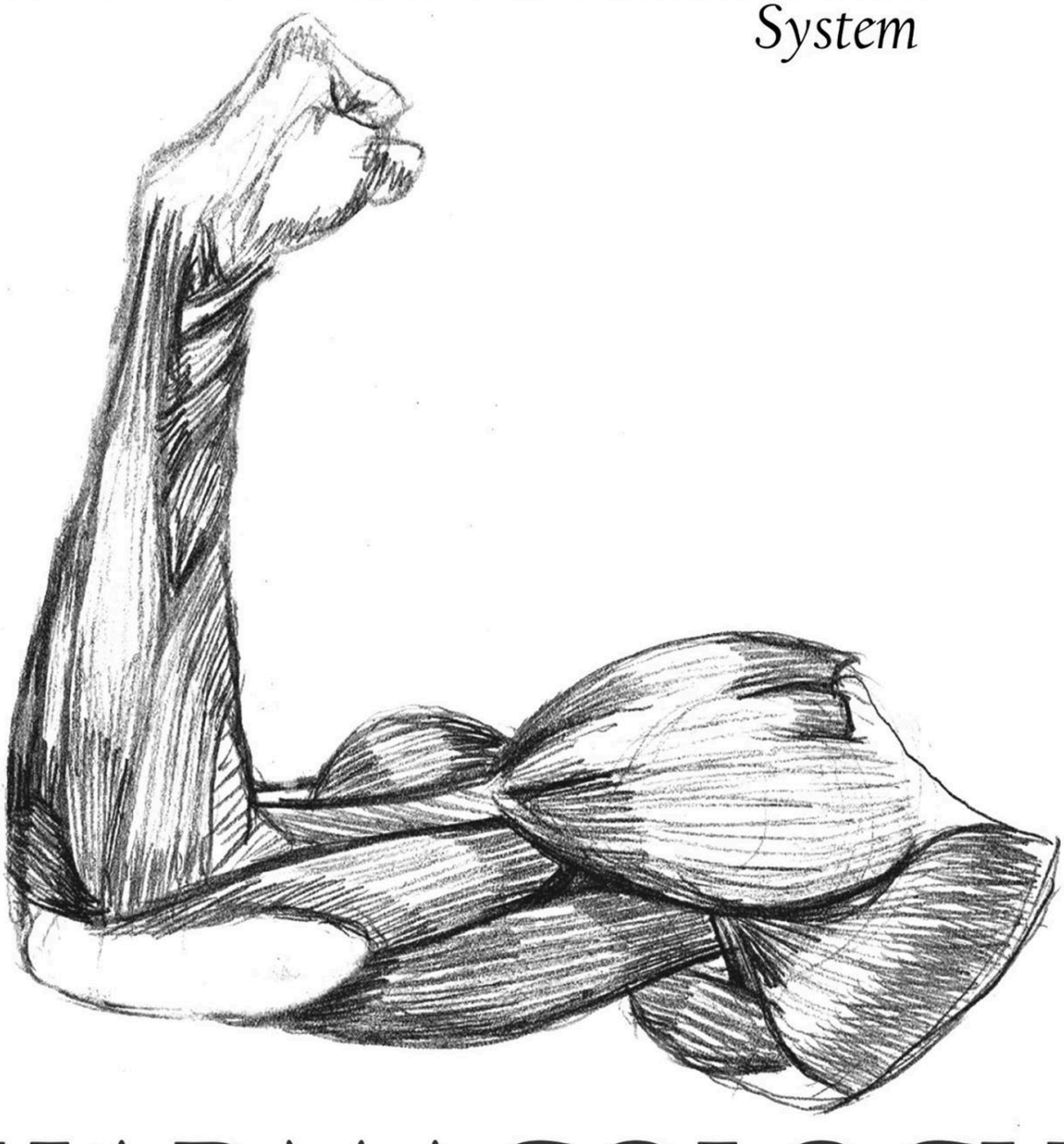
Medical Committee
The University of Jordan

The Skin and MUSCULOSKELETAL *System*



PHARMACOLOGY

Book: lippincott chapter 36 - (nonsteroidal anti-inflammatory drugs)

BY MOHAMED F. ABU ALIA

Anti-inflammatory, Antipyretic, and Analgesic Agents

36

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I. OVERVIEW

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of the immune system can result in inflammation, leading to immune-mediated diseases such as rheumatoid arthritis (RA). Normally, the immune system can differentiate between self and nonself. In RA, white blood cells (WBCs) view the synovium (tissue that nourishes cartilage and bone) as nonself and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes (the cell-mediated part of the immune system), which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity. The release of cytokines then causes 1) increased cellular infiltration into the endothelium due to release of histamines, kinins, and vasodilatory prostaglandins; 2) increased production of C-reactive protein by hepatocytes (a marker for inflammation); 3) increased production and release of proteolytic enzymes by chondrocytes (cells that maintain cartilage), leading to degradation of cartilage and joint space narrowing; 4) increased osteoclast activity (osteoclasts regulate bone breakdown), resulting in focal bone erosions and bone demineralization around joints; and 5) systemic manifestations in certain organs such as the heart. In addition to T-lymphocyte activation, B lymphocytes are also involved and produce rheumatoid factor (inflammatory marker) and other autoantibodies with the purpose of maintaining inflammation. These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, significant pain, and reduction in quality of life. Pharmacotherapy in the management of RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, and halting or slowing disease progression. The agents to be discussed (Figure 36.1) include nonsteroidal

NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Celecoxib CELEBREX
Diclofenac CATAFLAM, FLECTOR, PENNSAID, VOLTAREN
Diflunisal DOLOBID
Etodolac
Fenoprofen NALFON
Flurbiprofen ANSAID
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac ACULAR, ACUVAIL, TORADOL
Ketoprofen
Meclofenamate
Mefenamic acid PONSTEL
Meloxicam MOBIC
Methyl salicylate WINTERGREEN OIL
Nabumetone
Naproxen ALEVE, ANAPROX, NAPROSYN
Oxaprozin DAYPRO
Piroxicam FELDENE
Salsalate
Sulindac CLINORIL
Tolmetin TOLMETIN SODIUM

OTHER ANALGESICS

Acetaminophen (***Paracetamol***) OFIRMEV, TYLENOL

Figure 36.1
Summary of anti-inflammatory drugs. NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase.
(Figure continues on next page.)

DRUGS FOR RHEUMATOID ARTHRITIS

Abatacept ORENCIA
Adalimumab HUMIRA
Anakinra KINERET
Certolizumab CIMZIA
Etanercept ENBREL
Golimumab SIMPONI
Hydroxychloroquine PLAQUENIL
Infliximab REMICADE
Leflunomide ARAVA
Methotrexate RHEUMATREX, TREXALL
Rituximab RITUXAN
Tocilizumab ACTEMRA
Tofacitinib XELJANZ

DRUGS FOR GOUT

Allopurinol ZYLOPRIM
Colchicine COLCRYS
Febuxostat ULORIC
Pegloticase KRYSTEXXA
Probenecid BENEMID

Figure 36.1 (Continued)
Summary of anti-inflammatory drugs.

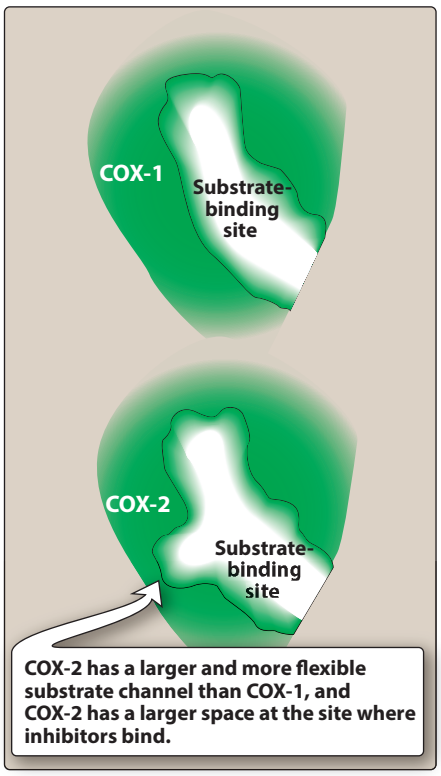

Figure 36.2
Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2.

anti-inflammatory drugs (NSAIDs) and *celecoxib* (cyclooxygenase-2 inhibitor), *acetaminophen*, and disease-modifying antirheumatic drugs (DMARDs). Additionally, agents used for the treatment of gout and migraine headache are reviewed.

II. PROSTAGLANDINS

The NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.]

A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins.

B. Synthesis of prostaglandins

Arachidonic acid is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.

1. **Cyclooxygenase pathway:** All eicosanoids with ring structures (that is, the prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation. COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. Differences in binding site shape have permitted the development of selective COX-2 inhibitors (Figure 36.2). Another distinguishing characteristic of COX-2 is that its expression is induced by inflammatory mediators like TNF-α and IL-1 but can also be pharmacologically inhibited by glucocorticoids (Figure 36.3), which may contribute to the significant anti-inflammatory effects of these drugs.

2. **Lipoxygenase pathway:** Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes (Figure 36.3).

Antileukotriene drugs, such as *zileuton*, *zafirlukast*, and *montelukast*, are treatment options for asthma (see Chapter 29).

C. Actions of prostaglandins

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G-coupled proteins. Prostaglandins and their metabolites, produced endogenously in tissues, act as local signals that fine-tune the response of a specific cell type. Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site. For example, the release of thromboxane A_2 (TXA_2) from platelets during tissue injury triggers the recruitment of new platelets for aggregation, as well as local vasoconstriction. However, prostacyclin (PGI_2), produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostanoids.

D. Therapeutic uses of prostaglandins

Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes. Therefore, they find use for a number of disorders discussed below.

E. Alprostadil

Alprostadil [al-PROS-ta-dil] is a PGE_1 that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. Therapeutically, *alprostadil* can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible. PGE_1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible. The use of *alprostadil* for erectile dysfunction is discussed in Chapter 32.

F. Lubiprostone

Lubiprostone [loo-bee-PROS-tone] is a PGE_1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion (see Chapter 31). Nausea and diarrhea are the most common side effects of *lubiprostone* (Figure 36.4). Nausea can be decreased if taken with food.

G. Misoprostol

Misoprostol [mye-soe-PROST-ole], a PGE_1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. *Misoprostol* interacts with prostaglandin receptors on parietal cells within

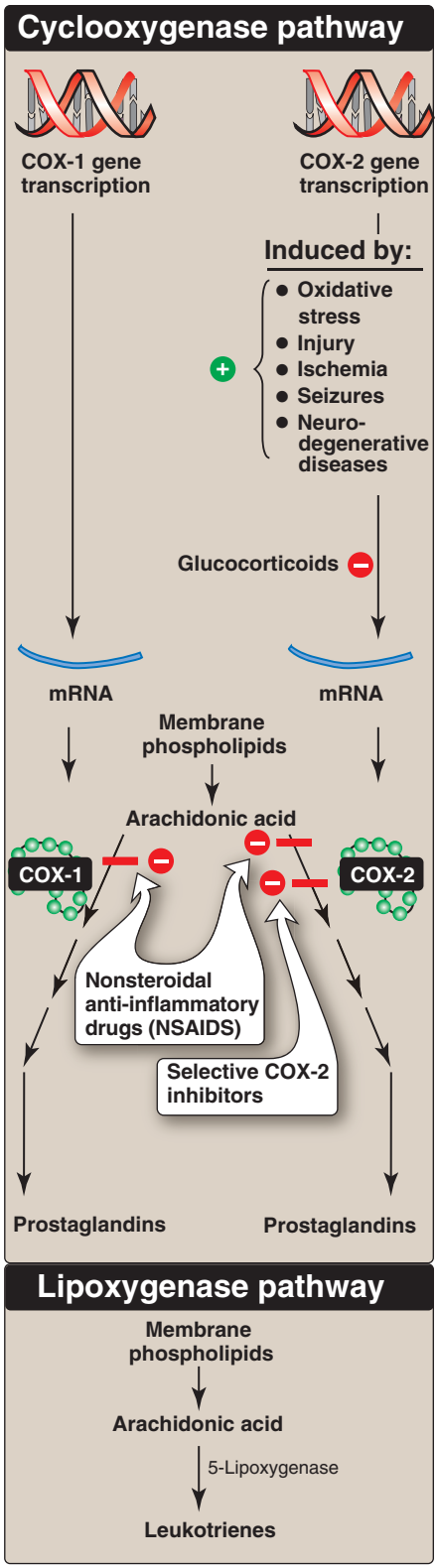

Figure 36.3
Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase.

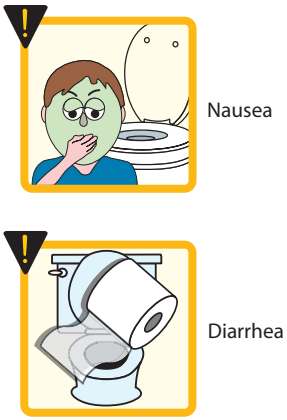

Figure 36.4
Some adverse reactions to *lubiprostone*.

the stomach, reducing gastric acid secretion. Furthermore, *misoprostol* has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects decreases the incidence of gastric ulcers caused by NSAIDs. [Note: There is a combination product containing *diclofenac* and *misoprostol*.] *Misoprostol* is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. *Misoprostol* has the potential risk to induce abortion in pregnant women. Therefore, the drug is contraindicated during pregnancy. Its use is limited by common side effects including diarrhea and abdominal pain.

H. Prostaglandin $F_{2\alpha}$ analogs

Bimatoprost [bih-MAT-o-prost], *latanoprost* [la-TAN-oh-prost], *tafluprost* [TAF-loo-prost], and *travoprost* [TRA-voe-prost] are $PGF_{2\alpha}$ analogs that are indicated for the treatment of open-angle glaucoma. By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure. They are administered as ophthalmic solutions once a day and are as effective as *timolol* or better in reducing intraocular pressure. *Bimatoprost* increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis. Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.

I. Prostacyclin (PGI_2) analogs

Epoprostenol [ee-poe-PROST-en-ol], the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin (*iloprost* [EYE-loe-prost] and *treprostinil* [tre-PROS-ti-nil]) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension. These drugs mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. These agents all have a short half-life. *Epoprostenol* and *treprostinil* are administered as a continuous intravenous infusion, and *treprostinil* may also be administered orally or via inhalation or subcutaneous infusion. Inhaled *iloprost* requires frequent dosing due to the short half-life (Figure 36.5). Dizziness, headache, flushing, and fainting are the most common adverse effects (Figure 36.6). Bronchospasm and cough can also occur after inhalation of *iloprost*.

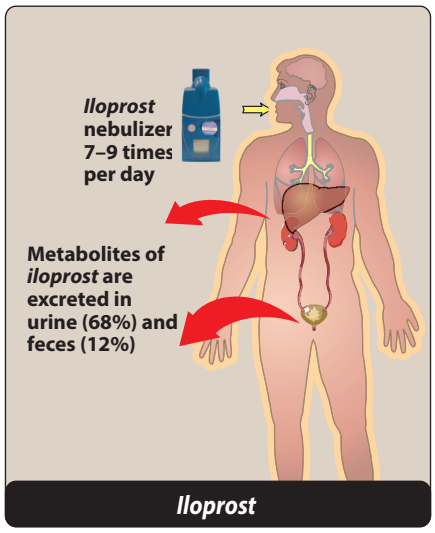

Figure 36.5
Administration and fate of *iloprost*.

III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of salicylic acid (*aspirin* [AS-pir-in], *diflunisal* [dye-FLOO-ni-sal], *salsalate* [SAL-sa-late]), propionic acid (*ibuprofen* [eye-bue-PROE-fen], *fenoprofen* [fen-oh-PROE-fen], *flurbiprofen* [flure-BI-proe-fen], *ketoprofen* [kee-toe-PROE-fen], *naproxen* [na-PROX-en], *oxaprozin* [ox-a-PROE-zin]), acetic acid (*diclofenac* [dye-KLOE-fen-ak], *etodolac* [ee-toe-DOE-lak], *indomethacin* [in-doe-METH-a-sin], *ketorolac* [kee-toe-ROLE-ak], *nabumetone* [na-BUE-me-tone], *sulindac* [sul-IN-dak], *tolmetin* [TOLE-met-in]), enolic acid (*meloxicam* [mel-OKS-i-kam], *piroxicam* [peer-OX-i-kam]), fenamates (*mefenamic* [me-fe-NAM-ik]

acid, *meclofenamate* [me-kloe-fen-AM-ate]), and the selective COX-2 inhibitor (*celecoxib* [sel-e-KOX-ib]). They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. [Note: Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, while inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.]

A. Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It has gained much more usage at lower doses for the prevention of cardiovascular events such as stroke and myocardial infarction (MI). *Aspirin* is often differentiated from other NSAIDs, since it is an irreversible inhibitor of cyclooxygenase activity.

1. Mechanism of action: *Aspirin* is a weak organic acid that irreversibly acetylates (and, thus, inactivates) cyclooxygenase (Figure 36.7). The other NSAIDs are all reversible inhibitors of cyclooxygenase. The NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect; Figure 36.8). However, as outlined below, not all NSAIDs are equally effective in each of these actions.

a. Anti-inflammatory actions: Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation in which prostaglandins act as mediators. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.

b. Analgesic action: PGE_2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs. No single NSAID has demonstrated superior efficacy over another, and all agents are generally considered to have equivalent efficacy. The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. One exception is *ketorolac*, which can be used for more severe pain but for only a short duration.

c. Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The NSAIDs lower body temperature in patients with fever by impeding PGE_2 synthesis and release. These agents essentially reset the "thermostat"

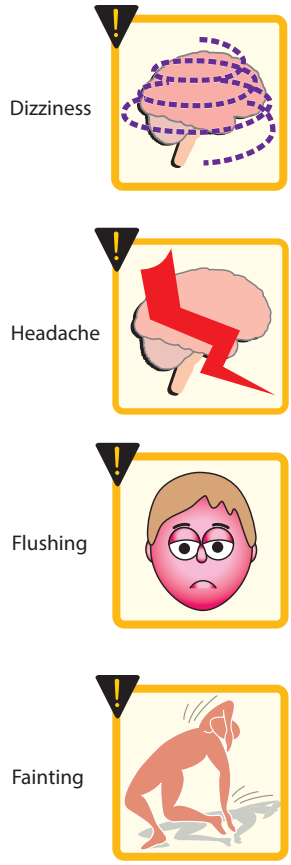

Figure 36.6
Some adverse reactions to *iloprost*.

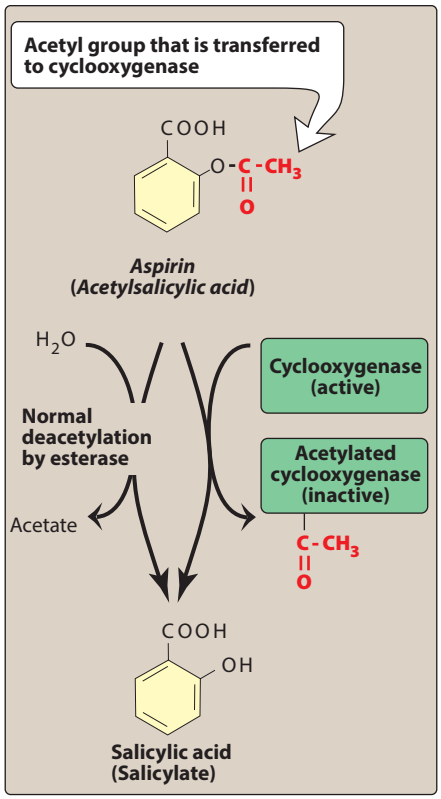

Figure 36.7
Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.

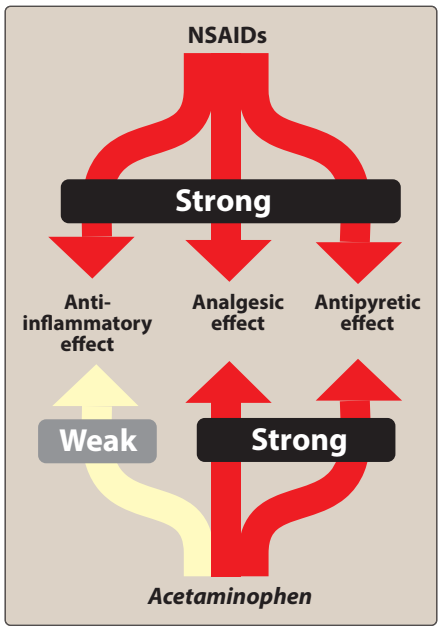

Figure 36.8
Actions of nonsteroidal anti-inflammatory drugs (NSAIDs) and *acetaminophen*.

toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. NSAIDs have no effect on normal body temperature.

2. Therapeutic uses:

a. Anti-inflammatory and analgesic uses: NSAIDs are used in the treatment of osteoarthritis, gout, and RA. These agents are also used to treat common conditions (for example, headache, arthralgia, myalgia, and dysmenorrhea) requiring analgesia. Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized. The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 36.9). For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

b. Antipyretic uses: *Aspirin*, *ibuprofen*, and *naproxen* may be used to treat fever. [Note: *Aspirin* should be avoided in patients less than 20 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome (a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death).]

c. Cardiovascular applications: *Aspirin* is used to inhibit platelet aggregation. Low-dose *aspirin* inhibits COX-1–mediated production of TXA_2, thereby reducing TXA_2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events. Low doses (doses less than 325 mg; many classify it as doses of 75 to 162 mg—commonly 81 mg) of *aspirin* are used prophylactically to 1) reduce the risk of recurrent cardiovascular events and/or death in patients with previous MI or unstable angina pectoris, 2) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had a prior TIA or stroke, and 3) reduce the risk of cardiovascular events or death in high-risk patients such as those with chronic stable angina or diabetes. As *aspirin* irreversibly inhibits COX-1 (Figure 36.10) the antiplatelet effects persist for the life of the platelet. Chronic use of low doses allows for continued inhibition as new platelets are generated. *Aspirin* is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.

d. External applications: *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs.

3. Pharmacokinetics:

a. Aspirin: After oral administration, *aspirin* is rapidly deacetylated by esterases in the body, thereby producing salicylate. Unionized salicylates are passively absorbed mostly from the upper small

intestine (dissolution of the tablets is favored at the higher pH of the gut). Salicylates (except for *diflunisal*) cross both the blood–brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more (Figure 36.11). Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion. At low doses of *aspirin* (less than 2 g/day), uric acid secretion is decreased, whereas at high doses, uric acid secretion may be unchanged or increased. Therefore, *aspirin* is avoided in gout or in patients taking *probenecid*.

b. Other NSAIDs: Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example, *nabumetone* and *sulindac*) have active metabolites. Elimination of active drug and metabolites is primarily via the urine.

4. Adverse events: Because of the associated adverse events below, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. Gastrointestinal: The most common adverse effects of NSAIDs are GI related, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI_2) inhibits gastric acid secretion, and PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients with a high risk for GI events, proton pump inhibitors or *misoprostol* should be used concomitantly to prevent NSAID-induced ulcers (see Chapter 31).

b. Increased risk of bleeding (antiplatelet effect): TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. *Aspirin* irreversibly inhibits COX-1–mediated TXA_2 formation, while other NSAIDs reversibly inhibit the production of TXA_2. Because platelets lack nuclei, they cannot synthesize new enzyme when inhibited by *aspirin*, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days). Because of the decrease in TXA_2 production, platelet aggregation (the first step in thrombus formation) is reduced, producing an antiplatelet effect with a prolonged bleeding time. For this reason, *aspirin* is often held, or not given, at least 1 week prior to surgery. NSAIDs other than *aspirin* are not utilized for their antiplatelet effect but can still prolong bleeding time. [Note: As agents become more COX-2 selective, they are

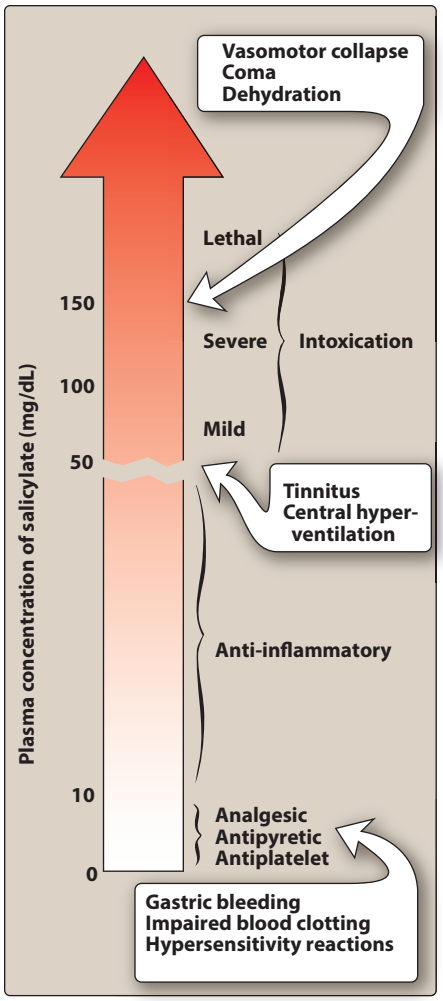

Figure 36.9
Dose-dependent effects of salicylate.

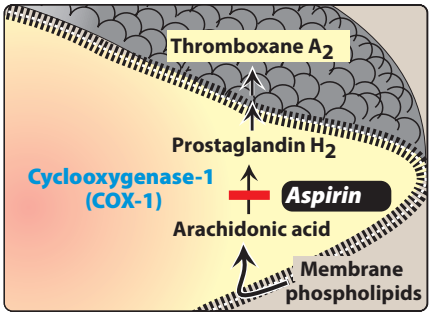

Figure 36.10
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

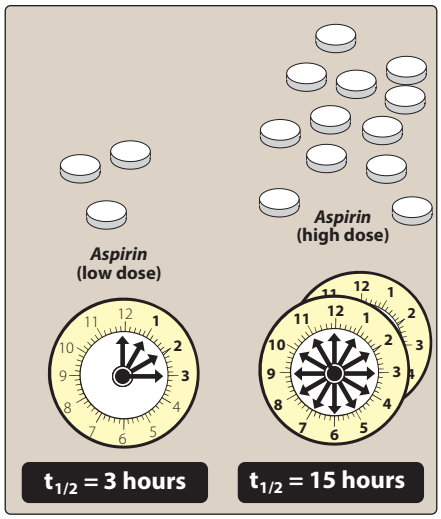

Figure 36.11
Effect of dose on the half-life of *aspirin*.

expected to have less effect on platelet inhibition and bleeding time.] NSAIDs can also block *aspirin* binding to cyclooxygenase when used concomitantly. Patients who take *aspirin* for cardioprotection should avoid concomitant NSAID use if possible.

c. **Actions on the kidney:** NSAIDs prevent the synthesis of PGE_2 and PGI_2, prostaglandins that are responsible for maintaining renal blood flow (Figure 36.12). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema in some patients. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications.

d. **Cardiac effects:** Agents such as *aspirin*, with a very high degree of COX-1 selectivity, have shown a cardiovascular protective effect thought to be due to a reduction in the production of TXA_2. Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI_2 production mediated by COX-2. An increased risk for cardiovascular events, including MI and stroke, has been associated with all NSAIDs except *aspirin*. Use of NSAIDs, other than *aspirin*, is discouraged in patients with established cardiovascular disease. For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, *naproxen* appears to be the least likely to be harmful. NSAID use should be limited to the lowest dose possible for the shortest duration.

e. **Other side effects:** NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and, therefore, increase the risk of exacerbations of asthma. Central nervous system (CNS) adverse events, such as headache,

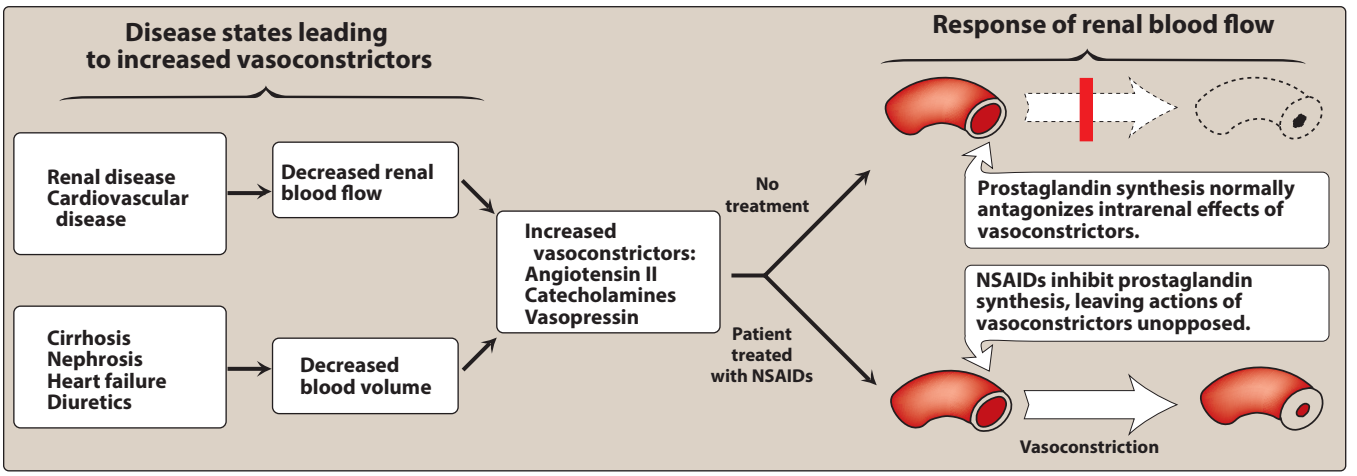

Figure 36.12
Renal effect of NSAIDs inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs.

tinnitus, and dizziness, may occur. Approximately 15% of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Fatal anaphylactic shock is rare. Patients with severe hypersensitivity to *aspirin* should avoid using NSAIDs.

f. Drug interactions: Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in increased concentration of free salicylate. Alternatively, *aspirin* can displace other highly protein-bound drugs, such as *warfarin*, *phenytoin*, or *valproic acid*, resulting in higher free concentrations of these agents (Figure 36.13).

g. Toxicity: Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result (Figure 36.9). Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *aspirin* can cause death in children.

h. Pregnancy: Most NSAIDs are pregnancy risk category C in the first two trimesters. [Note: *Acetaminophen* is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

B. Celecoxib

Celecoxib [SEL-e-KOX-ib], a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1 (Figure 36.14). Unlike the inhibition of COX-1 by *aspirin* (which is rapid and irreversible), the inhibition of COX-2 is reversible.

1. Therapeutic uses: *Celecoxib* is approved for the treatment of RA, osteoarthritis, and acute mild to moderate pain. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain.

2. Pharmacokinetics: *Celecoxib* is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in feces and urine. The half-life is about 11 hours, and the drug may be dosed once or twice daily. The dosage should be reduced in those with moderate hepatic impairment, and *celecoxib* should be avoided in patients with severe hepatic or renal disease.

3. Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. *Celecoxib*, when used without concomitant *aspirin* therapy, is associated with less GI bleeding and dyspepsia than other NSAIDs. However, this benefit is lost when *aspirin* is added to *celecoxib* therapy. Patients who are at high risk of ulcers and require *aspirin* for cardiovascular prevention should avoid the use of *celecoxib*. Like other NSAIDs, the

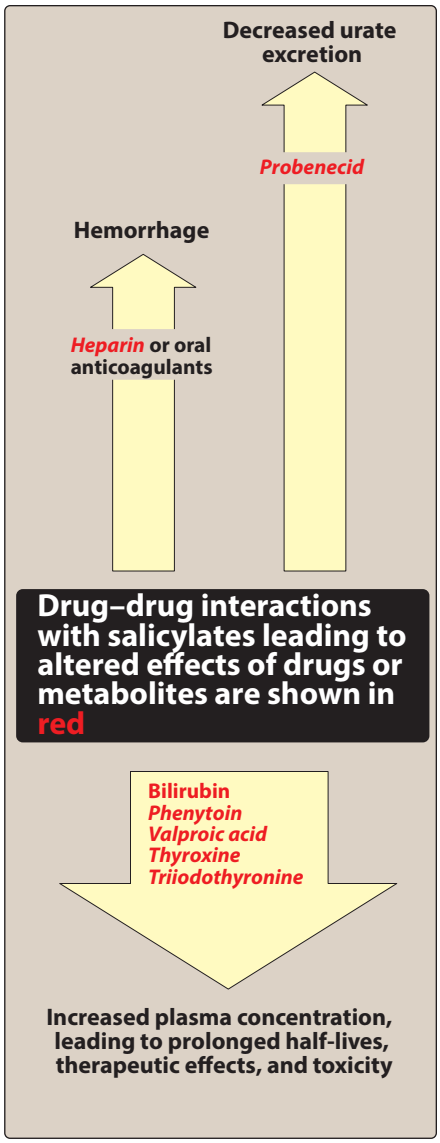

Figure 36.13
Drugs interacting with salicylates.

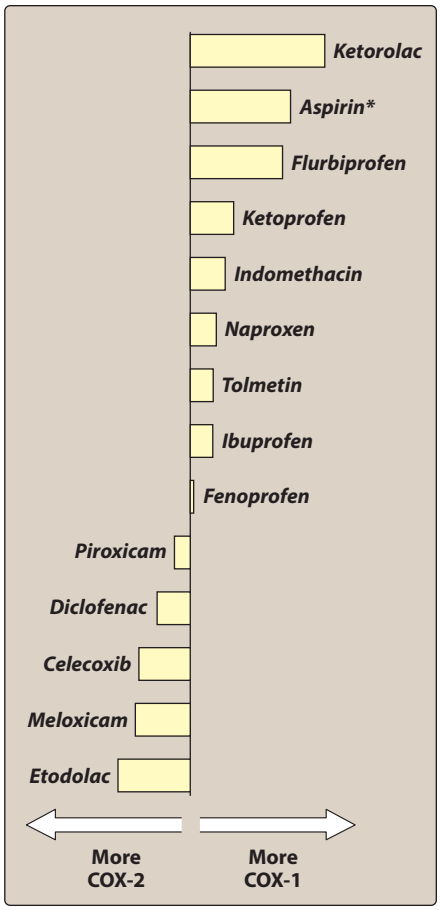

Figure 36.14
Relative selectivity of some commonly used NSAIDs. Data shown as the logarithm of their ratio of IC_{80} (drug concentration to achieve 80% inhibition of cyclooxygenase). **Aspirin* graphed for IC_{50} value due to it showing significantly more COX-1 selectivity at lower doses and graph using higher concentrations does not accurately reflect the usage or selectivity of *aspirin*.

drug has a similar risk for cardiovascular events. *Celecoxib* should be used with caution in patients who are allergic to sulfonamides. Patients who have had anaphylactoid reactions to *aspirin* or non-selective NSAIDs may be at risk for similar effects with *celecoxib*. Inhibitors of CYP2C9, such as *fluconazole* and *fluvastatin*, may increase serum levels of *celecoxib*.

Figure 36.15 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

IV. ACETAMINOPHEN

Acetaminophen [a-SEET-a-MIN-oh-fen] (*N*-acetyl-*p*-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. *Acetaminophen* has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. *Acetaminophen* does not affect platelet function or increase bleeding time. It is not considered to be an NSAID.

A. Therapeutic uses

Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti-inflammatory action of NSAIDs. *Acetaminophen* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with *aspirin*).

B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal circumstances, *acetaminophen* is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *acetaminophen* is hydroxylated to form *N*-acetyl-*p*-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of *acetaminophen*, NAPQI reacts with the sulfhydryl group of glutathione, which is produced by the liver, forming a nontoxic substance (Figure 36.16). *Acetaminophen* and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

C. Adverse effects

At normal therapeutic doses, *acetaminophen* is virtually free of significant adverse effects. With large doses of *acetaminophen*, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (Figure 36.16). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of *acetaminophen*-induced hepatotoxicity. [Note: *N-acetylcysteine*, which contains sulfhydryl groups to which the toxic metabolite can bind, is an antidote

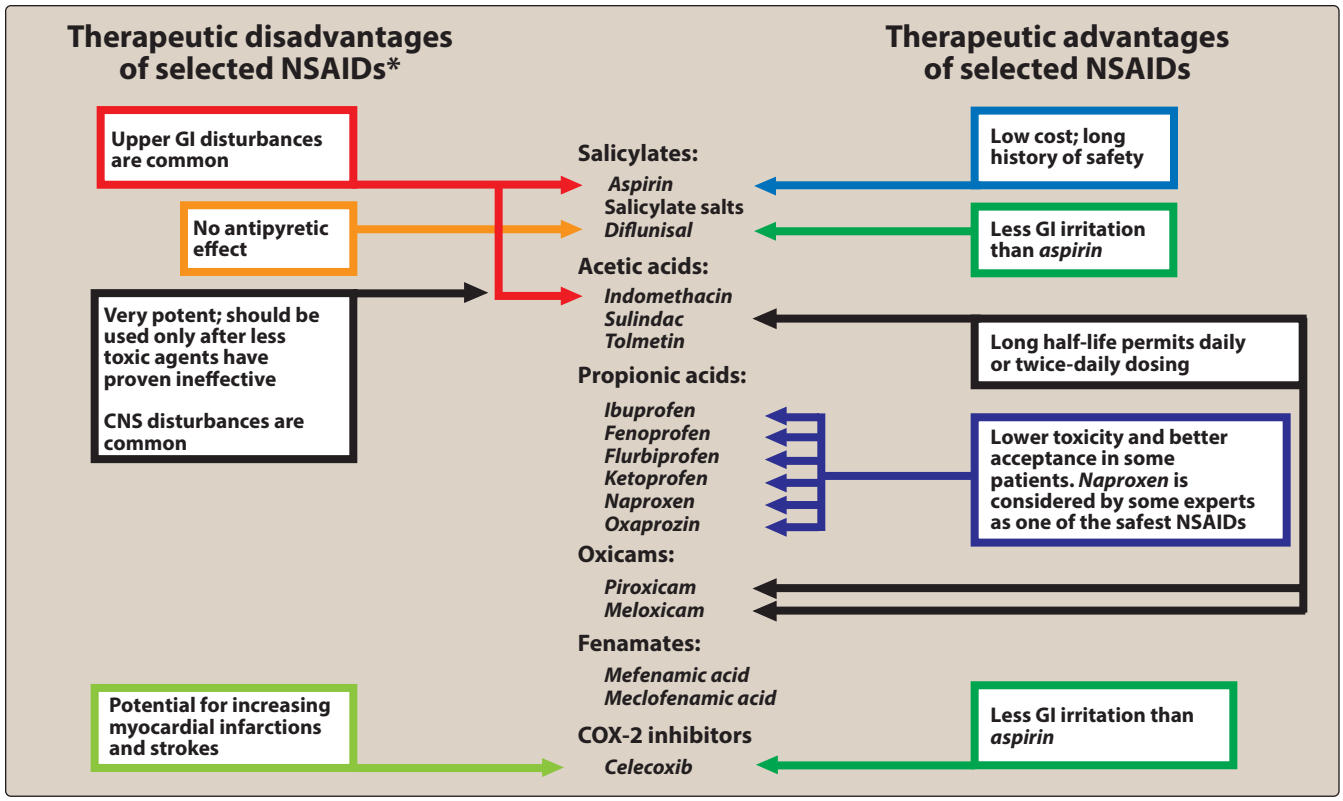

Figure 36.15
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke.

in cases of overdose (see Chapter 48).] *Acetaminophen* should be avoided in patients with severe hepatic impairment.

V. DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. When a patient is diagnosed with RA, DMARDs should be started within 3 months to help stop the progression of the disease at the earlier stages. NSAIDs or corticosteroids may also be used for relief of symptoms if needed.

A. Choice of drug

No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary. Monotherapy may be initiated with any of the DMARDs (*methotrexate*, *leflunomide*, *hydroxychloroquine*, or *sulfasalazine*) for patients with low disease activity. For patients with moderate to high disease activity or inadequate response to monotherapy, combination DMARD therapy (usually *methotrexate* based) or use of anti-TNF drugs (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*) may be needed. For patients with more established disease, use of other biologic therapies

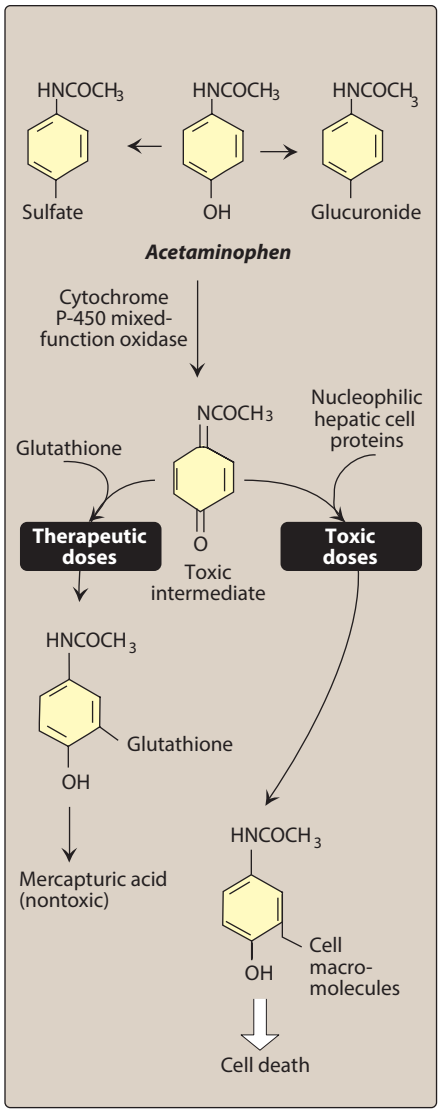

Figure 36.16
Metabolism of *acetaminophen*.

(for example, *abatacept*, *rituximab*) can be considered. Most of these agents are contraindicated for use in pregnant women.

B. Methotrexate

Methotrexate [meth-oh-TREX-ate], used alone or in combination therapy, has become a mainstay of treatment in patients with rheumatoid or psoriatic arthritis. *Methotrexate* is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. Response to *methotrexate* occurs within 3 to 6 weeks of starting treatment; it can also slow the appearance of new erosions within involved joints. The other DMARDs can be added to *methotrexate* therapy if there is partial or no response to maximum doses of *methotrexate*. Doses of *methotrexate* required for RA treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects. The most common side effects observed after *methotrexate* treatment of RA are mucosal ulceration and nausea. Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Taking *leucovorin* (*folinic acid*) once daily after *methotrexate* reduces the severity of adverse effects. *Folic acid* taken on off-days is widely used.] Periodic liver enzyme tests, complete blood counts, and monitoring for signs of infection are recommended.

C. Hydroxychloroquine

Hydroxychloroquine [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA, often combined with *methotrexate*. This agent is also used in the treatment of lupus and malaria. Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. *Hydroxychloroquine* has less effects on the liver and immune system than other DMARDs; however, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits. It may also cause CNS disturbances, GI upset, and skin discoloration and eruptions.

D. Leflunomide

Leflunomide [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). Activated proliferating lymphocytes require constant DNA synthesis to proliferate. Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis. After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH (Figure 36.17). *Leflunomide* is approved for the treatment of RA. It can be used as monotherapy or in combination with *methotrexate*. The most common adverse effects are headache, diarrhea, and nausea. Other untoward effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia. It is not recommended in patients with liver disease, because of a risk of hepatotoxicity. Monitoring parameters include signs of infection, complete blood counts, and liver enzymes.

E. Minocycline

Minocycline [mi-noe-SYE-kleen], a tetracycline antibiotic, is considered to be a DMARD. Although *minocycline* has been shown to be effective in the treatment of early RA, it is generally not utilized as first-line therapy. *Minocycline* can be used as monotherapy or in combination with other DMARDs.

F. Sulfasalazine

Sulfasalazine [sul-fa-SAH-la-zeen] is also used for early, mild RA in combination with *methotrexate* and/or *hydroxychloroquine*. Onset of activity is 1 to 3 months, and it is associated with leukopenia. Its mechanism of action in treating RA is unclear.

G. Glucocorticoids

Glucocorticoids (see Chapter 27) are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until DMARDs are effective. Timely dose reductions and cessation are necessary to avoid adverse effects associated with long-term use.

VI. BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF-α inhibitors (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy. As with DMARDs, the decision to continue or stop a biological agent can often be made within 3 months after initiation of therapy. If a patient has failed therapy with one TNF-α inhibitor, a trial with a different TNF-α inhibitor or a non-TNF biologic therapy (*abatacept*, *rituximab*, *tocilizumab*, *tofacitinib*) is appropriate. TNF-α inhibitors can be administered with any of the other drugs for RA, except for the non-TNF biologic therapies (due to increased risk of infection).

Patients receiving TNF-α inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia. Live vaccinations should not be administered while on TNF-α inhibitor therapy. These agents should be used very cautiously in those with heart failure, as they can cause and/or worsen preexisting heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors. Characteristics of the TNF-α inhibitors and other biologic therapies are outlined below.

A. Adalimumab

Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF-α, thereby interfering with endogenous TNF-α

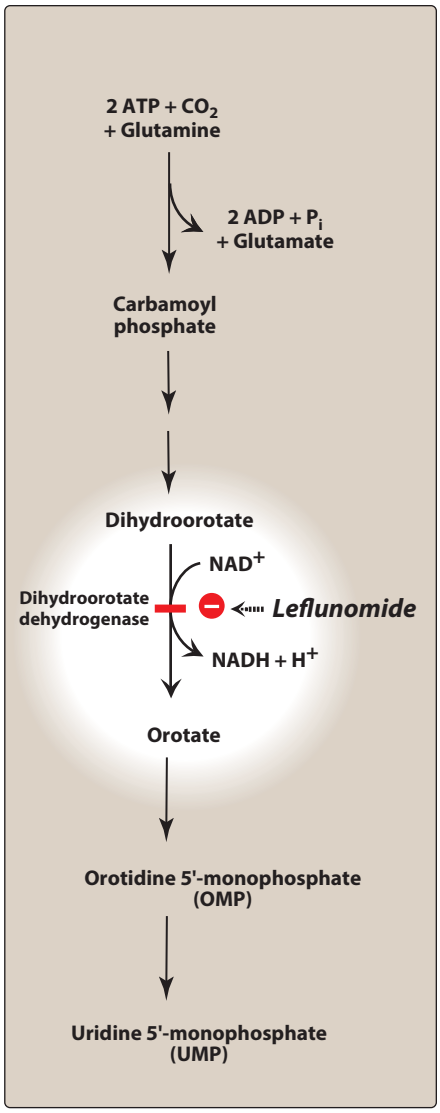

Figure 36.17
Site of action of *leflunomide*.

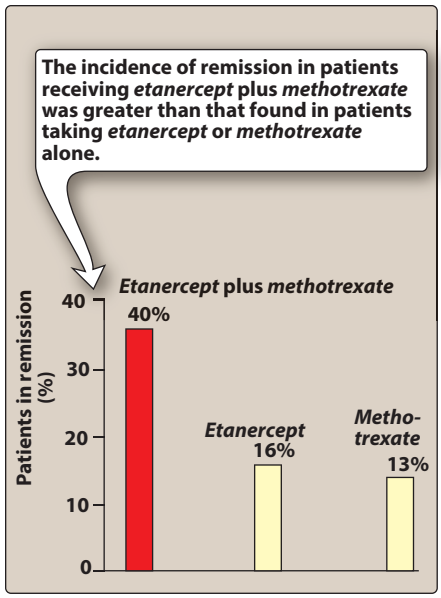

Figure 36.18
Incidence of remission from the symptoms of RA after 1 year of therapy.

activity by blocking its interaction with cell surface receptors. This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with *methotrexate*. It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease. *Adalimumab* is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infections, such as urinary tract infections, upper respiratory tract infections, and sinusitis.

B. Certolizumab pegol

Certolizumab [ser-toe-LIZ-oo-mab] is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions. It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. It has similar indications to *adalimumab*. Adverse effects are similar to other TNF-α inhibitors.

C. Etanercept

Etanercept [ee-TAN-er-cept] is a genetically engineered, soluble, recombinant, fully human receptor fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with *methotrexate*. It is also approved for use in ankylosing spondylitis and psoriasis. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in retarding the RA disease process, improving function, and achieving remission (Figure 36.18). *Etanercept* is given subcutaneously twice a week. The drug is generally well tolerated. As with all TNF-α inhibitors, it can increase the risk for infections, malignancy, and new or worsening heart failure.

D. Golimumab

Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. This compound is administered subcutaneously once a month in combination with *methotrexate* or other nonbiologic DMARDs. *Golimumab* may increase hepatic enzymes. Reactivation of hepatitis B may occur in chronic carriers. As with other TNF-α inhibitors, this drug may increase the risk of malignancies and serious infections.

E. Infliximab

Infliximab [in-FLIX-i-mab] is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α and inhibits binding with its receptors. *Infliximab* is approved for use in combination with *methotrexate* in patients with RA who have had inadequate response to *methotrexate* monotherapy. This agent is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies, resulting in reduced efficacy. Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease. *Infliximab* is administered as an IV infusion every 8 weeks. Infusion

site reactions, such as fever, chills, pruritus, and urticaria, may occur. Infections (for example, pneumonia, cellulitis, and activation of latent tuberculosis), leukopenia, and neutropenia have also been reported.

F. Abatacept

T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (that is, macrophages or B cells) must interact with the receptor on the T cell and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. *Abatacept* [a-BAT-ah-cept] is a soluble recombinant fusion protein that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation. This agent is indicated for patients with moderate to severe RA who have had an inadequate response to DMARDs or TNF-α inhibitors. *Abatacept* is administered as an IV infusion every 4 weeks. Common adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF-α inhibitors is not recommended due to increased risk of serious infections.

G. Rituximab

B lymphocytes are derived from the bone marrow and are necessary for efficient immune response. In RA, however, B cells can perpetuate the inflammatory process in the synovium by 1) activating T lymphocytes, 2) producing autoantibodies and rheumatoid factor, and 3) producing proinflammatory cytokines, such as TNF-α and IL-1. *Rituximab* [ri-TUK-si-mab] is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion. This agent is indicated for use in combination with *methotrexate* for patients with moderate to severe RA who have had an inadequate response to TNF-α inhibitors. *Rituximab* is administered as an intravenous infusion every 16 to 24 weeks. To reduce the severity of infusion reactions, *methylprednisolone* is administered 30 minutes prior to each infusion. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints with this agent and typically occur during the first infusion.

H. Tocilizumab

Tocilizumab [toe-si-LIZ-ue-mab] is a monoclonal antibody that inhibits the actions of IL-6 by blocking the IL-6 receptor. *Tocilizumab* is administered as an intravenous infusion every 4 weeks. The drug can be used as monotherapy or in combination with *methotrexate* or other nonbiologic DMARDs for patients with moderate to severe RA.

I. Tofacitinib

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane. Cytokines, growth factors, interferons, ILs, and erythropoietin can lead to an increase in Janus kinase activity and activation of the immune system. *Tofacitinib* [toe-fa-SYE-ti-nib] is an oral inhibitor of Janus kinases indicated for the treatment of moderate to severe RA in patients who have had an inadequate response

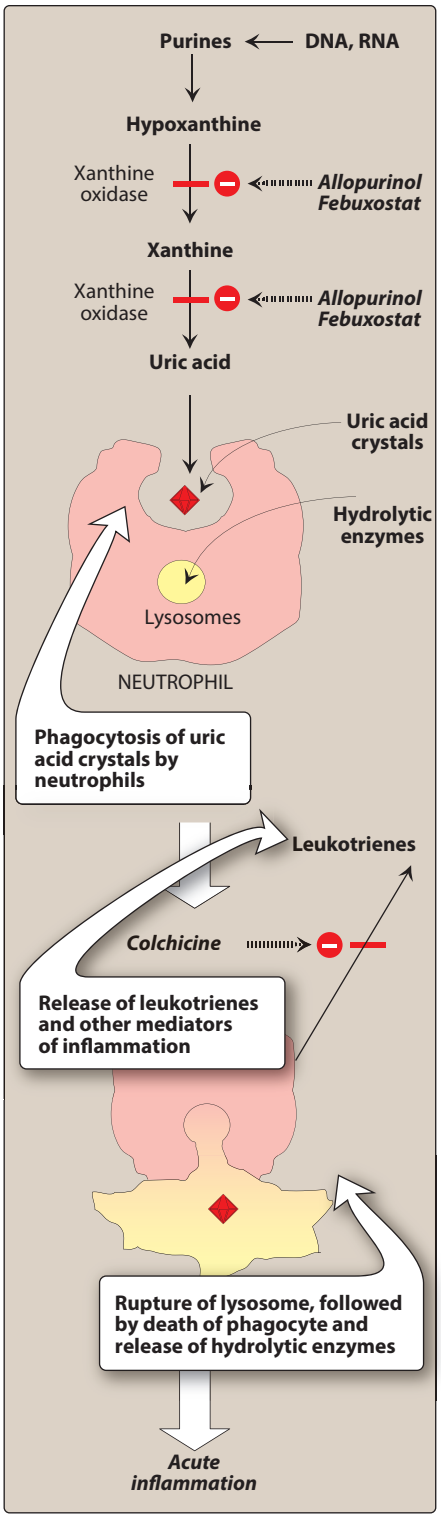

Figure 36.19
Role of uric acid in the inflammation of gout.

or intolerance to *methotrexate*. Metabolism of *tofacitinib* is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is taken with potent inhibitors or inducers of this isoenzyme. Hemoglobin concentrations must be greater than 9 g/dL to start *tofacitinib* and must be monitored during therapy due to the risk for anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. *Tofacitinib* treatment may also increase the risk for secondary malignancy, opportunistic infections, renal, or hepatic dysfunction.

J. Anakinra

IL-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption. *Anakinra* [an-a-KIN-ra] is an IL-1 receptor antagonist. *Anakinra* treatment leads to a modest reduction in the signs and symptoms of moderate to severe RA in patients who have failed one or more DMARDs. This agent is associated with neutropenia and is infrequently used in the treatment of RA.

VII. DRUGS USED FOR THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 36.19). The cause of hyperuricemia is an imbalance between overproduction of uric acid and/or the inability of the patient to excrete it via renal elimination. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

A. Treatment of acute gout

Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, or *colchicine* are effective alternatives for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, with systemic corticosteroid therapy for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

B. Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the

use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.]

C. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.

1. **Mechanism of action:** *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles.

2. **Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: *Colchicine* must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks for safety reasons. *Colchicine* is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.

3. **Pharmacokinetics:** *Colchicine* is administered orally and is rapidly absorbed from the GI tract. *Colchicine* is recycled in the bile and is excreted unchanged in feces or urine.

4. **Adverse effects:** *Colchicine* may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 36.20). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. Dosage adjustments are required in patients taking CYP3A4 inhibitors, like *clarithromycin*, *itraconazole*, and protease inhibitors. For patients with severe renal impairment, the dose should be reduced.

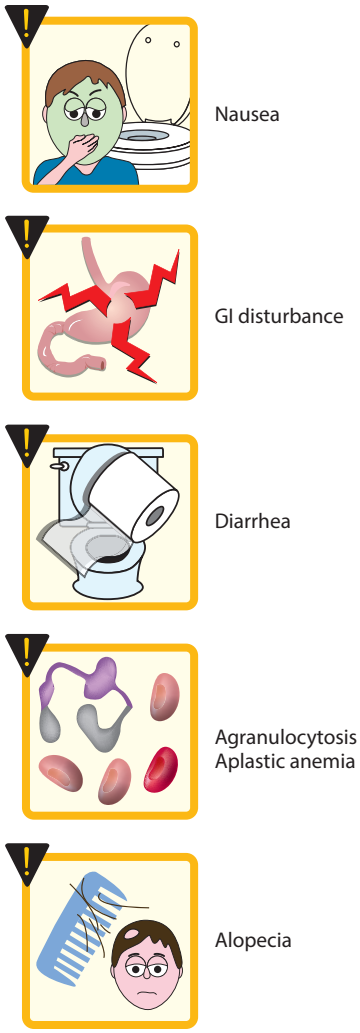

Figure 36.20
Some adverse effects of *colchicine*. GI = gastrointestinal.

D. Allopurinol

Allopurinol [al-oh-PURE-i-nole], a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (Figure 36.19).

1. **Therapeutic uses:** *Allopurinol* is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

2. **Pharmacokinetics:** *Allopurinol* is completely absorbed after oral administration. The primary metabolite is alloxanthine (oxypurinol), which is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosage. The drug and its active metabolite are excreted in the feces and urine. The dosage should be reduced if the creatinine clearance is less than 50 mL/min.

3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, *colchicine*, NSAIDs, or corticosteroids can be administered concurrently. *Allopurinol* interferes with the metabolism of *6-mercaptopurine*, the immunosuppressant *azathioprine*, and *theophylline*, requiring a reduction in dosage of these drugs.

E. Febuxostat

Febuxostat [feb-UX-oh-stat], a xanthine oxidase inhibitor, is structurally unrelated to *allopurinol*; however, it has the same indications. In addition, the same drug interactions with *6-mercaptopurine*, *azathioprine*, and *theophylline* apply. Its adverse effect profile is similar to that of *allopurinol*, although the risk for rash and hypersensitivity reactions may be reduced. *Febuxostat* does not have the same degree of renal elimination as *allopurinol* and thus requires less adjustment in those with reduced renal function.

F. Probenecid

Probenecid [proe-BEN-a-sid] is a uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. *Probenecid* blocks the tubular secretion of *penicillin* and is sometimes used to increase levels of β-lactam antibiotics. It also inhibits the excretion of *methotrexate*, *naproxen*, *ketoprofen*, and *indomethacin*. *Probenecid* should be avoided if the creatinine clearance is less than 50 mL/min.

G. Pegloticase

Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. *Pegloticase* is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks.

VIII. DRUGS USED TO TREAT HEADACHE

The most common types of headaches are migraine, tension-type, and cluster headaches. Migraine can usually be distinguished from cluster headaches and tension-type headaches by its characteristics as shown

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

Figure 36.21
Characteristics of migraine, cluster, and tension-type headaches.

in Figure 36.21. Migraines, for example, present as a pulsatile, throbbing pain, whereas cluster headaches present as excruciating, sharp, steady pain. This is in contrast to tension-type headaches, which present as dull pain, with a persistent, tightening feeling in the head. Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually unilateral. The headaches significantly affect quality of life and result in considerable health care costs. Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines (Figure 36.22).

A. Types of migraine

There are two main types of migraine headaches. The first, migraine without aura, is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). The majority of patients with migraine do not have aura. In the second type, migraine with aura, the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual (flashes, zigzag lines, and glare), occurring approximately 20 to 40 minutes before headache pain begins. In the 15% of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache in migraines with or without auras is similar. Women are threefold more likely than men to experience either type of migraine.

TRIPTANS
Almotriptan AXERT
Eletriptan RELPAX
Frovatriptan FROVA
Naratriptan AMERGE
Rizatriptan MAXALT
Sumatriptan IMITREX, ALSUMA
Zolmitriptan ZOMIG

ERGOTS
Dihydroergotamine MIGRANAL, VARIOUS

NSAIDs
Aspirin BAYER, BUFFERIN, ECOTRIN
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac TORADOL
Naproxen ALEVE, ANAPROX, NAPROSYN

PROPHYLACTIC AGENTS
Anticonvulsants
Beta-blockers
Calcium channel blockers
Tricyclic antidepressants

Figure 36.22
Summary of drugs used to treat migraine headache.

B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. The hypoperfusion persists throughout the aura and well into the headache phase. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial vasodilation, which leads to release of neuroactive molecules, such as substance P, neurokinin A, and calcitonin gene–related peptide.

C. Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics such as NSAIDs and antiemetics (for example, *prochlorperazine*) to control vomiting. Opioids are reserved as rescue medication when other treatments of a severe migraine attack are not successful. Specific migraine therapy includes triptans and ergot alkaloids, which are 5-$HT_{1B/1D}$ receptor and 5-HT_{1D} receptor agonists, respectively. It has been proposed that activation of 5-HT_1 receptors by these agents leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

1. **Triptans:** This class of drugs includes *almotriptan* [al-moe-TRIP-tan], *eletriptan* [el-e-TRIP-tan], *frovatriptan* [froe-va-TRIP-tan], *naratriptan* [nar-a-TRIP-tan], *rizatriptan* [rye-za-TRIP-tan], *sumatriptan* [soo-ma-TRIP-tan], and *zolmitriptan* [zole-ma-TRIP-tan]. *Sumatriptan* was the first available triptan, and is the prototype of this class. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70% of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with *dihydroergotamine* and the vasoconstriction caused by *ergotamine* (see below) are much less pronounced with the triptans. *Sumatriptan* is given subcutaneously, intranasally, or orally (*sumatriptan* is also available in a combination product with *naproxen*). *Zolmitriptan* is available orally and by nasal spray. [Note: All other agents are taken orally.] The onset of the parenteral drug *sumatriptan* is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. *Frovatriptan* is the longest-acting triptan, with a half-life of more than 24 hours. Individual responses to triptans vary, and a trial of more than one triptan may be necessary

before treatment is successful. Elevation of blood pressure and other cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. Dizziness and malaise have also been seen with the use of triptans.

2. **Ergot alkaloids:** *Ergotamine* [er-GOT-a-meen] and *dihydroergotamine* [dye-hye-droe-er-GOT-a-meen], a semisynthetic derivative of *ergotamine*, are ergot alkaloids approved for the treatment of migraine headaches. The action of the ergot alkaloids is complex, with ability to bind to 5-HT_1 receptors, α receptors, and dopamine receptors. 5-HT_1 receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents. *Ergotamine* is currently available sublingually and is mostly effective when used in the early stages of the migraine. It is also available as an oral tablet or suppository containing both *ergotamine* and caffeine. *Ergotamine* is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches. *Dihydroergotamine* is administered intravenously or intranasally and has an efficacy similar to that of *sumatriptan*. The use of *dihydroergotamine* is limited to severe cases of migraines. Nausea is a common adverse effect. *Ergotamine* and *dihydroergotamine* are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors.

D. Prophylaxis for migraine headache

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. β-Blockers are the drugs of choice for migraine prophylaxis (Figure 36.23). *Propranolol* and other β-blockers, such as *metoprolol*, *atenolol*, *and nadolol*, have been shown to be effective. The calcium channel blocker *verapamil* is an alternative. Anticonvulsants (*divalproex*) and antidepressants (tricyclics) have also shown effectiveness in preventing migraine. Antidepressants are especially useful for migraine prophylaxis in patients with comorbid depression.

E. Drugs for tension and cluster headache

Analgesics such as NSAIDs (for example, *naproxen* and *ibuprofen*), *acetaminophen*, and *aspirin* are used for symptomatic relief of tension headaches. *Acetaminophen* and/or *aspirin* may also be combined with caffeine. [Note: Caffeine is believed to increase the central effectiveness of *acetaminophen* and *aspirin*.] *Butalbital*, a barbiturate, in combination with *acetaminophen* or *aspirin* with or without caffeine is also used in tension headaches. Inhalation of 100% oxygen and triptans (especially *sumatriptan*) are used as first-line abortive strategies for cluster headache.

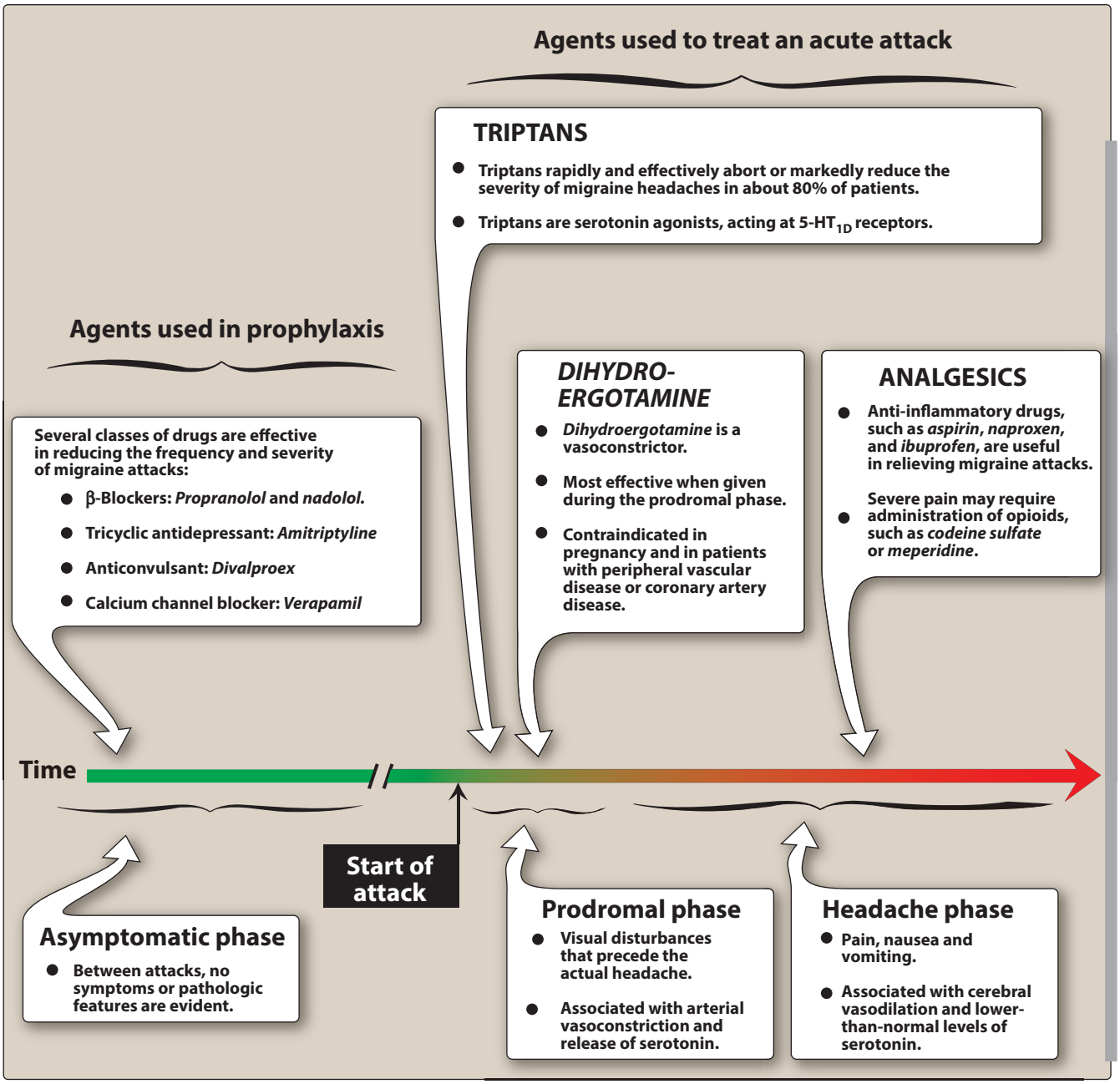

Figure 36.23
Drugs useful in the treatment and prophylaxis of migraine headaches.

Study Questions

Choose the ONE best answer.

36.1 A 64-year-old male presents with mild to moderate musculoskeletal back pain after playing golf. He states he has tried acetaminophen and that it did not help. His past medical history includes diabetes, hypertension, hyperlipidemia, gastric ulcer (resolved), and coronary artery disease. Which of the following is the most appropriate NSAID regimen to treat this patient's pain?

A. Celecoxib.
B. Indomethacin and omeprazole.
C. Naproxen and omeprazole.
D. Naproxen.

Correct answer = C. This patient is at high risk of future ulcers, due to the history of gastric ulcer. Therefore, using a regimen that includes an agent that is more COX-2 selective or a proton pump inhibitor is warranted. Therefore, D is incorrect. Choices A and B are incorrect because this patient has significant cardiovascular risk and a history of coronary artery disease. Naproxen is thought of as the safest NSAID regarding cardiovascular disease, though it still can present risks. Therefore, C is correct as it uses the first-choice NSAID with the GI protection of a proton pump inhibitor.

36.2 Which of the following correctly represents the mechanism of action of tofacitinib in the treatment of RA?

A. TNF-α inhibitor.
B. Inhibitor of Janus kinases.
C. IL-6 receptor blocker.
D. Dihydrofolate reductase inhibitor.

Correct answer = B. Methotrexate inhibits dihydrofolate reductase. Etanercept is a TNF-α inhibitor. An IL-6 inhibitor is tocilizumab. Tofacitinib is an inhibitor of Janus kinase 1, 3, and, to a lesser extent, 2.

36.3 A 64-year-old male presents with signs and symptoms of an acute gouty flare. His doctor wishes to treat him accordingly to improve his symptoms. Which of the following strategies would be the LEAST likely to acutely improve his gout symptoms and pain?

A. Naproxen.
B. Colchicine.
C. Probenecid.
D. Prednisone.

Correct answer = C. Probenecid is a uricosuric agent indicated to lower serum urate levels to prevent gout attacks. It is not indicated during acute gout flares and should not be started until after the resolution of an acute attack. Naproxen, colchicine, and prednisone all represent viable treatment options that acutely reduce pain and inflammation associated with acute gout attacks.

36.4 Which of the following drugs for headache is contraindicated in patients with peripheral vascular disease?

A. Ergotamine.
B. Aspirin.
C. Acetaminophen.
D. Naproxen
E. Ibuprofen.

Correct answer = A. Ergotamine is contraindicated in peripheral vascular disease since it is a significant vasoconstrictor.