaminophen and aspirin (Excedrin®), aspirin (Bayer®), ibuprofen (Advil®, Motrin® IB), and naproxen sodium (Aleve®).[3]

Despite the numerous analgesic products on pharmacy shelves in the United States, there are only 5 active analgesic ingredients: acetaminophen, aspirin, ibuprofen, ketoprofen, and naproxen sodium. Acetaminophen is a simple analgesic and antipyretic. The others are nonselective nonsteroidal anti-inflammatory drugs (NSAIDs); however, they exert their anti-inflammatory effects only at prescription doses. Each of these agents possesses unique properties that affect their suitability for individual patients. The following review highlights important information about these agents that can help pharmacists recommend appropriate analgesic therapies for individual patients, including analgesic, antipyretic, and anti-inflammatory potency, indications and contraindications, dosing, side effects, effects on concomitant diseases or conditions, and drug-to-drug interactions.

Pharmacists play an important role in ensuring that OTC analgesics are used appropriately. Careful consideration of patient characteristics (eg, age, condition to be treated, concomitant conditions and therapies) and medication profiles (safety, tolerability, efficacy) should guide analgesic choice. Specific patient questions in Sections 2 and 3 highlight these important issues that pharmacists face daily when recommending OTC analgesics.

Acetaminophen

Acetaminophen has both analgesic and antipyretic properties, and is commonly used to treat fever as well as pain. Its analgesic mechanism has not been fully understood; however, it is believed to increase the pain threshold within the brain.[4] Acetaminophen reduces fever via direct action on hypothalamic heat-regulating centers (increasing dissipation of body heat) and inhibits the action of endogenous pyrogens. Acetaminophen produces minimal effects on prostaglandin synthesis; however, greater inhibition has been observed in the central nervous system (CNS) versus the periphery.[5] Its analgesic/antipyretic potency is similar to that of aspirin; it is devoid of anti-inflammatory effects.

Patient Selection

Acetaminophen can be safely recommended for most patients requiring an analgesic for the management of mild-to-moderate pain, including many of those who have conditions that prohibit the use of aspirin or other OTC NSAIDs. Cross-sensitivity between salicylates and acetaminophen is rare, so acetaminophen can generally be recommended in patients who are allergic to aspirin or who have conditions commonly associated with aspirin hypersensitivity such as nasal polyps, asthma, or chronic urticaria.[6] Acetaminophen has a lower risk for gastrointestinal (GI) complications and bleeding than does aspirin or other OTC NSAIDs.[7-9] This makes acetaminophen the optimal choice for patients at increased risk for GI toxicity such as older patients, patients with a history of GI bleeding, and patients who use anticoagulants or corticosteroids.[10-12] Acetaminophen is rated FDA pregnancy Category B. Drugs in this category can be recommended for occasional use for women in any stage of pregnancy. Acetaminophen also can be recommended for women who are breast-feeding; it is excreted in the breast milk in low concentrations, but no adverse events in nursing infants have been reported.[13] Finally, acetaminophen is not associated with the development of Reye's syndrome in children with febrile viral illnesses and is safe to recommend for children during the flu and chickenpox seasons.[14]

The American Geriatrics Society recommends acetaminophen as first-line therapy for mild-to-moderate pain in elderly patients,[15] and the American College of Rheumatology recommends acetaminophen as initial pharmacologic therapy for patients with osteoarthritis, the most common form of arthritis in the United States.[16] These recommendations are largely based on the accepted efficacy of acetaminophen in relieving noninflammatory pain and its relative safety, especially in older patients. The National Kidney Foundation also considers acetaminophen the OTC analgesic of choice for patients with underlying renal disease due to its safe GI profile and because it does not inhibit renal prostaglandin synthesis.[17] Acetaminophen is also considered a preferred OTC analgesic for patients with cardiovascular disease and with chronic liver disease. Acetaminophen has been studied in adults with chronic liver disease using single and multiple therapeutic doses.[18, 19] These studies have demonstrated no evidence of hepatotoxicity or adverse clinical reactions to acetaminophen. At recommended doses, acetaminophen can be used safely in patients with chronic liver disease. Furthermore, acetaminophen is available in a wide selection of dosage forms

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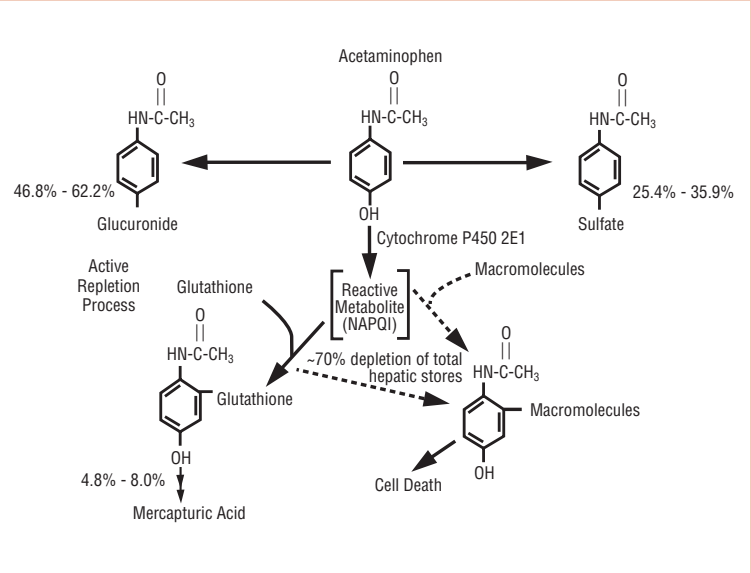
(tablets, caplets, chewable tablets, liquids, and suppositories) and is relatively inexpensive, attributes that may improve compliance and acceptability in all patients.

Dosing

Appropriate acetaminophen dosing is dependent on the dosage form selected and the age of the patient. Consumers are often confused by the differences in formulations, especially those designed for infants and children. The distinction between these preparations is an important one, as infants' drops are considerably more concentrated than most children's suspensions, liquids, and elixirs. Oral doses in adults should not exceed 4 g daily.

Figure 1 **Acetaminophen metabolism**



NAPQI, *N*-acetyl-*p*-benzoquinone imine.

Side Effects

Acetaminophen has no known GI, renal, or cardiovascular side effects at recommended doses. Hypersensitivity has been reported, most commonly as rash.[6] Rare cases of neutropenia, thrombocytopenia, and pancytopenia with acetaminophen have been reported.

Overdose

Acute liver damage may occur when massive overdoses of acetaminophen are ingested. In such situations, the metabolic pathways (Figure 1) can be altered, and the ability to detoxify *N*-acetyl-*p*-benzoquinone imine (NAPQI), a highly reactive intermediate, may be insufficient.[20] The oral administration of acetylcysteine can reduce the progression of acute acetaminophen toxicity when administered promptly (within 24 hours of ingestion), most likely by replenishment of glutathione and subsequent restoration of the ability to detoxify NAPQI.[6] It is important to note that even in overdose situations, the incidence of acetaminophen-associated acute liver damage is relatively low.[21]

Drug-to-Drug Interactions

Acetaminophen is an appropriate choice for analgesia in patients who are taking other medications, as few significant drug-to-drug interactions have been identified. Acetaminophen is a preferred analgesic because of its lack of platelet effects. There is conflicting evidence regarding the potential increased risk of excessive anticoagulation with acetaminophen therapy. Therefore, it would be prudent to recommend frequent international normalized ratio monitoring in patients receiving concomitant warfarin therapy.[22, 23]

Patient Counseling

Consumers purchasing OTC analgesics should be advised that fever and pain lasting longer than 5 days in children, and 10 days in adults and should be evaluated by a physician, as it could be a sign of a more serious underlying condition. Patients who consume 3 or more alcoholic beverages daily also should seek the advice of their physician before taking any OTC analgesic. Importantly, consumers should be reminded to read the labels of all the medications they are taking, as many preparations contain multiple active ingredients.

Aspirin

Aspirin has antipyretic, analgesic, anti-inflammatory, and antiplatelet activity. Like acetaminophen, aspirin reduces fever by direct action on hypothalamic heat-regulating centers and inhibits the action of endogenous pyrogens.[6] The analgesic and anti-inflammatory properties of aspirin are mediated primarily through inhibition of the enzyme cyclooxygenase (COX), although direct effects within the CNS may also contribute to pain relief. COX catalyses the conversion of arachidonic acid into a number of compounds, including prostaglandins and thromboxanes, involved in normal physiologic functions and inflammation. Nonselective NSAIDs, such as aspirin, decrease the production of prostaglandins and thromboxanes by inhibiting the metabolism of arachidonic acid. The COX enzyme exists in 2 isoforms, COX-1 and COX-2, which perform different functions and are usually present in different

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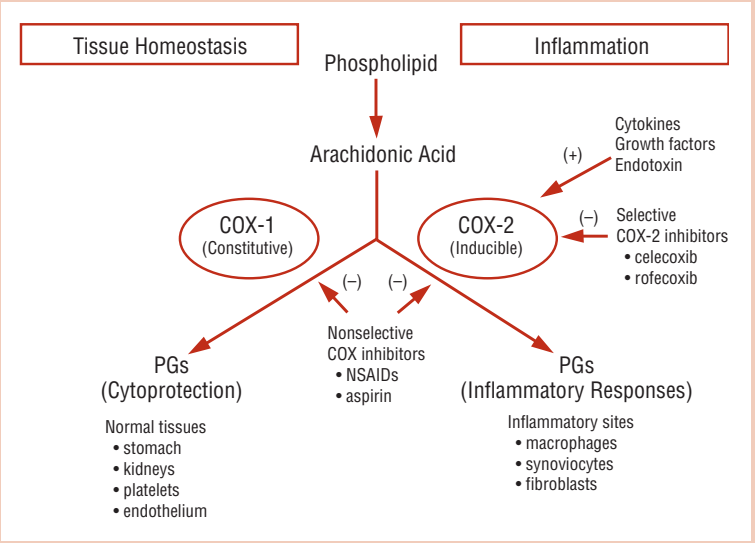
tissues (Figure 2).[24] Aspirin and other nonselective NSAIDs block the activity of both isoforms. COX-1 mediates prostaglandins that maintain the integrity of the GI mucosa and protect the surface epithelial cells. COX-2 induces proinflammatory prostaglandins, which cause the stiffness, swelling, and pain that accompany an illness or injury.

Aspirin inhibits platelet function by irreversible acetylation of platelet COX. Subsequent reductions in thromboxane A_2 production result in reduced platelet aggregation. This effect has beneficial cardiovascular implications, as it reduces the risk of myocardial infarction and other adverse cardiovascular outcomes[25-27]; however, it can result in prolonged bleeding in patients undergoing surgical procedures or who are receiving concomitant anticoagulant therapy.[28]

Figure 2 **Effects of NSAID on the arachidonic acid cascade[24]**



The role of cyclooxygenase isoforms 1 and 2 in normal and inflamed tissue.
NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; PGs, prostaglandins.
Adapted with permission from Stovitz SD, Johnson RJ. *Phys Sportsmed.* 2003;31:35-40.

Patient Selection

Whereas it is widely accepted that aspirin can effectively reduce pain, fever, and inflammation, it can cause serious toxicities, especially in certain at-risk populations. Many of its toxicities are related to its nonspecific activity on the arachidonic acid cascade, which results in decreased levels of both cytoprotective and inflammatory prostaglandins.

GI toxicity is a potentially serious complication that occurs more frequently in older patients, in patients with a history of GI bleeding, and in those who use corticosteroids concomitantly.[10-12] Even the low doses of aspirin typically used for cardioprotection are associated with an increased risk for GI bleeding.[29-31] Use of enteric-coated or buffered aspirin does not eliminate this risk. In one review of 550 incident cases of upper GI bleeding and 1202 controls, relative risks (95% confidence interval [CI]) associated with the regular use of low doses (≤325 mg) of plain, enteric-coated, and buffered aspirin products were 2.6 (1.7-4.0), 2.7 (1.4-5.3), and 3.1 (1.3-7.6), respectively.[32]

Aspirin may elevate blood pressure in hypertensive individuals; however, its propensity to exacerbate hypertension may not be as great as that of other NSAIDs.[33, 34] The pressor effects of NSAIDs are likely related to inhibition of prostaglandin synthesis (Figure 3), reduced renal vasodilation, increased sodium retention, peripheral vasoconstriction, and/or effects on the responsiveness to other substances that modify blood pressure such as renin or angiotensin II. Aspirin must be recommended with caution in patients with diminished renal function, as such patients may rely on renal prostaglandin production to maintain adequate kidney perfusion and function.[35]

Because aspirin irreversibly inhibits platelet function, it should be used with caution in patients at risk for bleeding (patients with severe liver damage, hypoprothrombinemia, vitamin K deficiency, or hemophilia), or who are taking other medications that can prolong bleeding time.[6]

Pregnant women or women who are breast-feeding should consult their physicians before taking aspirin. Aspirin ingestion during pregnancy can adversely affect the mother (eg, cause anemia, hemorrhage, prolonged gestation, or prolonged labor) and the fetus.[36] Because there is evidence of human fetal risk, aspirin is rated FDA pregnancy Category D.[37] Aspirin is excreted in the breast milk in low concentrations, a potential risk to nursing infants.

Aspirin is contraindicated in children and adolescents with febrile or viral illnesses, as its use in such patients has been associated with the development of Reye's syndrome, a potentially life-threatening acquired encephalopathy.[6]

Dosing

Aspirin dosing varies, not only with patient age and indication but also with product formulation. Lower

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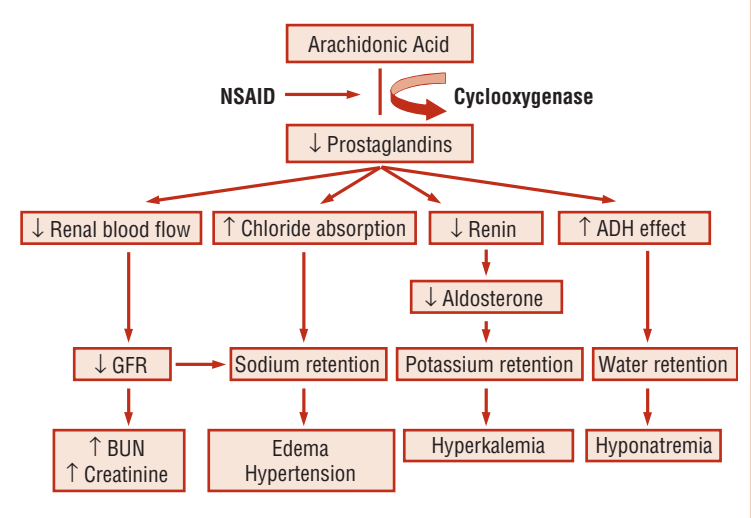
doses are typically recommended for cardioprotection and higher doses for analgesia. Because aspirin is available in a wide variety of formulations of varying concentrations, it is important for pharmacists to ensure that patients understand the proper dosing and administration of their chosen aspirin product.

Side Effects

In addition to the GI, cardiorenal, and hematologic effects discussed above, aspirin hypersensitivity can occur and is most common among individuals with nasal polyps, asthma, or chronic urticaria.[6] Pharmacists should question patients carefully about reported aspirin intolerance, as many patients who initially state that they are allergic to aspirin have experienced stomach upset or other GI discomfort, but do not suffer from true aspirin hypersensitivity.

Figure 3 **Renal effects of NSAID-mediated prostaglandin inhibition[35]**



NSAID, nonsteroidal anti-inflammatory drug; ADH, alcohol dehydrogenase; GFR, glomerular filtration rate; BUN, blood urea nitrogen.

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Overdose

Excessive doses of aspirin can result in a wide range of symptoms, ranging from headache, dizziness, and tinnitus in mild overdose to serious CNS disturbances and metabolic disorders that can lead to death in more severe intoxication.[6] Caution should be exercised in patients with renal or hepatic dysfunction, as well as in children with fever and dehydration, as they are more prone to salicylate intoxication than otherwise healthy individuals.

Drug-to-Drug Interactions

Aspirin can interact with a variety of commonly prescribed medications, including other NSAIDs (increased GI toxicity, decreased NSAID concentrations); oral anticoagulants and heparin (prolonged bleeding); oral hypoglycemics and insulin (potentiated hypoglycemic effects); methotrexate (methotrexate toxicity); nitroglycerin (hypotension); angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics (blunted antihypertensive effect); probenecid and sulfinpyrazone (decreased uricosuric effect); and lithium and valproic acid (lithium and valproic acid toxicity).[37]

Patient Counseling

In addition to the general patient counseling recommendations for all OTC analgesics described above, patients considering aspirin therapy should be advised to take the drug with food or milk (or at least a full glass of water) and avoid lying down for 15 to 30 minutes after each dose to avoid esophageal irritation.[13] They should be further advised to contact their physician if they experience new-onset hearing problems, shortness of breath, or bleeding, all of which may be early signs of salicylate toxicity.

Aspirin can degrade over time, so patients should be told to dispose of any product that develops a strong vinegar odor, an indication the product is outdated.

Nonsalicylate OTC NSAIDs (Ibuprofen, Ketoprofen, Naproxen Sodium)

Like aspirin, the nonsalicylate OTC NSAIDs are nonspecific inhibitors of COX and have analgesic, antipyretic, and anti-inflammatory activities. The anti-inflammatory activities of NSAIDs are generally negligible at recommended OTC doses, but healthcare providers commonly suggest higher doses in order to achieve anti-inflammatory effects; however this can increase the risk for NSAID-related GI side effects.[16] OTC NSAIDs do not produce the same antiplatelet effect as aspirin (binding to COX is reversible and antiplatelet effects are short lived), and are not considered useful for cardioprotection.[38, 39]

Patient Selection

Like aspirin, NSAID therapy is considered generally effective for mild-to-moderate analgesia, but poses excessive risks in certain patient populations. Patients who are older, who have a history of GI bleeding, or who

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use corticosteroids are at increased risk for serious GI events (Figure 4).[10, 12, 40-42] Patients who regularly consume alcohol may also have increased risk.[8, 43]

Patients with renal insufficiency, congestive heart failure, or hypertension are at increased risk of cardiorenal toxicity with NSAIDs.[33-35] Patients with such conditions likely rely more heavily on renal prostaglandins to maintain normal renal blood flow and function than otherwise healthy individuals. Use in patients with such risks could result in reduced renal function and/or exacerbation of hypertension and heart failure.

Women who are pregnant or nursing should discuss potential OTC NSAID use with their physicians prior to initiating therapy, especially in light of a recent population-based cohort study.[44] Data regarding the use of NSAIDs and other nonprescription analgesics were collected from 1063 pregnant women who were members of a single healthcare delivery system in northern California. Pregnancy outcomes (successful carriage or miscarriage) were determined for a period of up to 20 weeks (the time period during which miscarriages occur). Of the 1055 women who provided complete information during their interviews, 53 (5%) reported using NSAIDs since their last menstrual period. After adjusting for potential confounding factors (Cox proportional hazard regression analysis), an association between prenatal NSAID use was detected (adjusted hazard ratio, 1.8%; 95% CI, 1.0 to 3.2). The risk of miscarriage was greatest among women who had used NSAIDs around the time of conception (adjusted hazard ratio 5.6; 95% CI 2.3 to 13.7) or had used NSAIDs for a period of more than 1 week (adjusted hazard ratio 8.1; 95% CI 2.8 to 23.4).[44] OTC NSAIDs are rated FDA pregnancy Category B during the first and second trimesters of pregnancy and Category D during the third, and are generally preferred over aspirin (but after acetaminophen) in breast-feeding women.[36]

Dosing

Doses of OTC analgesics are product specific. However, patients may be inclined to use higher doses (or were instructed to by their physicians). Pharmacists should caution patients against this practice, as higher doses are associated with greater risk for GI complications.

Side Effects

In addition to the toxicities discussed above (GI, hematologic, and renal), OTC NSAIDs can cause drowsiness or dizziness.

Drug-to-Drug Interactions

OTC NSAIDs can potentially interact with a number of commonly prescribed medications, including diuretics and ACE inhibitors.[45] When used chronically, NSAIDs can negate the cardioprotective effects of low-dose aspirin by reducing the inhibitory effects of aspirin on platelet aggregation.[38, 46]

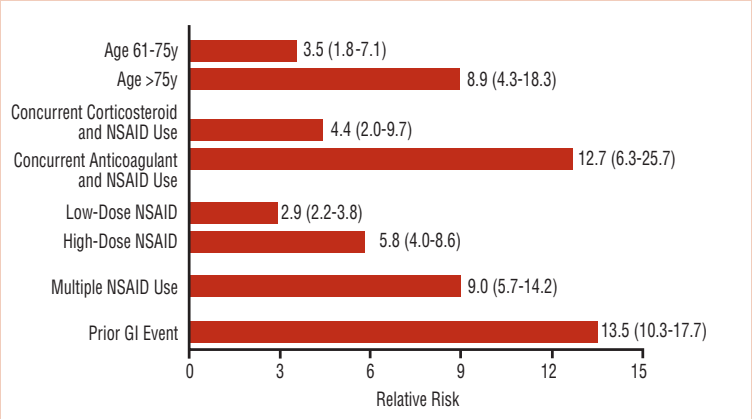
Patient Counseling

In addition to the general patient counseling recommendations for all OTC analgesics described above, patients considering OTC NSAID therapy should be advised to take the medication with food or milk (or at least a full glass of water) and avoid lying down for 15 to 30 minutes after each dose to avoid esophageal irritation.[13] Because ibuprofen and ketoprofen have shorter half lives than naproxen sodium, they may be preferable in patients at risk for NSAID toxicities.

Combination Products

Combination OTC analgesic and cough and cold preparations pose a particular risk to consumers. Combined use of 2 or more products can result in inadvertent excess dosing, increased side effects, and drug-to-drug interactions. Common ingredients in combination preparations include caffeine (which may improve analgesia, but can interfere with sleep, increase blood pressure, or aggravate peptic ulcer disease), antihistamines (which may improve analgesia, but can cause drowsiness), and decongestants (which can cause excitation and aggravate hypertension). Pharmacists can help guide consumers through the selection process to ensure that they purchase a product that will treat their symptoms without exposure to excessive doses or unnecessary agents.

Figure 4 **Risk factors for serious GI adverse events with NSAIDs: Relative Risks[10,12,40-42]**



GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Section 2: Common Pain Conditions

Section 2: Common Pain Conditions

Q Osteoarthritis

Question 1: A 72-year-old, sedentary woman who is 50 pounds overweight has recently been diagnosed with osteoarthritis (OA) in her knees and hips. She has no other health conditions and is not taking any other medications. She is a social drinker and does not smoke. She asks her pharmacist why her family doctor is recommending OTC acetaminophen for her OA pain: "Shouldn't I be taking a prescription pain medication for arthritis pain?"

A Answer 1: The American College of Rheumatology recommends acetaminophen as initial drug therapy for OA, the most common form of arthritis.[16] The efficacy of acetaminophen in mild-to-moderate joint pain has been shown to be similar to that afforded by NSAIDs.[16] It is generally safe and well tolerated, and is relatively inexpensive.

Patients sometimes perceive acetaminophen as a less effective drug than other OTC analgesics. However, in OA, pain relief provided by acetaminophen is generally comparable to that of OTC NSAIDs.[16, 47] Anti-inflammatory activity is usually not necessary to achieve adequate symptom relief, as most patients with OA experience no inflammation or only mild inflammation that is localized to the joint.[16] However, recommended doses of OTC NSAIDs are inadequate to provide anti-inflammatory effects and, thus, confer no advantage over acetaminophen.

Safety and tolerability issues are of particular concern in the population most susceptible to OA—the elderly.[48] Many of these patients have conditions that may predispose them to risks, such as hypertension,[33, 34] heart failure,[35] and diminished renal function,[35] which are typically associated with NSAID therapy. Older patients are more likely to experience GI side effects or bleeding with NSAIDs than younger patients,[11, 12] and are more likely to be taking medications chronically that could potentially interact with NSAIDs such as diuretics and ACE inhibitors.[45] Acetaminophen is an excellent choice in these patients because it has few significant drug interactions, and at recommended doses, it is rarely associated with adverse cardiovascular[6] or renal effects.[35] Furthermore, it is associated with a lower risk for GI complications than NSAIDs.[7-9] There is conflicting evidence regarding the potential increased risk of excessive anticoagulation with acetaminophen therapy. Therefore, it would be prudent to recommend frequent INR monitoring after initiation of acetaminophen in patients receiving concomitant warfarin therapy.[22, 23]

As with any drug therapy for OA, acetaminophen should be used in conjunction with nondrug therapies recommended by their physicians such as weight loss (in overweight patients), physical therapy, exercise programs, assistive devices, and participation in self-management programs.[16, 47]

Q Osteoarthritis

Question 2: The patient described in question 1 returns months later complaining that she is taking acetaminophen for her arthritis and is still having trouble with pain and stiffness. What options are available for her and how does she choose the best one?

A Answer 2: Before recommending additional therapies, the pharmacist should first confirm that the patient is consistently taking the drug at recommended dosage intervals. If pain persists despite proper administration, the patient should be referred back to her physician for re-evaluation.

OTC NSAIDs can be recommended for additional relief in patients waiting to see their physicians or for those with advanced OA; however, it is important to first evaluate risks for GI and renal toxicity.[16] Risk factors for NSAID-associated GI toxicity include advanced age (≥65 years), comorbid medical conditions (eg, hypertension, congestive heart failure), history of peptic ulcer disease or upper GI bleeding, or concomitant oral corticosteroid or anticoagulant therapy. Smoking and alcohol consumption may also increase the risk for GI toxicities with NSAIDs; however, the relationship is not as clear. Patients with intrinsic renal disease may be at increased risk for reversible renal failure with NSAID therapy, especially those who are older (≥65 years), have hypertension and/or congestive heart failure, or are taking diuretics or ACE inhibitors. If the patient has minimal risk for such toxicities, OTC NSAIDs can be recommended as add-on or alternative therapy in such patients.

Topical alternatives can be recommended in patients who are not candidates for oral OTC NSAID therapy. Capsaicin cream has been shown to relieve pain in patients with OA, but is often associated with local discomfort (burning sensation).[16]

While widely advertised to consumers, the role of dietary supplements in OA treatment remains unclear. The long-term oral administration of glucosamine sulfate has been shown to improve symptoms, including pain relief, in two 3-year clinical trials.[49, 50] Beneficial effects on disease progression were also reported. However, the place of this and other supplements remains controversial, especially since available products can contain significantly different amounts of active ingredients.[51]

Patients who are not candidates for additional OTC therapies should be reassured that prescription alternatives are available. These include COX-2 inhibitors, combination therapy with NSAIDs and cytoprotective agents (eg, misoprostol or proton pump inhibitors), nonacetylated salicylates, tramadol, opioids, or intraarticular glucocorticoids or hyaluronan.[16]

Q&A

Q Osteoarthritis

Question 3: Weeks later, the patient from question 1 returns again and says she heard some commercials on TV for COX-2 inhibitors and asks her pharmacist why the new COX-2 inhibitors were not recommended initially as first-line therapy for her OA.

A Answer 3: Drug selection involves the consideration of a number of factors, including efficacy, safety, convenience, and cost-effectiveness. Additional considerations include an individual's preference and/or ability to pay for certain medications.

The COX-2 inhibitors (ie, celecoxib, rofecoxib, valdecoxib) have demonstrated efficacy comparable to nonselective NSAIDs in the treatment of OA and are commonly reserved for patients who do not respond to first-line OTC therapy, who cannot tolerate nonspecific NSAIDS, who are undergoing surgery, or who are receiving concomitant warfarin therapy.[16] COX-2 inhibitors may be desirable in such patients because they appear to have a more favorable GI profile than nonselective NSAIDs,[16, 52] although they are not without GI risk. COX-2 inhibitors do not affect platelet aggregation or bleeding.[38] Like nonspecific NSAIDs, COX-2 inhibitors can cause renal toxicity and should be used with caution in at-risk patients (patients with hypertension, congestive heart failure, or mild-to-moderate renal insufficiency) and avoided in patients with severe renal insufficiency.[16]

The COX-2 inhibitors are relatively expensive; celecoxib costs approximately $2/day and rofecoxib costs approximately $1.50/day. Some patients are unable or unwilling to pay for such expensive therapies. COX-2 inhibitors are not universally part of all drug plan formularies, meaning that patients must sometimes pay high prices for them even if they have prescription drug coverage. Indiscriminate prescribing of such expensive therapies can also, over time, trigger increases in premiums and copays for prescription drug coverage.

Economic decisions regarding the use of a COX-2 inhibitor, rather than a nonselective NSAID, transcend more than just the cost of the drug. Several other factors, including GI risk profile and the use of concomitant aspirin for cardioprotection must be taken into account to realize the total cost implications. Pharmacists can help counsel patients on the economic consequences of NSAID use by realizing that first-line use of COX-2 inhibitors for moderate-to-severe arthritis pain may not be cost-effective in patients with average risk for GI complications.

For those who do not respond to acetaminophen, the incremental cost to prevent an NSAID-related ulcer is closely linked to a patient's risk for NSAID-related adverse events. Data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) indicate that serious GI complications occur in 7.3 of every 1000 patients with OA and 13 of every 1000 patients with rheumatoid arthritis who take prescription NSAIDs for 1 year.[53] In the United States, these events lead to approximately 100,000 additional hospitalizations and 16,500 deaths annually. The majority of these events occurred with no prior symptoms. Management of NSAID-related GI toxicities accounts for nearly one third of the annual cost of caring for patients with arthritis.[54] The annual direct costs of treating serious GI complications exceed $2 billion annually.[53]

Studies have assessed the role of initial NSAID choice and patient risk for the development of adverse GI complications[55, 56] using symptom-driven, decision analytic models to compare treatment strategies. Results show that although the use of a COX-2 inhibitor leads to a reduction in clinically important GI complications the incremental costs to achieve these benefits are closely linked to a patient's risk for developing an adverse event. The evidence that COX-2 inhibitors should be reserved for patients at high risk for GI complications reflects their acceptable incremental cost-effectiveness ratio for high-risk patient groups, as they can reduce complication costs.[55, 57] This further underscores the importance of identifying NSAID users at increased risk for adverse events.

Section 2: Common Pain Conditions

Q&A

Q Dysmenorrhea

Question 4: A 38-year-old otherwise healthy female explains to her pharmacist that she is now experiencing menstrual cramps with the onset of her periods. She states that she recently stopped taking oral contraceptives, which she had been using consistently for years. She asks, "Is this cramping something I should be concerned about?"

A Answer 4: Dysmenorrhea, or severe cramping pain in the lower abdomen (or lower back and/or upper thighs) occurring just prior to or during menses, is a common condition affecting approximately 75% of menstruating women. In most younger women, dysmenorrhea is not associated with pelvic pathology and is related to the release of prostaglandins $F_{2\alpha}$ and E_2 from the endometrium and the release of vasopressin from the pituitary gland during menses.[58, 59] It may have a genetic component, as women who have primary dysmenorrhea commonly report that their mothers had similar symptoms.[60] Pelvic pathology resulting in secondary dysmenorrhea is more common in women >20 years of age.[58] It is difficult to differentiate primary and secondary dysmenorrhea based on symptoms alone; pain symptoms have a similar onset (1 to 2 days prior to menses) and duration (48 to 72 hours). (Pain that gets progressively worse may be indicative of endometriosis.) Treatment strategies for primary and secondary dysmenorrhea are different; therefore, it is important that patients discuss their symptoms with their healthcare providers and have their symptoms properly evaluated.

Oral contraceptives are the mainstay of therapy for primary dysmenorrhea.[58, 59, 61] Because they suppress ovulation, they reduce levels of prostaglandins that stimulate uterine activity and produce pain.

Q Dysmenorrhea

Question 5: The patient in question 4 would like to avoid returning to oral contraceptives for pain relief. She inquires, "What are my options?"

A Answer 5: Nonspecific NSAIDs are highly effective (72% of women participating in 51 clinical trials achieved significant pain relief versus 15% of women treated with placebo)[62] and are commonly used to relieve the symptoms of primary dysmenorrhea. However, because they are nonspecific, they also have GI, renal, and hematologic effects, which may lead to toxicities in some patients. (See Sections 1 & 3.) The addition of topical heat to non-specific NSAID therapy may shorten the duration of pain, but does not appear to influence the overall level of pain relief.[63]

The COX-2 inhibitors celecoxib and rofecoxib are both approved for the treatment of primary dysmenorrhea, but are available only by prescription.[64, 65] Because their effect on the arachidonic acid cascade is more specific than that of traditional NSAIDs (selectively inhibit COX-2), they are somewhat less likely to induce undesirable GI and hematologic effects.

The treatment of secondary dysmenorrhea is directed at correcting any treatable underlying condition(s). Gonadotropin-releasing hormone and medroxyprogesterone acetate are 2 pharmacologic therapies sometimes used to treat secondary dysmenorrhea.

Q Dysmenorrhea

Question 6: The patient in question 4 returns and complains that she is still having pain with her period. Her doctor gave her a prescription for nifedipine, a drug that her grandmother takes for angina. She asks, "Why is my doctor prescribing this for me?"

A Answer 6: Nifedipine may produce symptom relief in some patients with dysmenorrhea by reducing uterine activity and contractility, and subsequently reducing intrauterine pressure and pain. Limited data are available to support the use of nifedipine for this indication. In one small, uncontrolled study, single doses of nifedipine 20 mg to 40 mg administered during the first menstrual day in 10 women reduced myometrial activity and relieved pain within 10 to 30 minutes.[66]

Q Headaches

Question 7: A 30-year-old female patient with seasonal allergies complains to her pharmacist that she has been consuming naproxen sodium for the past 3 weeks in an attempt to get rid of her "sinus" headache. Upon questioning, the pharmacist determines that she is taking the naproxen sodium correctly. She is also taking loratadine once daily to control her allergy symptoms and pseudoephedrine as needed to control nasal stuffiness. She asks the pharmacist, "Can you recommend something more effective for this type of headache?"

A Answer 7: Patients such as this who experience headaches (or pain) for prolonged periods should be referred to their physicians for proper evaluation. Identification of primary and secondary headache disorders is the first step in the management process.

The Headache Classification Subcommittee of the International Headache Society has defined 3 primary headache disorders: migraine with and without aura, tension-type headache, and cluster headache. Both migraine and tension headaches are common among women (18.2%[67] and 27% to 47%,[68] respectively). Migraine is characterized by recurring (>5 attacks), long-lasting (4 to 72 hours) headaches. Diagnosis requires that at least 2 of the following be present: unilateral pain, throbbing pain, moderate-to-severe pain, or pain that worsens with activity. Patients also must report nausea and/or vomiting or photophobia and phonophobia. In contrast, tension headaches are typically bilateral, have a pressing/tightening quality, are not aggravated by routine physical activity, and are present for <15 days a month. Nausea and vomiting are typically absent as are photophobia or phonophobia. (Patients with tension headaches may report photophobia or phonophobia, but not both.)

Secondary headaches are symptoms of underlying pathology such as tumors, temporal arteritis, intracranial hypertension, or subarachnoid hemorrhage. Pain caused by a sinus condition technically would be considered a secondary headache, and treatment should be targeted at correction of the underlying condition (eg, antibiotics for bacterial sinus infections).

Upon examination, the physician is likely to find that this patient is truly experiencing migraine headaches.

Q Headaches

Question 8: A 40-year-old female patient with a history of frequent migraine headaches asks, "Isn't there anything I can do to stop getting these headaches?"

A Answer 8: Preventive therapy is recommended for patients with migraine headaches that substantially affect their lives; however, effective therapies are largely under-utilized.[69] Preventive therapy may also be useful for patients who have frequent headaches or who cannot use, or who overuse, acute therapies.

According to the US Headache Consortium, the goals of preventive therapy are to: (1) reduce attack frequency, severity, and duration, (2) improve responsiveness to treatment of acute attacks, and (3) improve function and reduce disability.[69] Patients should be advised that several prescription medications have demonstrated safety and efficacy as preventative migraine therapies and that their physicians can best evaluate the need for such medications. The efficacy profiles of most nonpharmacologic preventive measures are not as well established. The Consortium reported that relaxation training, thermal biofeedback combined with relaxation training, and cognitive-behavioral therapy all appear to be modestly effective in preventing migraine (versus no treatment).[70]

Preventive measures are not likely to prevent all migraine headaches, but may reduce the severity and/or duration of those that occur despite therapy.

Section 2: Common Pain Conditions

Q Injuries of Soft Tissue, Tendons, Ligaments, or Bones

Question 9: An 18-year-old, male high school athlete is diagnosed with a severely sprained ankle. He is otherwise healthy and taking no other medications. His mother requests a recommendation to reduce "swelling" to ease pain.

A Answer 9: Sprains are ligament injuries (tears) that can cause disabling pain. The healing process, which typically lasts 3 weeks or more, involves 3 phases: inflammation, proliferation, and maturation.[71] The initial inflammatory phase is painful, but is necessary for proper healing. It protects the injured structure from further use, clears away cell and matrix debris, and may facilitate the proliferative healing response. However, the inflammatory response triggered by the injury may be greater than is necessary to achieve these goals and the associated pain may make rehabilitation difficult. Inflammation may also contribute to fibrosis, which is not harmful in fibrotic tissues such as ligaments, but is undesirable in nonfibrotic tissues such as muscles. Therefore, it is desirable to relieve pain without completely suppressing inflammation.

Rest, ice, compression, and elevation (RICE) are commonly recommended for patients with sprains; however, strong data supporting these interventions are lacking. Whereas acetaminophen may be expected to reduce pain without disrupting the vital inflammation process in sprains, no placebo-controlled studies have evaluated its use in this population. The clinical utility of nonspecific NSAIDs is debatable, as conflicting results have been reported in clinical trials. There is some evidence from animal studies that the suppression of inflammation caused by COX-2 inhibition may actually be detrimental to mechanical healing, especially in the early healing phase.[72] Whereas recommended doses of OTC nonspecific NSAIDs are generally too low to cause significant suppression of inflammation, many are taken at higher doses that do inhibit inflammation. Until the relationship between NSAID use and healing is better understood, it is best to recommend that patients utilize the lowest effective NSAID doses to avoid suppression of inflammation and interference with healing. If lower doses do not provide adequate pain relief, the substitution or addition of acetaminophen would be preferable to increasing the NSAID dose in these patients. Short-term NSAID use is generally safe and well tolerated in the typically young, and otherwise healthy population that is most susceptible to sprains.

Q Injuries of Soft Tissue, Tendons, Ligaments, or Bones

Question 10: A 48-year-old female inquires about how best to treat the pain associated with her "tennis elbow." She has diet-controlled type 2 diabetes and is otherwise healthy. She asks the pharmacist, "Would ibuprofen be a good choice for me?

A Answer 10: "Tennis elbow" is a type of tendon injury. Tendon injuries or "tendinopathies" are painful, but commonly devoid of inflammation.[73] Rather, most are degenerative in nature. Pain relief is desirable in such injuries, as it allows continued moderate use, which can prevent further degeneration.

Nonspecific NSAIDs may provide adequate pain relief in patients with tendon injuries. Of 9 published, placebo-controlled studies of their use in patients with chronic tendon injuries, the findings of 5 demonstrated improved pain scores compared with placebo.[73] However, their efficacy is likely due to their analgesic, rather than their anti-inflammatory properties. While there are no studies that have directly examined the use of acetaminophen in the treatment of tendinopathies, acetaminophen would be expected to provide adequate pain relief based on the fact that the pain related to these injuries is not due to inflammation. Controlled trials are needed to document the efficacy of acetaminophen for this indication.

Q Injuries of Soft Tissue, Tendons, Ligaments, or Bones

Question 11: A 27-year-old, male "weekend warrior" runs his first marathon and complains to his pharmacist of significant muscle soreness. "I think I really overdid it; what can you give me to relieve the pain?"

A Answer 11: Delayed-onset muscle soreness (DOMS) typically occurs 12 to 48 hours following intensive repetitive muscle use. It is associated with structural muscle damage (as evidenced by creatine kinase elevations and evidence of localized damage to sarcomere subunits), but a limited inflammatory response.[74]

Acetaminophen is generally safe and well tolerated, and is devoid of anti-inflammatory effects that may delay or prevent healing, though there is no documented evidence for this indication.

Nonselective NSAIDs are commonly recommended for the relief of DOMS; however, their use for this indication is not well supported by the published literature. Whereas some studies have reported improvements in subjective pain scores, others have observed no differences compared with placebo.[74] Most studies reported that NSAIDs had no effect on underlying structural damage (as evidenced by lack of improvement in creatine kinase levels); however, others reported worsening. The nonspecific NSAIDs do not appear to improve muscle performance.

Q Injuries of Soft Tissue, Tendons, Ligaments, or Bones

Question 12: An adolescent girl has fractured her leg and comes into the pharmacy with a cast. Her parents are also present and ask the pharmacist, "What can you recommend as a pain reliever for our daughter?"

A Answer 12: Whereas fractures are defined as injuries to the bone, they are typically associated with soft tissue injuries (muscles, ligaments) as well, and initial pain is often severe enough to require opioid analgesia for adequate relief.[75, 76]

Bone healing occurs in 4 phases: inflammation, proliferation, maturation, and callus formation.[75, 76] As in other musculoskeletal injuries, inflammation is a necessary response, as it protects the injured structure from further use, clears away cell and matrix debris, and may facilitate cellular proliferation. COX-2, which is inhibited by both nonspecific NSAIDs and COX-2 inhibitors, regulates inflammation and callus formation.[75] For this reason, acetaminophen may theoretically be a better choice for mild-to-moderate pain associated with fractures, as it does not inhibit inflammation and, therefore, would not be expected to interfere with bone healing.

Q Injuries of Soft Tissue, Tendons, Ligaments, or Bones

Question 13: A teenage boy comes in after his soccer game. He tells the pharmacist that the team doctor told him he had a pulled hamstring muscle. "I really need something for pain, but I have to tell you that I don't like to swallow pills. Is there anything you can give me that would help?"

A Answer 13: Muscle injuries such as this patient describes are typically caused by acute stretching that tears the muscle-tendon unit.[74] Similar muscle injuries can be caused by direct nonpenetrating hits. The healing process is characterized by inflammation, proliferation, and maturation phases. The inflammation phase is necessary for proper healing, as it protects the injured muscle from further use, clears away cell and matrix debris, and may facilitate cellular proliferation.

Acetaminophen has not been adequately studied in stretch-induced muscle injuries or muscle contusions; however, it would be possible that its lack of anti-inflammatory effect would be beneficial, allowing the inflammatory process to promote healing. Acetaminophen is available in a wide variety of dosage forms; such as chewable tablets and suspensions that can facilitate compliance, especially in patients who cannot or do not like swallowing tablets.

NSAIDs' efficacy in relieving pain associated with stretch-induced muscle injuries also is not well documented. Interestingly, in one double-blind, placebo-controlled study, NSAID use in patients with severe hamstring injuries was associated with significantly increased persistent pain at day 7 compared with placebo.[77] Furthermore, nonselective activity on the arachidonic acid cascade may inhibit inflammation and interfere with healing.

Low Back Pain

Question 14: A 42-year-old, overweight male "put his back out" over the weekend and asks the pharmacist, "What would you recommend I take to relieve the pain so I can return to work?"

Answer 14: Acetaminophen should be considered first-line therapy for the relief of mild-to-moderate back pain. It is effective and well tolerated in this patient population.[78] Patients must be counseled, however, to take recommended doses consistently (4 to 6 times daily, to a maximum of 4 g) to derive full benefit.

NSAIDs are another option for short-term relief of mild-to-moderate back pain. In a systematic review of 51 randomized, double-blind controlled trials, NSAIDs were more effective than placebo and possibly more effective than acetaminophen in relieving mild-to-moderate low back pain.[79] There were no significant differences among the NSAIDs tested. Side effects associated with the use of NSAIDs in this analysis included abdominal pain, diarrhea, edema, dry mouth, rash, dizziness, headache, and tiredness.

Prescription options for patients who do not experience adequate pain relief with first-line OTC therapies include higher doses of nonspecific NSAIDs or initiation of COX-2 inhibitors. In a single 4-week, randomized, controlled trial, the COX-2 inhibitor rofecoxib (25 mg or 50 mg daily) administered in the morning produced significantly greater improvement in back pain intensity than did placebo ($P<.001$).[80] Pain relief occurred rapidly and was evident as early as bedtime after the first dose. Because the COX-2 inhibitors are generally associated with reduced risk for GI and hematologic toxicities, they may be preferred over nonspecific NSAIDs in certain at-risk populations. (See Section 3.) However, like the nonspecific NSAIDs, COX-2 inhibitors can cause edema and aggravate hypertension and should be used with caution in patients with underlying cardiovascular disease.

Muscle relaxants may be recommended for patients experiencing moderate-to-severe lower back pain. Cyclobenzaprine, the only muscle relaxant that has been well studied in the treatment of this condition, provides only modest relief of symptoms compared with placebo and is associated with drowsiness.[81] (A new, lower dose formulation may cause less drowsiness than that observed in earlier studies with the higher dose formulation.) Symptom relief is greatest early (within the first 4 days of therapy); therefore, long-term use is generally not recommended. In the primary care setting, muscle relaxants are often prescribed in conjunction with NSAIDs. In a single observational study, such combinations were associated with improved patient outcomes (vs NSAIDs alone, muscle relaxants alone, narcotics, and acetaminophen).[82]

Section 3: Special Considerations

Section 3: Special Considerations

Q Pain in the Elderly

Question 1: A young woman picking up her grandmother's prescriptions comments, "My grandmother is very old and debilitated with Alzheimer's disease and high blood pressure, and she suffered a stroke last year. I'd like to save her some money by eliminating the pain medication, as pain is the least of her problems."

A Answer 1: The increased incidence of disease in the elderly population necessitates proper pain management as an especially important part of elder care. Unfortunately, this is typically complicated by the elderly's diminished abilities to adequately perceive and communicate pain. With the elderly, nociceptive mechanisms do not respond to stimuli in the same way as younger people and may lead to the perception of other stimuli as painful. Patients with problems including dementia, cognitive and speech deficits following a stroke, and potential difficulty hearing, may not be able to communicate their pain effectively to their caregivers.[83] Their reactions to pain, such as struggling and outbursts when a tender joint is handled or night wanderings, may be interpreted as "disruptive behavior."

These complications will often result in the elderly's pain remaining untreated or undertreated. This can lead to other health issues, including disruptive behaviors and difficulty sleeping. Subsequently, inadequate pain relief can result in the unnecessary use of antipsychotic medications and sleep aids, which are, in turn associated with functional impairment and falls. Therefore, even if pain does not appear to be a primary problem, it contributes to a patient's overall condition.

It is important that analgesics for elderly patients be carefully selected. Some of the known toxicities of NSAIDs are more common in older patients and in patients with certain diseases or conditions that are common in the elderly population. Age is an accepted risk factor for NSAID-induced GI toxicity, starting as early as age 50 in some reports and rising with advancing age.[10-12] In one nested case-control study, the risk for upper GI bleeding was increased 3-fold in patients aged 60 to 69 years, 4-fold in patients 70 to 79 years, and 10-fold in patients ≥80 years of age.[10] NSAIDs can increase blood pressure in hypertensive individuals[33] and diminish renal function in patients who rely heavily on renal prostaglandins to maintain normal renal blood flow and function.[35] When used chronically, NSAIDs can negate the cardioprotective effects of low-dose aspirin (by interfering with the effects of aspirin on platelet function).[38, 46] Furthermore, they can interact with other drugs commonly utilized in older patients (eg, diuretics, ACE inhibitors).[45]

NSAID use in elderly patients can be decreased successfully without compromising pain control. In a community-based program in 1566 regular NSAID users, face-to-face educational visits with prescribers resulted in a 7% to 10% reduction in NSAID use over the course of 1 year; no deterioration in symptoms or function was observed.[84] In a nursing home study, NSAID use was decreased by 73% in patients in the intervention group and 11% in patients in the control group (P=.0001) following staff education programs. There was no change in GI drug usage, and no significant changes from baseline in health questionnaire responses; although there was a slight but significant increase in arthritis pain, this corresponded with a significant decrease in other pain.[85]

The American College of Rheumatology[16] and the American Geriatrics Society[15] both recommend that acetaminophen be used first-line for the management of mild-to-moderate pain in elderly patients because it has a favorable efficacy, safety, and drug-to-drug interaction profile. Acetaminophen can be recommended safely for patients with diminished hepatic function[18, 19] and is available in a variety of dosage forms that may ease administration in patients who cannot, or will not, swallow tablets.

Q Pain in the Elderly

Question 2: A middle-aged woman is admitting both her parents into an assisted-living facility for the first time. She meets with the pharmacist servicing the facility to discuss her parents' various prescription medications. She asks the pharmacist, "What does your facility dispense to patients for common (mild-to-moderate) pain?"

A Answer 2: The American Geriatrics Society recommends acetaminophen as initial therapy for mild-to-moderate pain in elderly patients.[15] This recommendation is based largely on the known efficacy of acetaminophen in relieving mild-to-moderate pain and its improved safety profile compared with NSAIDs in elderly patients. (See answer 1, above.)

Despite this recommendation, NSAID use among the elderly remains high. There has been much interest recently in educational programs designed for professionals who routinely care for elderly patients and their potential to reduce unnecessary NSAID use in this population. Interventions such as face-to-face visits (community physicians), formal education programs (nursing homes), and reminders (eg, notation in charts) have been proposed as methods to change NSAID utilization patterns among the elderly. Such programs have been tested among treaters of both community-dwelling and institutionalized elderly patients and have been shown effective in reducing NSAID use and increasing acetaminophen use without negatively affecting patient status.[84, 85]

The woman in this question can be assured, however, that efforts to reduce NSAID use among the elderly does not mean that her parents' pain will go untreated. In 2000, the Joint Commission on Accreditation of Healthcare Organizations published new pain management standards that emphasize the importance of pain assessment (the "fifth vital sign") and the implementation of policies and procedures to ensure that pain is adequately recognized and treated.[86]

Q Gastrointestinal Conditions and Considerations

Question 3: An elderly gentleman is purchasing his monthly antacid medication for his chronically upset stomach at the same time he is purchasing low-dose aspirin for cardioprotection and naproxen sodium for his occasional back pain. He asks the pharmacist, "Are there any problems in using all of these medications together?"

A Answer 3: In otherwise healthy individuals, the occasional concomitant use of naproxen sodium and low-dose aspirin is generally associated with minimal risks. However, in older patients and patients with underlying GI disorders, the risks of toxicity associated with this combination may be increased. Furthermore, chronic coadministration of an NSAID (with the possible exception of naproxen sodium) and low-dose aspirin could result in reduced cardioprotection.

GI toxicities associated with NSAIDs comprise an entire range of events, from bothersome symptoms (eg, heartburn, nausea, dyspepsia, abdominal pain) to the development of mucosal lesions and, in some cases, life-threatening complications such as perforation and bleeding.[87, 88] Studies examining the relationships between NSAIDs and GI events have identified a number of risk factors for their occurrence: increasing age, prior history of GI problems (eg, upper GI bleeding/perforation), increasing doses of NSAIDs, concomitant use of oral corticosteroids, and concomitant use of anticoagulants.[9, 10, 12, 40, 41]

The mechanisms of GI toxicity have been best studied with aspirin and are believed to result from alterations in the gastric mucosal barrier caused by reduced prostaglandin synthesis, mucus and bicarbonate secretion, submucosal blood flow, mucosal adenosine triphosphate, cell turnover, and platelet function (irreversible).[88] Similar mechanisms likely contribute to GI toxicity with nonaspirin NSAIDs. These agents may also cause pH-dependent local irritation, increased leukotriene and toxic oxygen metabolite formation, and reduced levels of the protective sulfhydryl glutathione.

The COX-2 inhibitors[76] and acetaminophen[9] have demonstrated improved GI safety profiles, as opposed to aspirin and nonspecific NSAIDs, likely because their effect on blocking the COX-1 and cytoprotective prostaglandins is reduced (COX-2 inhibitors) or absent (acetaminophen).[89] Evidence to date suggests that from a GI perspective, acetaminophen is the safest choice, followed by COX-2 inhibitors, nonspecific NSAIDs, and aspirin.[76, 90, 91]

Another consideration in this patient is the potential for chronic administration of NSAIDs to negate the cardioprotective effects of low-dose aspirin (by interfering with the effects of aspirin on platelet function).[38, 46, 92] This interaction appears to be most problematic among patients who chronically use NSAIDs and aspirin together.[46] (See Patients With Cardiovascular or Renal Disease.)

As the patient in this question has 3 reasons to avoid NSAID use—he is elderly, he was purchasing an antacid (an indication of some GI discomfort), and he is taking low-dose aspirin for cardioprotection—it would be prudent to suggest that he discuss his symptoms and OTC medication use with his physician. In the interim he should be advised to continue his low-dose aspirin regimen and use acetaminophen for his occasional back pain.

Q Patients With a History of Liver Disease

Question 4: An elderly woman with diagnosed chronic liver disease is purchasing an NSAID and dismisses the pharmacist's recommendation to consider acetaminophen instead. "Why would you recommend acetaminophen knowing that I have liver damage?"

A Answer 4: It is a common misconception that patients with preexisting liver disease are more susceptible to drug-induced hepatic toxicity. Whereas acetaminophen may cause acute liver damage in massive overdose (usually intentional), the actual incidence of acute liver damage is low, especially if treatment is promptly implemented.

Acetaminophen is metabolized primarily in the liver by glucuronidation, sulfation, and oxidation, with less than 9% of a recommended dose excreted unchanged in the urine.[93] Approximately one half to one-third of a recommended dose is conjugated with glucuronide and one fourth to one third with sulfate; both reactions form nontoxic metabolites that are eliminated in the bile or excreted in the urine. Less than 10% of a recommended dose is metabolized by cytochrome P-450 2E1 (CYP2E1) to form the highly reactive intermediate *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is almost instantaneously deactivated by hepatocellular stores of glutathione from nontoxic cysteine and mercapturic conjugates. Based on this pattern, factors that induce CYP2E1 activity and/or reduce hepatic glutathione stores significantly could theoretically increase the risk for acute liver damage.

In patients with chronic liver disease, the half-life of acetaminophen is prolonged[94, 95]; however, the metabolic pathway appears to be relatively unchanged.[95] Factors that theoretically increase the risk for acute liver damage are not present. In fact, CYP450 levels are *reduced*[96-98] and glutathione stores are *increased*.[99, 100] In clinical studies conducted in patients with chronic liver disease, there was no clinical or laboratory evidence of liver toxicity associated with acetaminophen use.[18, 19]

For these reasons, the recommended dose of acetaminophen remains a safe analgesic/antipyretic choice in patients with chronic liver disease.

Q Patients With a History of Alcohol Abuse

Question 5: A 24-year-old male complains of a nasty hangover and low back pain from his weekly "binge." He requests a recommendation for relieving the pain he typically experiences from his "partying." Upon further questioning, it is apparent that he regularly consumes large amounts of alcohol, usually 3 or more drinks daily.

A Answer 5: The risk/benefit assessment of OTC analgesic therapy in patients with a history of alcohol abuse is similar to that which should be conducted in any patient. Important considerations include risk factors for GI toxicity, underlying cardiac and renal status, and concomitant drug therapies.

Chronic alcohol consumption may increase the risk for NSAID-associated GI toxicity. Other risk factors include increasing age, positive history of ulcers and GI bleeding, and use of oral corticosteroids or anticoagulants.[9, 10, 12, 40, 41] In an interview-based case control study of 1224 patients hospitalized for acute major upper GI bleeding and 2945 neighbor controls, the risk for upper GI bleeding increased with increasing alcohol consumption in the entire study population, with relative risks (95% CI) of 0.9 (0.8-1.2), 1.3 (1.0-1.7), 1.4 (1.0-2.0), and 2.8 (2.0 -3.9) for 1-6 drinks/week, 7-13 drinks/week, 14-20 drinks/week and ≥21 drinks/week, respectively, compared with <1 drink/week.[43] Among regular aspirin users (use at least every other day the week prior to the event), any level of drinking increased the risk for acute major upper GI bleeding (multivariate relative risk (MVRR) (95% CI), 2.8 (2.1-3.8) and 7.0 (5.2-9.3) for regular users of ≤325 mg and >325 mg, respectively). Among current drinkers, even occasional aspirin use was associated with increased risk for upper GI bleeding (MVRR (95% CI), 2.4 (1.9-3.0)) at all levels. In a separate mail survey conducted by the American College of Gastroenterology, drinking (level not described) was associated with a 2-fold increased risk for GI bleeding that appeared to be at least additive to that associated with recent NSAID use.[8]

Patients with renal insufficiency, congestive heart failure, or hypertension are at increased risk of cardiorenal toxicity with NSAIDs.[33-35] Acetaminophen can be used without similar risks in these patient populations. (See Patients with Cardiovascular or Renal Disease.)

The current misconception that alcoholic patients appear to be predisposed to hepatic injury with the use of recommended doses of acetaminophen is based largely on retrospective reports of liver toxicity associated with acetaminophen ingestion in alcoholic patients. Close examination of these reports reveals no clear relationship, with many patients having multiple medical problems and no confirmation of how much acetaminophen the patients actually ingested. Contrasting these data are 7 methodologically sound studies as extensively reviewed by Dart and colleagues to determine whether recommended doses of acetaminophen (≤4g/day) are safe in adult alcoholic patients.[101] Class I (randomized, controlled, and blinded clinical trials) and Class II (prospective, nonrandomized or nonblinded clinical trials) reports concluded that acetaminophen at recommended doses is not associated with hepatic injury in alcoholic patients.

In one recent prospective, placebo-controlled study, the administration of maximum recommended doses of acetaminophen to confirmed drinkers (n=102) for 2 days resulted in similar changes in hepatic enzymes and INR as patients who received placebo (n=99).[102] These findings supported those reported in an earlier pilot study in which the administration of acetaminophen 4 g daily for 5 days to subjects with chronic liver disease (N=6) did not result in accumulation or hepatotoxicity, and administration of acetaminophen 4 g daily for 13 days in 20 subjects with stable chronic liver disease (6 with alcoholic liver disease) was well tolerated and did not alter clinical status.[18]

The all-too-common misconception about acetaminophen causing hepatic injury at recommended doses is generally attributable to a lack of thorough understanding of the metabolism of acetaminophen in alcoholic patients. It is crucial to differentiate between acute concurrent ingestion of alcohol and acetaminophen in the blood and ingestion of acetaminophen without alcohol in the blood. The concurrent ingestion of alcohol and acetaminophen produces classic competitive inhibition and actually reduces the amount of injurious metabolite (NAPQI) produced.[103] In contrast, chronic alcohol ingestion does increase the level of CYP2E1 within the hepatocyte. At large doses (eg, 10 g) of acetaminophen, a history of recent alcoholism may increase the likelihood of liver injury. However, the findings of published and ongoing studies indicate that the use of a recommended dosage (eg, 1 g qid) of acetaminophen does not produce liver injury in alcoholic patients.[102]

Q Patients With Cardiovascular or Renal Disease

Question 6: The pharmacy student working in the pharmacy asks, "Shouldn't we warn all patients equally about the risk of renal failure when we dispense NSAIDs?"

A Answer 6: In healthy patients, the risk of developing renal failure with NSAIDs is minimal. In a subset of participants in the Physicians Health Study (N=11,032 apparently healthy male physicians with normal renal function at baseline), the use of OTC analgesics (aspirin, nonaspirin NSAIDs, or acetaminophen) over a period of 14 years (12 to >2500 pills over the study period) was not associated with renal toxicity (increased serum creatinine/reduced creatinine clearance levels),[104] suggesting that the use of analgesics in healthy persons does not pose significant renal risks.

In contrast, OTC analgesic use in patients with hypertension, severe renal insufficiency, congestive heart failure, or other disorders of salt and water retention should be warned about the risks of analgesic use. Patients with such conditions likely rely more heavily on renal prostaglandins to maintain normal renal blood flow and function than otherwise healthy individuals.[35] Inhibition of prostaglandin synthesis in such patients can reduce renal blood flow and glomerular filtration rate (resulting in increased blood urea nitrogen and creatinine levels), increase chloride absorption and sodium retention (resulting in edema and hypertension), reduce renin and aldosterone activity (resulting in elevated potassium levels), and increase the effect of antidiuretic hormone (resulting in water retention and hypervolemia).

Q Patients With Cardiovascular or Renal Disease

Question 7: A 75-year-old woman with hypertension and congestive heart failure who is taking a diuretic asks the pharmacist's assistance in selecting an analgesic for occasional aches and pains.

A Answer 7: Acetaminophen is the clear first choice for this patient. She is older and therefore at increased risk for NSAID-associated GI toxicity.[11, 12] She has hypertension and congestive heart failure, conditions that place her at increased risk for NSAID-induced elevations in blood pressure and renal toxicity.[33, 35] Furthermore, she has conditions for which drugs that interact with NSAIDs are commonly prescribed (eg, diuretics, ACE inhibitors).[45]

Whereas randomized clinical trials evaluating the effects of NSAIDs on blood pressure have provided contradictory evidence of a relationship,[34] results of a meta-analysis of 54 studies demonstrated that NSAIDs (including aspirin) had little effect on blood pressure in normotensive individuals, but caused clinically significant increases in mean arterial blood pressure in hypertensive patients.[33] This relationship appears to extend to COX-2 inhibitors. In a 6-week, randomized, double-blind study of celecoxib and rofecoxib use in older hypertensive patients with osteoarthritis (N=810), both agents were associated with edema and elevations in systolic blood pressure (rofecoxib > celecoxib).[105]

Q Patients With Cardiovascular or Renal Disease

Question 8: A 53-year-old woman is refilling her supply of baby aspirin to prevent heart attacks. She comments, "Everyone over 40 should do the same, as baby aspirin is harmless and good for the heart."

A Answer 8: Whereas evidence clearly supports the beneficial effects of aspirin on reducing cardiovascular risk, aspirin is not a benign drug and may pose unacceptable risks in certain patient populations.

The cardioprotective effect of aspirin is likely related to its ability to irreversibly inhibit COX-1 and prevent platelet production of thromboxane A_2.[106] In the Physicians Health Study (N=22,071), the administration of aspirin 325 mg every other day for a mean period of 5 years reduced the risk of a first heart attack significantly (44%; $P<.00001$ versus placebo).[25] Similarly, in an interim analysis of the United Kingdom Transient Ischaemic Attack aspirin trial, aspirin use reduced the combined risk of nonfatal major stroke, nonfatal myocardial infarction, vascular death, or nonvascular death by 18% versus placebo ($P=.01$).[26] However, even the lower doses of aspirin typically used for cardioprotection can cause GI toxicity. In several case-control studies, the risk for GI bleeding was increased 2- to 3-fold among low-dose (75 mg to 300 mg daily) aspirin users as opposed to the general population.[29-31]

Certain patient populations are at increased risk of experiencing aspirin-associated GI toxicities, including older patients, patients with a prior history of GI problems (eg, upper GI bleeding/perforation), regular alcohol users, and patients taking certain other medications (eg, oral corticosteroids, other NSAIDs).[9, 10, 12, 40, 41, 43, 46] Enteric-coated and buffered preparations are not void of GI toxicities. In one review of 550 incident cases of upper GI bleeding and 1202 controls, relative risks (RRs) associated with the regular use of low doses (≤325 mg) of plain, enteric-coated, and buffered aspirin were similar (RR (95% CI), 2.6 (1.7-4.0), 2.7 (1.4-5.3), and 3.1 (1.3-7.6), respectively).[32]

Q Patients With Cardiovascular or Renal Disease

Question 9: An elderly man with a history of cardiovascular complications and who, upon the advice of his physician, uses baby aspirin religiously for cardioprotection, asks the pharmacist, "How much ibuprofen should I take daily for mild pain associated with my hip replacement?"

A Answer 9: Intermittent NSAID use is unlikely to interfere significantly with the cardioprotective effects of low-dose aspirin. In a subgroup analysis of data from the 5-year Physicians' Health Study of aspirin for cardioprotection, physicians who used NSAIDs for up to 59 days per year (in addition to aspirin 325 mg every other day) were not at increased risk for MI (RR (95% CI), 1.21 (0.78-1.87)), but those who used NSAIDs for ≥60 days/year (plus aspirin) were (RR (95% CI), 2.86, (1.25-6.56)).[46] Physicians who used NSAIDs but not aspirin (the placebo group) were not at increased risk for MI, regardless of the frequency of use (RR (95% CI), 1.14 (0.81-1.60) and 0.21 (0.03-1.48) when used for ≤59 days and ≥60 days per year, respectively).

The interaction between NSAIDs and aspirin appears to be related to competitive binding to COX-1. When administered concomitantly short term (6 days), single daily doses of ibuprofen (400 mg) administered 2 hours before single daily doses of aspirin (81 mg) significantly reduced aspirin-induced platelet inhibition (mean degree of inhibition on day 6, 53%), but administration 2 hours after aspirin did not (mean degree of inhibition on day 6, 99%) ($P<.001$).[38] Multiple daily doses of ibuprofen (400 mg tid) reduced platelet inhibition regardless of whether it was administered 2 hours after or 2 hours before the daily aspirin dose. The antiplatelet effects of aspirin were not affected by concomitant administration of acetaminophen, rofecoxib, or diclofenac.

A separate concern in this elderly patient is the potential for NSAID-induced toxicities. Advanced age is an accepted risk factor for NSAID-associated GI toxicity.[10-12] Depending on his underlying health status, he may also be at increased risk for NSAID-associated cardiovascular or renal toxicities, which can occur in patients with hypertension,[33,34] congestive heart failure,[35] or diminished renal function.[35] He may be taking other medications that could potentially interact with NSAIDs such as diuretics and ACE inhibitors.[45]

For all of these reasons, acetaminophen would be a better choice than ibuprofen for this patient, who is seeking relief of mild pain while taking aspirin for cardioprotection.

Q Patients With Cardiovascular or Renal Disease

Question 10: A 54-year-old male is taking a combination product (acetaminophen, aspirin, and caffeine) for headaches and pseudoephedrine for nasal congestion. He also has a history of angina, hypertension and renal dysfunction. He asks the pharmacist, "Are there any risks associated with these medications?"

A Answer 10: OTC products such as acetaminophen, aspirin, ibuprofen, and naproxen sodium are available in an array of combinations targeting various populations and symptom clusters. OTC analgesics that previously were associated with one particular ingredient (eg, aspirin), are now available in fixed combinations containing alternate and/or additional active ingredients. Unless patients carefully read labels, they may unintentionally ingest ingredients they do not want or take excessive doses of ingredients that are in more than one product. This patient has chosen products that could potentially negatively impact his underlying health. Caffeine and pseudoephedrine could increase his heart rate and aggravate his angina and hypertension. Aspirin could also increase his blood pressure and/or affect his renal function. He may already be taking aspirin for cardioprotection, which could result in excessive doses. Pharmacists can play an important role in preventing toxicities associated with OTC analgesic use by questioning patients about their health and medication use and offering sound advice regarding which products are most appropriate in each situation.

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Posttest

Pharmacist Guide to Patients' Frequently Asked Questions

Post-Program Self-Assessment/Continuing Pharmacy Education Verification

If you wish to receive continuing pharmacy education credit and confirmation of your participation, please mail a photocopy of this completed form before May 31, 2007 to:

American Pharmacists Association
Education Services, Lockbox #4472
P.O. Box 85080
Richmond, VA 23285-4472

Instructions:
For each of the questions or incomplete statements below, indicate the most appropriate response on the answer form below.

1. Among OTC pain medications, which one of the following statements is true?
   a. Combination products have no value in the treatment of pain.
   b. Combination products should be tried first.
   c. Combination products have a greater potential for side effects.
   d. Combination products have an improved benefit-to-risk ratio over single agents.
2. In the context of multimodal interventions for OA, recommended first-line pharmacologic therapy is:
   a. Aspirin
   b. COX-2 inhibitors
   c. Nonselective NSAIDs
   d. Acetaminophen
3. Which of the following is considered the mainstay of therapy for primary dysmenorrhea?
   a. COX-2 inhibitors
   b. Oral contraceptives
   c. Nonselective NSAIDs
   d. None of the above
4. Why is inflammation an important part of the healing process?
   a. It protects the injured structure from further use.
   b. It clears away cell and matrix debris.
   c. It may facilitate proliferative healing.
   d. All of the above
5. The rank order (best to worst) for GI safety of analgesics is:
   a. COX-2 inhibitors, acetaminophen, nonselective NSAIDs, aspirin
   b. Acetaminophen, COX-2 inhibitors, nonselective NSAIDs, aspirin
   c. Acetaminophen, COX-2 inhibitors, aspirin, nonselective NSAIDs
   d. COX-2 inhibitors, acetaminophen, aspirin, nonselective NSAIDs
6. At doses of ≤4 g/day, acetaminophen has not been shown to increase the risk of bleeding in patients with chronic liver disease or a history of alcohol intake.
   a. True
   b. False
7. Which of the following statements regarding the use of nonselective NSAIDs for the treatment of chronic tendon injuries is true?
   a. Conflicting evidence exists regarding their analgesic efficacy in patients with chronic tendon injuries.
   b. Their efficacy is primarily related to anti-inflammatory properties.
   c. Both a and b are true.
   d. Neither a nor b is true.
8. Results of a meta-analysis that reflected 54 studies of NSAID effects on hypertension demonstrated that:
   a. NSAIDs had little effect on blood pressure in normotensive individuals.
   b. NSAIDs caused clinically significant increases in mean arterial blood pressure in hypertensive patients.
   c. NSAID effects on hypertension may be associated with obesity.
   d. a and b
   e. b and c
9. Which of the following statements about the use of OTC NSAIDs is true?
   a. The use of OTC NSAIDs causes only nuisance GI symptoms such as nausea and dyspepsia.
   b. OTC doses of ibuprofen do not have an increased risk of upper GI bleeding.
   c. The use of enteric-coated or buffered aspirin does not reduce GI bleeding risks.
   d. Addition of OTC low-dose aspirin does not increase the risk of serious upper GI bleeding in patients chronically taking NSAIDs.
10. Which of the following is *not* a risk factor for developing serious GI adverse events with the use of NSAIDs?
    a. Advanced age
    b. Male gender
    c. Concomitant use of an anticoagulant
    d. High NSAID dose
11. Which of the following statements is/are false?
    a. COX-2 inhibitors are associated with increased blood pressure.
    b. COX-2 inhibitors are associated with increased edema.
    c. a and b
    d. None of the above
12. Which of the following statements about analgesic cost-effectiveness is false?
    a. Prescribing COX-2 inhibitors may lead to a cost-effective reduction in clinically important GI adverse events in low-risk patient groups.
    b. COX-2 inhibitors may provide an acceptable incremental cost-effectiveness ratio in high-risk patient groups.
    c. Acetaminophen is superior to both selective and nonselective NSAIDs in averting GI events in an average-risk patient population.
    d. None of the above
13. When treating mild-to-moderate pain associated with OA, which of the following statements is true?
    a. COX-2 inhibitors are recommended by the ACR as first-line therapy.
    b. COX-2 inhibitors are commonly reserved for patients who cannot tolerate nonspecific NSAIDs.
    c. COX-2 inhibitors are typically used as first-line treatment due to their cost-effectiveness.
    d. None of the above
14. According to the US Headache Consortium, the goals of preventative treatment for migraine are to:
    a. Reduce attack frequency, severity, and duration
    b. Improve responsiveness to treatment of acute attacks
    c. a and b
    d. None of the above
15. Which of the following statements about the use of nonselective NSAIDs for the treatment of DOMS is true?
    a. Their use for the treatment of DOMS is well supported by the published literature.
    b. They effectively treat underlying structural damage.
    c. They improve muscle performance.
    d. All of the above are true.
    e. None of the above is true.

Please record your posttest answers:

1. ___ 2. ___ 3. ___ 4. ___ 5. ___ 6. ___ 7. ___ 8. ___ 9. ___ 10. ___ 11. ___ 12. ___ 13. ___ 14. ___ 15. ___

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The American Pharmacists Association would appreciate your comments regarding the quality of the information presented and thanks you for your participation.

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	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were fully met.	a	b	c	d
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3. The educational activity has enhanced my professional effectiveness and improved my ability to:				
A. Counsel and educate patients	a	b	c	d
B. Communicate with patients	a	b	c	d
C. Manage my pharmacy practice	a	b	c	d
4. The information presented was without promotional or commercial bias.	a	b	c	d
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6. Suggestions regarding this material or recommendations for future presentations:

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