CHAPTER 31

Opioid Analgesics & Antagonists

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CASE STUDY

A 60-year-old man with a history of moderate chronic obstructive pulmonary disease presents in the emergency department with a broken hip suffered in an automobile accident. He complains of severe pain. What is the most appropriate immediate treatment for his pain? Are any special precautions needed?

Morphine, the prototypical opioid agonist, has long been known to relieve severe pain with remarkable efficacy. The opium poppy is the source of crude opium from which Sertürner in 1803 isolated morphine, the pure alkaloid, naming it after Morpheus, the Greek god of dreams. It remains the standard against which all drugs that have strong analgesic action are compared. These drugs are collectively known as opioid analgesics and include not only the natural and semisynthetic alkaloid derivatives from opium but also synthetic surrogates, other opioid-like drugs whose actions are blocked by the nonselective antagonist naloxone, plus several endogenous peptides that interact with the different subtypes of opioid receptors.

BASIC PHARMACOLOGY OF THE OPIOID ANALGESICS

Source

Opium, the source of morphine, is obtained from the poppy, *Papaver somniferum* and *P album*. After incision, the poppy seed pod exudes a white substance that turns into a brown gum that is crude opium. Opium contains many alkaloids, the principal one being morphine, which is present in a concentration of about 10%. Codeine is synthesized commercially from morphine.

*Deceased

Classification & Chemistry

Opioid drugs include full agonists, partial agonists, and antagonists. Morphine is a full agonist at the **μ (mu)-opioid receptor,** the major analgesic opioid receptor (Table 31–1). In contrast, codeine functions as a partial (or "weak") μ-receptor agonist. Other opioid receptor subtypes include **δ (delta)** and **κ (kappa)** receptors. Simple substitution of an allyl group on the nitrogen of the full *agonist* morphine plus addition of a single hydroxyl group results in naloxone, a strong μ-receptor *antagonist*. The structures of some of these compounds are shown later in this chapter. Some opioids, eg, nalbuphine, are capable of producing an agonist (or partial agonist) effect at one opioid receptor subtype and an antagonist effect at another. The receptor activating properties and affinities of opioid analgesics can be manipulated by pharmaceutical chemistry; in addition, certain opioid analgesics are modified in the liver, resulting in compounds with greater analgesic action. Chemically, the opioids derived from opium are phenanthrene derivatives and include four or more fused rings, while most of the synthetic opioids are simpler molecules.

Endogenous Opioid Peptides

Opioid alkaloids (eg, morphine) produce analgesia through actions at receptors in the central nervous system (CNS) that respond to certain endogenous peptides with opioid-like pharmacologic properties. The general term currently used for these endogenous substances is **endogenous opioid peptides.**

TABLE 31–1 Opioid receptor subtypes, their functions, and their endogenous peptide affinities.

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins

Three families of endogenous opioid peptides have been described in detail: the **endorphins,** the pentapeptide **enkephalins** methionine-enkephalin **(met-enkephalin)** and leucine-enkephalin **(leu-enkephalin),** and the **dynorphins.** The three families of opioid receptors have overlapping affinities for these endogenous peptides (Table 31–1).

The endogenous opioid peptides are derived from three precursor proteins: prepro-opiomelanocortin (POMC), preproenkephalin (proenkephalin A), and preprodynorphin (proenkephalin B). POMC contains the met-enkephalin sequence, β-endorphin, and several nonopioid peptides, including adrenocorticotropic hormone (ACTH), β-lipotropin, and melanocyte-stimulating hormone. Preproenkephalin contains six copies of met-enkephalin and one copy of leu-enkephalin. Leu- and met-enkephalin have slightly higher affinity for the δ (delta) than for the μ-opioid receptor (Table 31–1). Preprodynorphin yields several active opioid peptides that contain the leu-enkephalin sequence. These are **dynorphin A, dynorphin B,** and α and β **neoendorphins.** The endogenous peptides **endomorphin-1** and **endomorphin-2** also possess many of the properties of opioid peptides, notably analgesia and high-affinity binding to the μ receptor. Endomorphin-1 and -2 selectively activate central and peripheral μ-opioid receptors but much about them remains unknown, including the identity of their preproendomorphin gene. Both the endogenous opioid precursor molecules and the endomorphins are present at CNS sites that have been implicated in pain modulation. Evidence suggests that they can be released during stressful conditions such as pain or the anticipation of pain and diminish the sensation of noxious stimuli. Whether acupuncture releases endogenous opioid peptides is under investigation.

In contrast to the analgesic role of leu- and met-enkephalin, an analgesic action of dynorphin A—through its binding to κ (kappa)-opioid receptors—remains controversial. Dynorphin A is also found in the dorsal horn of the spinal cord, where it may play a critical role in the *sensitization* of nociceptive neurotransmission. Increased levels of dynorphin can be found in the dorsal horn after tissue injury and inflammation. This elevated dynorphin level is proposed to increase pain and induce a state of long-lasting hyperalgesia. The pronociceptive action of dynorphin in the spinal cord appears to be independent of the opioid receptor system but dependent on the activation of the bradykinin receptor. Moreover, dynorphin A can bind and activate the *N*-methyl-D-aspartate (NMDA)-receptor complex, a site of action that is the focus of intense therapeutic development.

Recently, a novel receptor-ligand system homologous to the opioid peptides has been found. The principal receptor for this system is the G protein-coupled **orphanin opioid-receptor-like subtype 1 (ORL1).** Its endogenous ligand has been termed *nociceptin* by one group of investigators and **orphanin FQ** by another group. This ligand-receptor system is currently known as the *N/OFQ* system. Nociceptin is structurally similar to dynorphin except for the absence of an N-terminal tyrosine; it acts only at the ORL1 receptor, now known as **NOP.** The N/OFQ system is widely expressed in the CNS and periphery, reflecting its equally diverse biology and pharmacology. As a result of experiments using highly selective NOP receptor ligands, the N/OFQ system has been implicated in both pro- and anti-nociceptive activity as well as in the modulation of drug reward, learning, mood, anxiety, and cough processes, and of parkinsonism.

Pharmacokinetics

Some properties of clinically important opioids are summarized in Table 31–2.

A. Absorption

Most opioid analgesics are well absorbed when given by subcutaneous, intramuscular, and oral routes. However, because of the first-pass effect, the oral dose of the opioid (eg, morphine) may need to be much higher than the parenteral dose to elicit a therapeutic effect. Considerable interpatient variability exists in first-pass opioid metabolism, making prediction of an effective oral dose difficult. Certain analgesics such as codeine and oxycodone are effective orally because they have reduced first-pass metabolism. Nasal insufflation of certain opioids can result in rapid therapeutic blood levels by avoiding first-pass metabolism. Other routes of opioid administration include oral mucosa via lozenges, and transdermal via transdermal patches. The latter can provide delivery of potent analgesics over days. Recently an iontophoretic transdermal system has been introduced, allowing needle-free delivery of fentanyl for patient-controlled analgesia.

B. Distribution

The uptake of opioids by various organs and tissues is a function of both physiologic and chemical factors. Although all opioids bind to plasma proteins with varying affinity, the drugs rapidly leave the blood compartment and localize in highest concentrations in tissues that are highly perfused such as the brain, lungs, liver, kidneys, and spleen. Drug concentrations in skeletal muscle may be much lower, but this tissue serves as the main reservoir because of its greater bulk. Even though blood flow to fatty tissue is much lower than to the highly perfused tissues, accumulation

TABLE 31–2 Common opioid analgesics.

Generic Name	Receptor Effects[1]			Approximately Equivalent Dose (mg)	Oral:Parenteral Potency Ratio	Duration of Analgesia (hours)	Maximum Efficacy
	μ	δ	κ				
Morphine[2]	+++		+	10	Low	4–5	High
Hydromorphone	+++			1.5	Low	4–5	High
Oxymorphone	+++			1.5	Low	3–4	High
Methadone	+++			10	High	4–6	High
Meperidine	+++			60–100	Medium	2–4	High
Fentanyl	+++			0.1	Low	1–1.5	High
Sufentanil	+++	+	+	0.02	Parenteral only	1–1.5	High
Alfentanil	+++			Titrated	Parenteral only	0.25–0.75	High
Remifentanil	+++			Titrated[3]	Parenteral only	0.05[4]	High
Levorphanol	+++			2–3	High	4–5	High
Codeine	±			30–60	High	3–4	Low
Hydrocodone[5]	±			5–10	Medium	4–6	Moderate
Oxycodone[2,6]	++			4.5	Medium	3–4	Mod-High
Pentazocine	±		+	30–50	Medium	3–4	Moderate
Nalbuphine	−−		++	10	Parenteral only	3–6	High
Buprenorphine	±	−−	−−	0.3	Low	4–8	High
Butorphanol	±		+++	2	Parenteral only	3–4	High

[1]+++, ++, +, strong agonist; ±, partial agonist; −−, antagonist.

[2]Available in sustained-release forms, morphine (MS Contin); oxycodone (Oxy Contin).

[3]Administered as an infusion at 0.025–0.2 mcg/kg/min.

[4]Duration is dependent on a context-sensitive half-time of 3–4 minutes.

[5]Available in tablets containing acetaminophen (Norco, Vicodin, Lortab, others).

[6]Available in tablets containing acetaminophen (Percocet); aspirin (Percodan).

can be very important, particularly after frequent high-dose administration or continuous infusion of highly lipophilic opioids that are slowly metabolized, eg, fentanyl.

C. Metabolism

The opioids are converted in large part to polar metabolites (mostly glucuronides), which are then readily excreted by the kidneys. For example, morphine, which contains free hydroxyl groups, is primarily conjugated to morphine-3-glucuronide (M3G), a compound with neuroexcitatory properties. The neuroexcitatory effects of M3G do not appear to be mediated by μ receptors but rather by the GABA/glycinergic system. In contrast, approximately 10% of morphine is metabolized to morphine-6-glucuronide (M6G), an active metabolite with analgesic potency four to six times that of its parent compound. However, these relatively polar metabolites have limited ability to cross the blood-brain barrier and probably do not contribute significantly to the usual CNS effects of morphine given acutely. Nevertheless, accumulation of these metabolites may produce unexpected adverse effects in patients with renal failure or when exceptionally large doses of morphine are administered or high doses are administered over long periods. This can result in M3G-induced CNS excitation (seizures) or enhanced and prolonged opioid action produced by M6G. CNS uptake of M3G and, to a lesser extent, M6G can be enhanced by co-administration with probenecid or with drugs that inhibit the P-glycoprotein drug transporter. Like morphine, hydromorphone is metabolized by conjugation, yielding hydromorphone-3-glucuronide (H3G), which has CNS excitatory properties. However, hydromorphone has not been shown to form significant amounts of a 6-glucuronide metabolite.

The effects of these active metabolites should be considered in patients with renal impairment before the administration of morphine or hydromorphone, especially when given at high doses.

Esters (eg, heroin, remifentanil) are rapidly hydrolyzed by common tissue esterases. Heroin (diacetylmorphine) is hydrolyzed to monoacetylmorphine and finally to morphine, which is then conjugated with glucuronic acid.

Hepatic oxidative metabolism is the primary route of degradation of the phenylpiperidine opioids (meperidine, fentanyl, alfentanil, sufentanil) and eventually leaves only small quantities of the parent compound unchanged for excretion. However, accumulation of a demethylated metabolite of meperidine, normeperidine, may occur in patients with decreased renal function and in those receiving multiple high doses of the drug. In high concentrations, normeperidine may cause seizures. In contrast, no active metabolites of fentanyl have been reported. The P450 isozyme CYP3A4

metabolizes fentanyl by *N*-dealkylation in the liver. CYP3A4 is also present in the mucosa of the small intestine and contributes to the first-pass metabolism of fentanyl when it is taken orally. Codeine, oxycodone, and hydrocodone undergo metabolism in the liver by P450 isozyme CYP2D6, resulting in the production of metabolites of greater potency. For example, codeine is demethylated to morphine. Genetic polymorphism of CYP2D6 has been documented and linked to the variation in analgesic response seen among patients. Nevertheless, the metabolites of oxycodone and hydrocodone may be of minor consequence; the parent compounds are currently believed to be directly responsible for the majority of their analgesic actions. However, oxycodone and its metabolites can accumulate under conditions of renal failure and have been associated with prolonged action and sedation. In the case of codeine, conversion to morphine may be of greater importance because codeine itself has relatively low affinity for opioid receptors. As a result, patients may experience either no significant analgesic effect or an exaggerated response based on differences in metabolic conversion. For this reason, routine use of codeine, especially in pediatric age groups, is being reconsidered.

D. Excretion

Polar metabolites, including glucuronide conjugates of opioid analgesics, are excreted mainly in the urine. Small amounts of unchanged drug may also be found in the urine. In addition, glucuronide conjugates are found in the bile, but enterohepatic circulation represents only a small portion of the excretory process.

Pharmacodynamics

A. Mechanism of Action

Opioid agonists produce analgesia by binding to specific G protein-coupled receptors that are located in brain and spinal cord regions involved in the transmission and modulation of pain (Figure 31–1). Some effects may be mediated by opioid receptors on peripheral sensory nerve endings.

1. Receptor types—As noted previously, three major classes of opioid receptors (μ, δ, and κ) have been identified in various nervous system sites and in other tissues (Table 31–1). Each of the three major receptors has now been cloned. All are members of the G protein-coupled family of receptors and show significant amino acid sequence homologies. Multiple receptor subtypes have been proposed based on pharmacologic criteria, including μ_1, μ_2; δ_1, δ_2; and κ_1, κ_2, and κ_3. However, genes encoding only one subtype from each of the μ, δ, and κ receptor families have been isolated and characterized thus far. One plausible explanation is that μ-receptor subtypes arise from alternate splice variants of a common gene. This idea has been supported by the identification of receptor splice variants in mice and humans. Since an opioid may function with different potencies as an agonist, partial agonist, or antagonist at more than one receptor class or subtype, it is not surprising that these agents are capable of diverse pharmacologic effects.

2. Cellular actions—At the molecular level, opioid receptors form a family of proteins that physically couple to G proteins and through this interaction affect ion channel gating, modulate intracellular Ca^{2+} disposition, and alter protein phosphorylation (see Chapter 2). The opioids have two well-established direct G protein-coupled actions on neurons: (1) they close voltage-gated Ca^{2+} channels on presynaptic nerve terminals and thereby reduce transmitter release, and (2) they hyperpolarize and thus inhibit postsynaptic neurons by opening K^+ channels. Figure 31–1 schematically illustrates these effects. The presynaptic action—depressed transmitter release—has been demonstrated for release of a large number of neurotransmitters including glutamate, the principal excitatory amino acid released from nociceptive nerve terminals, as well as acetylcholine, norepinephrine, serotonin, and substance P.

3. Relation of physiologic effects to receptor type—The majority of currently available opioid analgesics act primarily at the μ-opioid receptor (Table 31–2). Analgesia and the euphoriant, respiratory depressant, and physical dependence properties of morphine result principally from actions at μ receptors. In fact, the μ receptor was originally defined using the relative potencies for clinical analgesia of a series of opioid alkaloids. However, opioid analgesic effects are complex and include interaction with δ and κ receptors. This is supported by the study of genetic knockouts of the μ, δ, and κ genes in mice. Delta-receptor agonists retain analgesic properties in δ receptor knockout mice. The development of μ-receptor–selective agonists could be clinically useful if their side-effect profiles (respiratory depression, risk of dependence) were more favorable than those found with current μ-receptor agonists, such as morphine. Although morphine does act at κ and δ receptor sites, it is unclear to what extent this contributes to its analgesic action. The endogenous opioid peptides differ from most of the alkaloids in their affinity for the δ and κ receptors (Table 31–1).

In an effort to develop opioid analgesics with a reduced incidence of respiratory depression or propensity for addiction and dependence, compounds that show preference for κ opioid receptors have been developed. Butorphanol and nalbuphine have shown some clinical success as analgesics, but they can cause dysphoric reactions and have limited potency. It is interesting that butorphanol has also been shown to cause significantly greater analgesia in women than in men. In fact, gender-based differences in analgesia mediated by μ- and δ-receptor activation have been widely reported.

4. Receptor distribution and neural mechanisms of analgesia—Opioid receptor binding sites have been localized autoradiographically with high-affinity radioligands and with antibodies to unique peptide sequences in each receptor subtype. All three major receptors are present in high concentrations in the dorsal horn of the spinal cord. Receptors are present both on spinal cord pain transmission neurons and on the primary afferents that relay the pain message to them (Figure 31–2, sites A and B). Although opioid agonists directly inhibit the dorsal horn pain transmission neurons, they also inhibit the release of excitatory transmitters from the primary afferents. Within the presynaptic terminals, there is evidence that heterodimerization of the μ-opioid

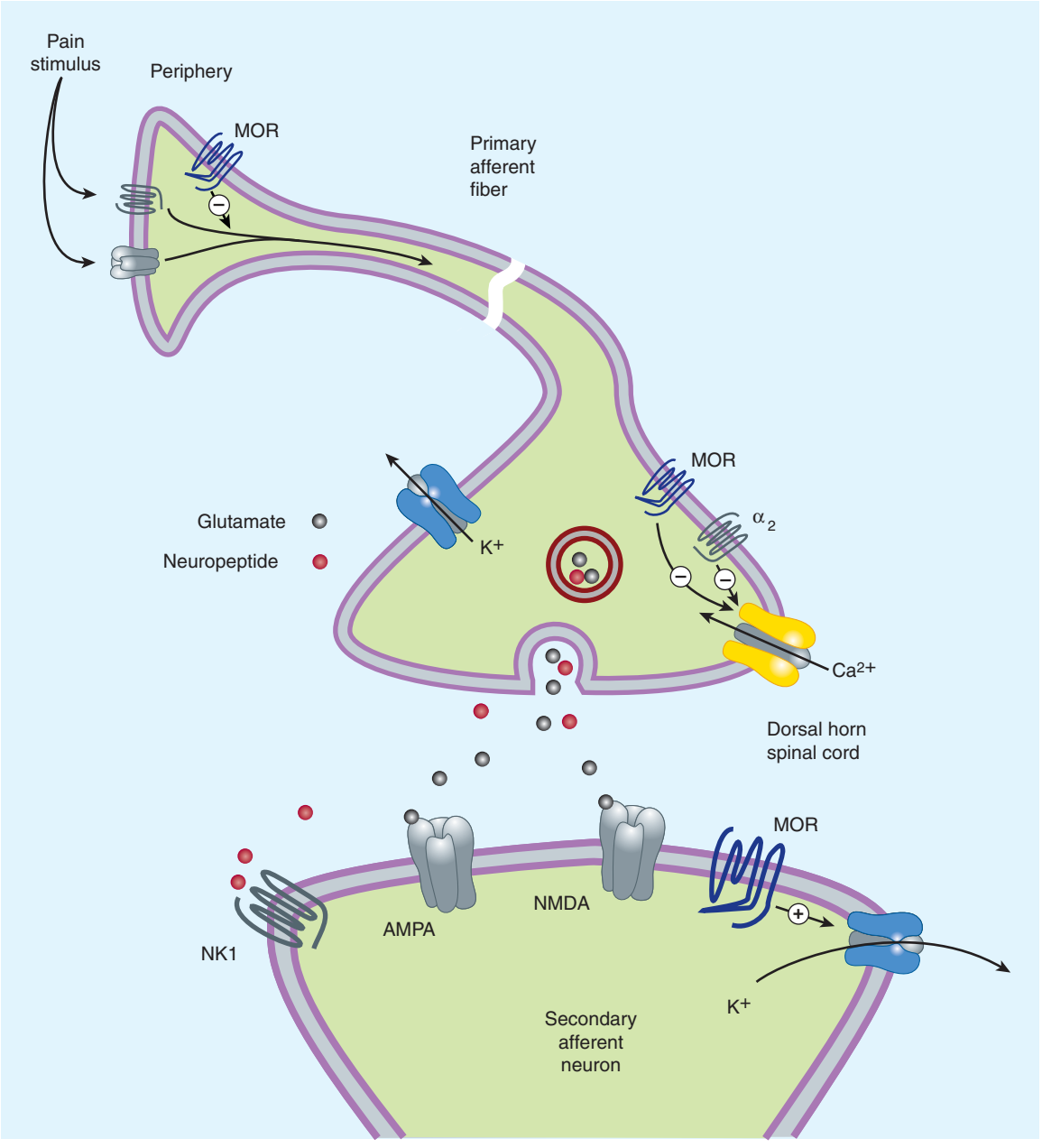


FIGURE 31–1 Potential receptor mechanisms of analgesic drugs. The primary afferent neuron (cell body not shown) originates in the periphery and carries pain signals to the dorsal horn of the spinal cord, where it synapses via glutamate and neuropeptide transmitters with the secondary neuron. Pain stimuli can be attenuated in the periphery (under inflammatory conditions) by opioids acting at μ-opioid receptors (MOR) or blocked in the afferent axon by local anesthetics (not shown). Action potentials reaching the dorsal horn can be attenuated at the presynaptic ending by opioids and by calcium blockers (ziconotide), α_2 agonists, and possibly, by drugs that increase synaptic concentrations of norepinephrine by blocking reuptake (tapentadol). Opioids also inhibit the postsynaptic neuron, as do certain neuropeptide antagonists acting at tachykinin (NK1) and other neuropeptide receptors.

and δ-opioid receptors contribute to μ-agonist efficacy (eg, inhibition of presynaptic voltage-gated calcium channel activity). On the other hand, a recent study using a transgenic mouse that expresses a δ–receptor-enhanced green fluorescent protein (eGFP) fusion protein shows little overlap of μ receptor and δ receptor in the dorsal root ganglion neurons. Importantly, the μ receptor is associated with TRPV1 and peptide (substance P)-expressing nociceptors, whereas δ-receptor expression predominates in the non-peptidergic population of nociceptors, including many primary afferents with myelinated axons. This is consistent with the action of intrathecal μ-receptor– and δ-receptor–selective ligands that are found to block heat versus mechanical pain processing, respectively. To what

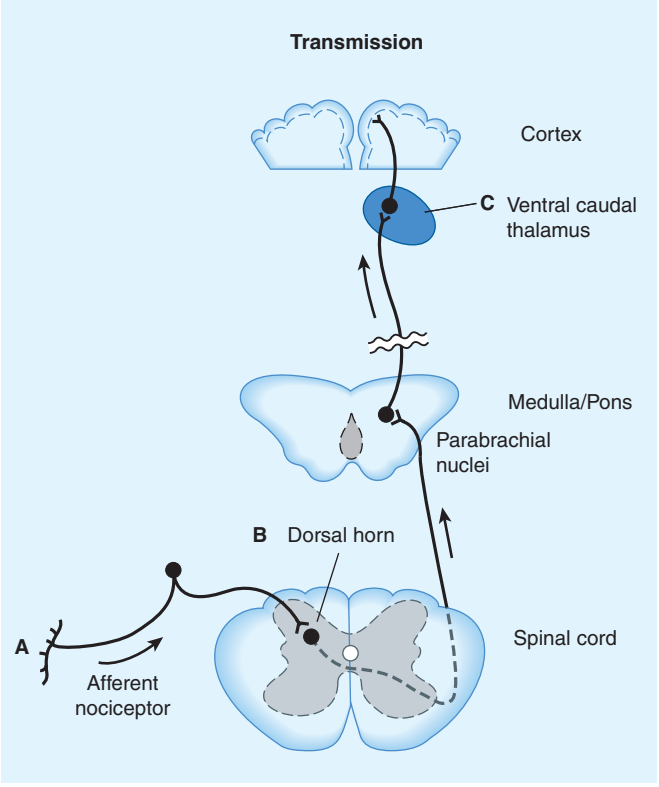


FIGURE 31–2 Putative sites of action of opioid analgesics. Sites of action on the afferent pain transmission pathway from the periphery to the higher centers are shown. **A:** Direct action of opioids on inflamed or damaged peripheral tissues (see Figure 31–1 for detail). **B:** Inhibition also occurs in the spinal cord (see Figure 31–1). **C:** Possible sites of action in the thalamus.

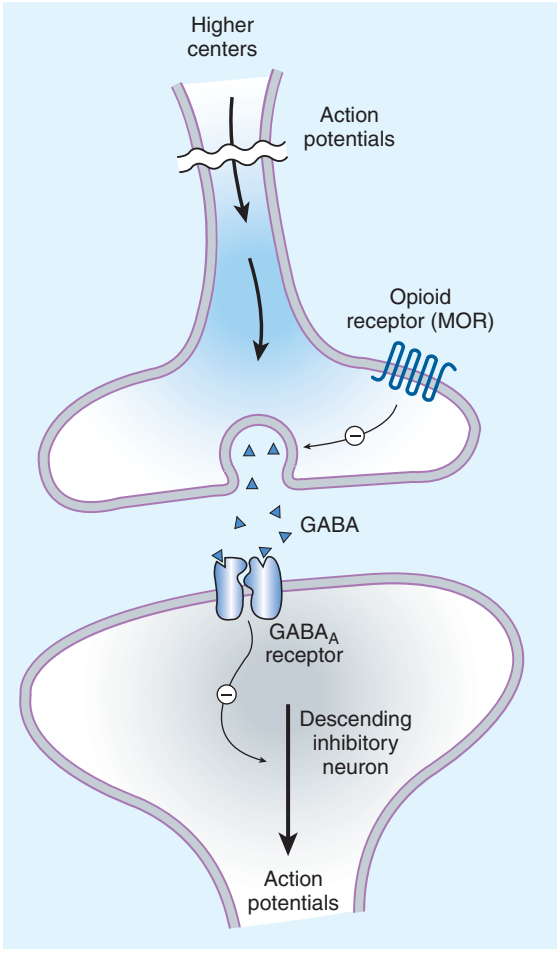


FIGURE 31–3 Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)–mediated analgesia on descending pathways. The pain-inhibitory neuron is indirectly activated by opioids (exogenous or endogenous), which inhibit an inhibitory (GABAergic) interneuron. This results in *enhanced* inhibition of nociceptive processing in the dorsal horn of the spinal cord (see Figure 31–4).

extent the differential expression of the μ receptor and δ receptor in the dorsal root ganglia is characteristic of neurons throughout the CNS remains to be determined.

Thus, opioids exert a powerful analgesic effect directly on the spinal cord. This *spinal action* has been exploited clinically by direct application of opioid agonists to the spinal cord, which provides a regional analgesic effect while reducing the unwanted respiratory depression, nausea and vomiting, and sedation that may occur from the *supraspinal actions* of systemically administered opioids.

Under most circumstances, opioids are given systemically and so act simultaneously at multiple sites. These include not only the ascending pathways of pain transmission beginning with specialized peripheral sensory terminals that transduce painful stimuli (Figure 31–2) but also descending (modulatory) pathways (Figure 31–3). At these sites as at others, opioids directly inhibit neurons; yet this action results in the *activation* of descending inhibitory neurons that send processes to the spinal cord and inhibit pain transmission neurons. This activation has been shown to result from the inhibition of inhibitory neurons in several locations (Figure 31–4). Taken together, interactions at these sites increase the overall analgesic effect of opioid agonists.

When pain-relieving opioid drugs are given systemically, they presumably act upon neuronal circuits normally regulated by endogenous opioid peptides. Part of the pain-relieving action of exogenous opioids involves the release of endogenous opioid peptides. An exogenous opioid agonist (eg, morphine) may act primarily and directly at the μ receptor, but this action may evoke the release of endogenous opioids that additionally act at δ and κ receptors. Thus, even a receptor-selective ligand can initiate a complex sequence of events involving multiple synapses, transmitters, and receptor types.

Animal and human clinical studies demonstrate that both endogenous and exogenous opioids can also produce opioid-mediated analgesia at sites *outside* the CNS. Pain associated with inflammation seems especially sensitive to these peripheral opioid actions. The presence of functional μ receptors on the peripheral terminals of sensory neurons supports this hypothesis.

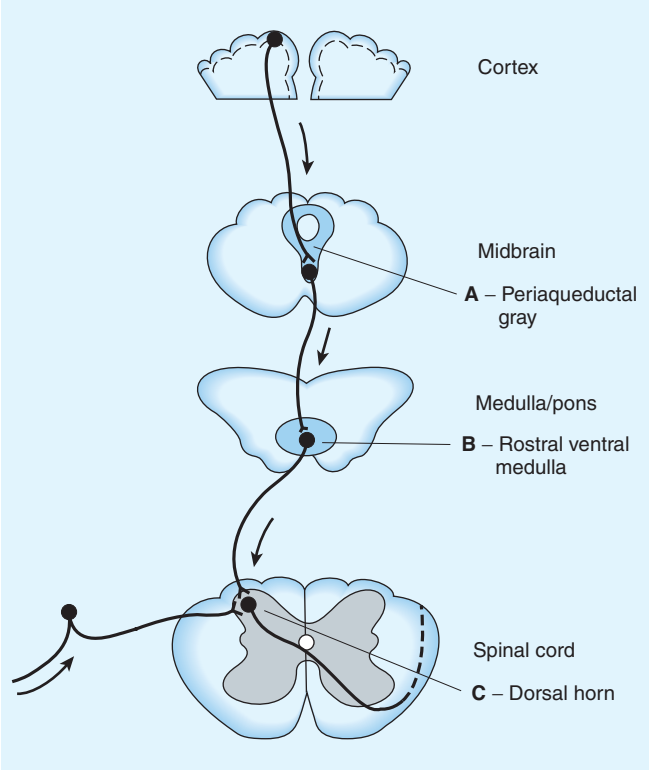


FIGURE 31–4 Opioid analgesic action on the descending inhibitory pathway. Sites of action of opioids on pain-modulating neurons in the midbrain and medulla including the midbrain periaqueductal gray area **(A),** rostral ventral medulla **(B),** and the locus caeruleus indirectly control pain transmission pathways by enhancing descending inhibition to the dorsal horn **(C).**

Furthermore, activation of peripheral μ receptors results in a decrease in sensory neuron activity and transmitter release. The endogenous release of β-endorphin produced by immune cells within injured or inflamed tissue represents one source of physiologic peripheral μ-receptor activation. Peripheral administration of opioids, eg, into the knees of patients following arthroscopic knee surgery, has shown clinical benefit up to 24 hours after administration. If they can be developed, opioids selective for a peripheral site would be useful adjuncts in the treatment of inflammatory pain (see Box: Ion Channels & Novel Analgesic Targets). Such compounds could have the additional benefit of reducing unwanted effects such as constipation.

5. Tolerance and dependence—With frequently repeated therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness; this loss of effectiveness is denoted tolerance. To reproduce the original response, a larger dose must be administered. Along with tolerance, physical dependence develops. Physical dependence is defined as a characteristic **withdrawal** or **abstinence syndrome** when a drug is stopped or an antagonist is administered (see also Chapter 32).

The mechanism of development of tolerance and physical dependence is poorly understood, but persistent activation of μ receptors such as occurs with the treatment of severe chronic pain appears to play a primary role in its induction and maintenance. Current concepts have shifted away from tolerance being driven by a simple up-regulation of the cyclic adenosine monophosphate (cAMP) system. Although this process is associated with tolerance, it is not sufficient to explain it. A second hypothesis for the development of opioid tolerance and dependence is based on the concept of **receptor recycling.** Normally, activation of μ receptors by endogenous ligands results in endocytosis followed by resensitization and recycling of the receptor to the plasma membrane (see Chapter 2). However, using genetically modified mice, research now shows that the *failure* of morphine to induce endocytosis of the μ-opioid receptor is an important component of tolerance and dependence. In contrast, methadone, a μ-receptor agonist used for the *treatment* of opioid tolerance and dependence, does induce receptor endocytosis. This suggests that maintenance of normal sensitivity of μ receptors requires reactivation by endocytosis and recycling. Another area of research suggests that the δ opioid receptor functions as an independent component in the maintenance of tolerance. In addition, the concept of **receptor uncoupling** has gained prominence. Under this hypothesis, tolerance is due to a dysfunction of structural interactions between the μ receptor and G proteins, second-messenger systems, and their target ion channels. Uncoupling and recoupling of μ receptor function is likely linked to receptor recycling. Moreover, the NMDA-receptor ion channel complex has been shown to play a critical role in tolerance development and maintenance because NMDA-receptor antagonists such as ketamine can block tolerance development. Although a role in endocytosis is not yet clearly defined, the development of novel NMDA-receptor antagonists or other strategies to recouple μ receptors to their target ion channels provides hope for achieving a clinically effective means to prevent or reverse opioid analgesic tolerance.

In addition to the development of tolerance, persistent administration of opioid analgesics has been observed to *increase* the sensation of pain leading to a state of hyperalgesia. This phenomenon has been observed with several opioid analgesics, including morphine, fentanyl, and remifentanil. Spinal dynorphin and activation of the bradykinin receptor have emerged as important candidates for the mediation of opioid-induced hyperalgesia.

B. Organ System Effects of Morphine and Its Surrogates

The actions described below for morphine, the prototypic opioid agonist, can also be observed with other opioid agonists, partial agonists, and those with mixed receptor effects. Characteristics of specific members of these groups are discussed below.

1. Central nervous system effects—The principal effects of opioid analgesics with affinity for μ receptors are on the CNS; the more important ones include analgesia, euphoria, sedation, and respiratory depression. With repeated use, a high degree of tolerance occurs to all of these effects (Table 31–3).

a. Analgesia—Pain consists of both sensory and affective (emotional) components. Opioid analgesics are unique in that they can reduce both aspects of the pain experience, especially the affective

Ion Channels & Novel Analgesic Targets

Even the most severe *acute* pain (lasting hours to days) can usually be well controlled—with significant but tolerable adverse effects—using currently available analgesics, especially the opioids. *Chronic* pain (lasting weeks to months), however, is not very satisfactorily managed with opioids. It is now known that in chronic pain, receptors on sensory nerve terminals in the periphery contribute to increased excitability of sensory nerve endings (peripheral sensitization). The hyperexcitable sensory neuron bombards the spinal cord, leading to increased excitability and synaptic alterations in the dorsal horn (central sensitization). Such changes appear to be important in chronic inflammatory and neuropathic pain states.

In the effort to discover better analgesic drugs for chronic pain, renewed attention is being paid to synaptic transmission in nociception and peripheral sensory transduction. Potentially important ion channels associated with these processes in the periphery include members of the transient receptor potential family such as the **capsaicin receptor, TRPV1** (which is activated by multiple noxious stimuli such as heat, protons, and products of inflammation) as well as TRPA1, activated by inflammatory mediators; and P2X receptors (which are responsive to purines released from tissue damage). Special types of tetrodotoxin-resistant voltage-gated sodium channels **(Nav 1.7, 1.8, 1.9)** are uniquely associated with nociceptive neurons in dorsal root ganglia. **Lidocaine** and **mexiletine,** which are useful in some chronic pain states, may act by blocking this class of channels. Genetic polymorphisms of Nav 1.7 are associated with either absence or predisposition to pain. Because of the importance of their peripheral sites of action, therapeutic strategies that deliver agents that block peripheral pain transduction or transmission have been introduced in the form of transdermal patches and balms. Such products that specifically target peripheral capsaicin receptors and sodium channel function are becoming available.

Ziconotide, a blocker of voltage-gated N-type calcium channels, is approved for intrathecal analgesia in patients with refractory chronic pain. It is a synthetic peptide related to the marine snail toxin ω-conotoxin, which selectively blocks these calcium channels. **Gabapentin/pregabalin,** anticonvulsant analogs of GABA (see Chapter 24), are effective treatments for neuropathic (nerve injury) pain and inflammatory pain acting at voltage-gated calcium channels containing the $\alpha_2\delta_1$ subunit. *N*-methyl-D-aspartate (NMDA) receptors appear to play a very important role in central sensitization at both spinal and supraspinal levels. Although certain NMDA antagonists have demonstrated analgesic activity (eg, **ketamine**), it has been difficult to find agents with an acceptably low profile of adverse effects or neurotoxicity. However, ketamine at very small doses appears to improve analgesia and reduce opioid requirements under conditions of opioid tolerance. In fact, ketamine applied topically has been claimed to have analgesic effects. GABA and acetylcholine (through nicotinic receptors) appear to control the central synaptic release of several transmitters involved in nociception. **Nicotine** itself and certain nicotine analogs cause analgesia, and their use for postoperative analgesia is under investigation. Finally, work on cannabinoids and vanilloids and their receptors suggest that **Δ9- tetrahydrocannabinol,** which acts primarily on CB_1 cannabinoid receptors, can synergize with μ-receptor analgesics and interact with the TRPV1 capsaicin receptor to produce analgesia under certain circumstances.

As our understanding of peripheral and central pain transduction improves, additional therapeutic targets and strategies will become available. Combined with our present knowledge of opioid analgesics, a "multimodal" approach to pain therapy is emerging, which allows the use of complementary compounds resulting in improved analgesia with fewer adverse effects.

aspect. In contrast, nonsteroidal anti-inflammatory analgesic drugs have no significant effect on the emotional aspects of pain.

b. Euphoria—Typically, patients or intravenous drug users who receive intravenous morphine experience a pleasant floating sensation with lessened anxiety and distress. However, dysphoria, an unpleasant state characterized by restlessness and malaise, may sometimes occur.

c. Sedation—Drowsiness and clouding of mentation are common effects of opioids. There is little or no amnesia. Sleep is induced by opioids more frequently in the elderly than in young, healthy individuals. Ordinarily, the patient can be easily aroused from this sleep. However, the combination of morphine with other central depressant drugs such as the sedative-hypnotics may result in very deep sleep. Marked sedation occurs more frequently with compounds closely related to the phenanthrene derivatives and less frequently with the synthetic agents such as meperidine and fentanyl. In standard analgesic doses, morphine (a phenanthrene) disrupts normal rapid eye movement (REM) and non-REM sleep patterns. This disrupting effect is probably characteristic of all opioids. In contrast to humans, a number of

TABLE 31–3 Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

species (cats, horses, cows, pigs) may manifest excitation rather than sedation when given opioids. These paradoxic effects are at least partially dose-dependent.

***d. Respiratory depression*—**All of the opioid analgesics can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms. Alveolar P_{CO_2} may increase, but the most reliable indicator of this depression is a depressed response to a carbon dioxide challenge. The respiratory depression is dose-related and is influenced significantly by the degree of sensory input occurring at the time. For example, it is possible to partially overcome opioid-induced respiratory depression by stimulation of various sorts. When strongly painful stimuli that have prevented the depressant action of a large dose of an opioid are relieved, respiratory depression may suddenly become marked. A small to moderate decrease in respiratory function, as measured by Pa_{CO_2} elevation, may be well tolerated in the patient without prior respiratory impairment. However, in individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, or cor pulmonale, this decrease in respiratory function may not be tolerated. Opioid-induced respiratory depression remains one of the most difficult clinical challenges in the treatment of severe pain. Research is ongoing to understand and develop analgesic agents and adjuncts that avoid this effect. Research to overcome this problem is focused on μ-receptor pharmacology and serotonin signaling pathways in the brainstem respiratory control centers.

***e. Cough suppression*—**Suppression of the cough reflex is a well-recognized action of opioids. Codeine in particular has been used to advantage in persons suffering from pathologic cough and in patients in whom it is necessary to maintain ventilation via an endotracheal tube. However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

***f. Miosis*—**Constriction of the pupils is seen with virtually all opioid agonists. Miosis is a pharmacologic action to which little or no tolerance develops (Table 31–3); thus, it is valuable in the diagnosis of opioid overdose. Even in highly tolerant addicts, miosis is seen. This action, which can be blocked by opioid antagonists, is mediated by parasympathetic pathways, which, in turn, can be blocked by atropine.

***g. Truncal rigidity*—**An intensification of tone in the large trunk muscles has been noted with a number of opioids. It was originally believed that truncal rigidity involved a spinal cord action of these drugs, but there is now evidence that it results from an action at supraspinal levels. Truncal rigidity reduces thoracic compliance and thus interferes with ventilation. The effect is most apparent when high doses of the highly lipid-soluble opioids (eg, fentanyl, sufentanil, alfentanil, remifentanil) are rapidly administered intravenously. Truncal rigidity may be overcome by administration of an opioid antagonist, which of course will also antagonize the analgesic action of the opioid. Preventing truncal rigidity while preserving analgesia requires the concomitant use of neuromuscular blocking agents.

***h. Nausea and vomiting*—**The opioid analgesics can activate the brainstem chemoreceptor trigger zone to produce nausea and vomiting. There may also be a vestibular component in this effect because ambulation seems to increase the incidence of nausea and vomiting.

***i. Temperature*—**Homeostatic regulation of body temperature is mediated in part by the action of endogenous opioid peptides in the brain. This has been supported by experiments demonstrating that administration of μ-opioid receptor agonists such as morphine administered to the anterior hypothalamus produces hyperthermia, whereas administration of κ agonists induces hypothermia.

2. Peripheral effects

***a. Cardiovascular system*—**Most opioids have no significant direct effects on the heart and, other than bradycardia, no major effects on cardiac rhythm. Meperidine is an exception to this generalization because its antimuscarinic action can result in tachycardia. Blood pressure is usually well maintained in subjects receiving opioids unless the cardiovascular system is stressed, in which case hypotension may occur. This hypotensive effect is probably due to peripheral arterial and venous dilation, which has been attributed to a number of mechanisms including central depression of vasomotor-stabilizing mechanisms and release of histamine. No consistent effect on cardiac output is seen, and the electrocardiogram is not significantly affected. However, caution should be exercised in patients with decreased blood volume, because the above mechanisms make these patients susceptible to hypotension. Opioid analgesics affect cerebral circulation minimally except when P_{CO_2} rises as a consequence of respiratory depression. Increased P_{CO_2} leads to cerebral vasodilation associated with a decrease in cerebral

vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

b. Gastrointestinal tract—Constipation has long been recognized as an effect of opioids, an effect that does not diminish with continued use. That is, tolerance does not develop to opioid-induced constipation (Table 31–3). Opioid receptors exist in high density in the gastrointestinal tract, and the constipating effects of the opioids are mediated through an action on the enteric nervous system (see Chapter 6) as well as the CNS. In the stomach, motility (rhythmic contraction and relaxation) may decrease but tone (persistent contraction) may increase—particularly in the central portion; gastric secretion of hydrochloric acid is decreased. Small intestine resting tone is increased, with periodic spasms, but the amplitude of nonpropulsive contractions is markedly decreased. In the large intestine, propulsive peristaltic waves are diminished and tone is increased; this delays passage of the fecal mass and allows increased absorption of water, which leads to constipation. The large bowel actions are the basis for the use of opioids in the management of diarrhea, and constipation is a major problem in the use of opioids for control of severe cancer pain.

c. Biliary tract—The opioids contract biliary smooth muscle, which can result in biliary colic. The sphincter of Oddi may constrict, resulting in reflux of biliary and pancreatic secretions and elevated plasma amylase and lipase levels.

d. Renal—Renal function is depressed by opioids. It is believed that in humans this is chiefly due to decreased renal plasma flow. In addition, μ opioids have been found to have an antidiuretic effect in humans. Mechanisms may involve both the CNS and peripheral sites. Opioids also enhance renal tubular sodium reabsorption. The role of opioid-induced changes in antidiuretic hormone (ADH) release is controversial. Ureteral and bladder tone are increased by therapeutic doses of the opioid analgesics. Increased sphincter tone may precipitate urinary retention, especially in postoperative patients. Occasionally, ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone.

e. Uterus—The opioid analgesics may prolong labor. The mechanism for this action is unclear, but both peripheral and central actions of the opioids can reduce uterine tone.

f. Neuroendocrine—Opioid analgesics stimulate the release of ADH, prolactin, and somatotropin but inhibit the release of luteinizing hormone. These effects suggest that endogenous opioid peptides, through effects in the hypothalamus, regulate these systems (Table 31–1).

g. Pruritus—Therapeutic doses of the opioid analgesics produce flushing and warming of the skin accompanied sometimes by sweating and itching; CNS effects and peripheral histamine release may be responsible for these reactions. Opioid-induced pruritus and occasionally urticaria appear more frequently when opioid analgesics are administered parenterally. In addition, when opioids such as morphine are administered to the neuraxis by the spinal or epidural route, their usefulness may be limited by intense pruritus over the lips and torso.

h. Miscellaneous—The opioids modulate the immune system by effects on lymphocyte proliferation, antibody production, and chemotaxis. In addition, leucocytes migrate to the site of tissue injury and release opioid peptides, which in turn help counter inflammatory pain. However, natural killer cell cytolytic activity and lymphocyte proliferative responses to mitogens are usually inhibited by opioids. Although the mechanisms involved are complex, activation of central opioid receptors could mediate a significant component of the changes observed in peripheral immune function. In general, these effects are mediated by the sympathetic nervous system in the case of acute administration and by the hypothalamic-pituitary-adrenal system in the case of prolonged administration of opioids.

C. Effects of Opioids with Both Agonist and Antagonist Actions

Buprenorphine is an opioid agonist that displays high binding affinity but low intrinsic activity at the μ receptor. Its slow rate of dissociation from the μ receptor has also made it an attractive alternative to methadone for the management of opioid withdrawal. It functions as an *antagonist* at the δ and κ receptors and for this reason is referred to as a "mixed agonist-antagonist." Although buprenorphine is used as an analgesic, it can antagonize the action of more potent μ agonists such as morphine. Buprenorphine also binds to ORL1, the orphanin receptor. Whether this property also participates in opposing μ receptor function is under study. Pentazocine and nalbuphine are other examples of opioid analgesics with mixed agonist-antagonist properties. Psychotomimetic effects, with hallucinations, nightmares, and anxiety, have been reported after use of drugs with mixed agonist-antagonist actions.

A combined buprenorphine HCl/naloxone HCl dihydrate preparation is now available as sublingual tablets and a sublingual film for use in a maintenance treatment plan that includes counseling, psychosocial support, and direction by physicians qualified under the Drug Addiction Treatment Act. Both formulations can be abused in a manner similar to other opioids, legal or illicit. The combination formulations can cause serious respiratory depression and death, particularly when extracted and injected intravenously in combination with benzodiazepines or other CNS depressants (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to self-administer benzodiazepines or other CNS depressants while taking the buprenorphine-naloxone combination.

■ CLINICAL PHARMACOLOGY OF THE OPIOID ANALGESICS

Successful treatment of pain is a challenging task that begins with careful attempts to assess the source and magnitude of the pain. The amount of pain experienced by the patient is often measured by means of a pain Numeric Rating Scale (NRS) or less frequently

by marking a line on a Visual Analog Scale (VAS) with word descriptors ranging from no pain (0) to excruciating pain (10). In either case, values indicate the magnitude of pain as: mild (1–3), moderate (4–6), or severe (7–10). A similar scale can be used with children and with patients who cannot speak; this scale depicts five faces ranging from smiling (no pain) to crying (maximum pain).

For a patient in severe pain, the administration of an opioid analgesic is usually considered a primary part of the overall management plan. Determining the route of administration (oral, parenteral, neuraxial), duration of drug action, ceiling effect (maximal intrinsic activity), duration of therapy, potential for adverse effects, and the patient's past experience with opioids all should be addressed. One of the principal errors made by physicians in this setting is failure to adequately assess a patient's pain and to match its severity with an appropriate level of therapy. Just as important is the principle that following delivery of the therapeutic plan, its effectiveness must be reevaluated and the plan modified, if necessary, if the response was excessive or inadequate.

Use of opioid drugs in acute situations may be contrasted with their use in chronic pain management, in which a multitude of other factors must be considered, including the development of tolerance to and physical dependence on opioid analgesics.

Clinical Use of Opioid Analgesics

A. Analgesia

Severe, *constant* pain is usually relieved with opioid analgesics with high intrinsic activity (see Table 31–2), whereas sharp, intermittent pain does not appear to be as effectively controlled.

The pain associated with cancer and other terminal illnesses must be treated aggressively and often requires a multidisciplinary approach for effective management. Such conditions may require continuous use of potent opioid analgesics and are associated with some degree of tolerance and dependence. *However, this should not be used as a barrier to providing patients with the best possible care and quality of life.* Research in the hospice movement has demonstrated that fixed-interval administration of opioid medication (ie, a regular dose at a scheduled time) is more effective in achieving pain relief than dosing on demand. New dosage forms of opioids that allow slower release of the drug are now available, eg, sustained-release forms of morphine (MS Contin) and oxycodone (OxyContin). Their purported advantage is a longer and more stable level of analgesia.

If disturbances of gastrointestinal function prevent the use of oral sustained-release morphine, the fentanyl transdermal system (fentanyl patch) can be used over long periods. Furthermore, buccal transmucosal fentanyl can be used for short episodes of breakthrough pain (see Alternative Routes of Administration). Administration of strong opioids by nasal insufflation has been shown to be efficacious, and nasal preparations are now available in some countries. Approval of such formulations in the USA is growing. In addition, stimulant drugs such as the amphetamines have been shown to enhance the analgesic actions of the opioids and thus may be very useful adjuncts in the patient with chronic pain.

Opioid analgesics are often used during obstetric labor. Because opioids cross the placental barrier and reach the fetus, care must be taken to minimize neonatal depression. If it occurs, immediate injection of the antagonist naloxone will reverse the depression. The phenylpiperidine drugs (eg, meperidine) appear to produce less depression, particularly respiratory depression, in newborn infants than does morphine; this may justify their use in obstetric practice.

The acute, severe pain of renal and biliary colic often requires a strong agonist opioid for adequate relief. However, the drug-induced increase in smooth muscle tone may cause a paradoxical *increase* in pain secondary to increased spasm. An increase in the dose of opioid is usually successful in providing adequate analgesia.

B. Acute Pulmonary Edema

The relief produced by intravenous morphine in dyspnea from pulmonary edema associated with left ventricular heart failure is remarkable. Proposed mechanisms include reduced anxiety (*perception* of shortness of breath) and reduced cardiac preload (reduced venous tone) and afterload (decreased peripheral resistance). However, if respiratory depression is a problem, furosemide may be preferred for the treatment of pulmonary edema. On the other hand, morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema.

C. Cough

Suppression of cough can be obtained at doses lower than those needed for analgesia. However, in recent years the use of opioid analgesics to allay cough has diminished largely because a number of effective synthetic compounds have been developed that are neither analgesic nor addictive. These agents are discussed below.

D. Diarrhea

Diarrhea from almost any cause can be controlled with the opioid analgesics, but if diarrhea is associated with infection such use must not substitute for appropriate chemotherapy. Crude opium preparations (eg, paregoric) were used in the past to control diarrhea, but now synthetic surrogates with more selective gastrointestinal effects and few or no CNS effects, eg, diphenoxylate or loperamide, are used. Several preparations are available specifically for this purpose (see Chapter 62).

E. Shivering

Although all opioid agonists have some propensity to reduce shivering, meperidine is reported to have the most pronounced antishivering properties. Meperidine apparently blocks shivering mainly through an action on subtypes of the α_2 adrenoceptor.

F. Applications in Anesthesia

The opioids are frequently used as premedicant drugs before anesthesia and surgery because of their sedative, anxiolytic, and analgesic properties. They are also used intraoperatively both as adjuncts to other anesthetic agents and, in high doses (eg, 0.02–0.075 mg/kg of fentanyl), as a primary component of the anesthetic regimen (see Chapter 25). Opioids are most commonly used in cardiovascular surgery and other types of high-risk surgery in which a primary goal is to minimize cardiovascular depression. In such situations, mechanical respiratory assistance must be provided.

Because of their direct action on the superficial neurons of the spinal cord dorsal horn, opioids can also be used as regional analgesics by administration into the epidural or subarachnoid spaces of the spinal column. A number of studies have demonstrated that long-lasting analgesia with minimal adverse effects can be achieved by epidural administration of 3–5 mg of morphine, followed by slow infusion through a catheter placed in the epidural space. It was initially assumed that the epidural application of opioids might selectively produce analgesia without impairment of motor, autonomic, or sensory functions other than pain. However, respiratory depression can occur after the drug is injected into the epidural space and may require reversal with naloxone. Effects such as pruritus and nausea and vomiting are common after epidural and subarachnoid administration of opioids and may also be reversed with naloxone if necessary. Currently, the epidural route is favored over subarachnoid administration because adverse effects are less common and robust outcome studies have shown a significant reduction in perioperative mortality and morbidity with the use of thoracic epidural analgesia. The use of low doses of local anesthetics in combination with fentanyl infused through a thoracic epidural catheter has become an accepted method of pain control in patients recovering from thoracic and major upper abdominal surgery. In rare cases, chronic pain management specialists may elect to surgically implant a programmable infusion pump connected to a spinal catheter for continuous infusion of opioids or other analgesic compounds.

G. Alternative Routes of Administration

Rectal suppositories of morphine and hydromorphone have been used when oral and parenteral routes are undesirable. The **transdermal patch** provides stable blood levels of drug and better pain control while avoiding the need for repeated parenteral injections. Fentanyl has been the most successful opioid in transdermal application and is indicated for the management of persistent unremitting pain. Because of the complication of fentanyl-induced respiratory depression, the Food and Drug Administration (FDA) recommends that introduction of a transdermal fentanyl patch (25 mcg/h) be reserved for patients with an established oral morphine requirement of at least 60 mg/d for 1 week or more. Extreme caution must be exercised in any patient initiating therapy or undergoing a dose increase because the peak effects may not be realized until 24–48 hours after patch application. The **intranasal** route avoids repeated parenteral drug injections and the first-pass metabolism of orally administered drugs. Butorphanol is the only opioid currently available in the USA in a nasal formulation, but more are expected. Another alternative to parenteral administration is the **buccal transmucosal** route, which uses a fentanyl citrate lozenge or a "lollipop" mounted on a stick.

Another type of pain control called **patient-controlled analgesia (PCA)** is now in widespread use for the management of breakthrough pain. With PCA, the patient controls a parenteral (usually intravenous) infusion device by pressing a button to deliver a preprogrammed dose of the desired opioid analgesic. Claims of better pain control using less opioid are supported by well-designed clinical trials, making this approach very useful in postoperative pain control. However, health care personnel must be very familiar with the use of PCAs to avoid overdosage secondary to misuse or improper programming. There is a proven risk of PCA-associated respiratory depression and hypoxia that requires careful monitoring of vital signs and sedation level, and provision of supplemental oxygen. This risk is increased if patients are concurrently prescribed medications with sedative properties such as benzodiazepines.

Toxicity & Undesired Effects

Direct toxic effects of the opioid analgesics that are extensions of their acute pharmacologic actions include respiratory depression, nausea, vomiting, and constipation (Table 31–4). In addition, tolerance and dependence, diagnosis and treatment of overdosage, and contraindications must be considered.

A. Tolerance and Dependence

Drug dependence of the opioid type is marked by a relatively specific withdrawal or abstinence syndrome. Just as there are pharmacologic differences between the various opioids, there are also differences in psychological dependence and the severity of withdrawal effects. For example, withdrawal from dependence on a strong agonist is associated with more severe withdrawal signs and symptoms than withdrawal from a mild or moderate agonist. Administration of an opioid *antagonist* to an opioid-dependent person is followed by brief but severe withdrawal symptoms (see antagonist-precipitated withdrawal, below). The potential for physical and psychological dependence of the partial agonist-antagonist opioids appears to be less than that of the strong agonist drugs.

1. Tolerance—Although development of tolerance begins with the first dose of an opioid, tolerance generally does not become clinically manifest until after 2–3 weeks of frequent exposure to ordinary therapeutic doses. Nevertheless, perioperative and critical care use of ultrapotent opioid analgesics such as remifentanil have been shown to induce opioid tolerance within hours. Tolerance develops most readily when large doses are given at short intervals and is minimized by giving small amounts of drug with longer intervals between doses.

Depending on the compound and the effect measured, the degree of tolerance may be as great as 35-fold. Marked tolerance may develop to the analgesic, sedating, and respiratory depressant effects. It is possible to produce respiratory arrest in a non-tolerant

TABLE 31–4 Adverse effects of the opioid analgesics.

Behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions)
Respiratory depression
Nausea and vomiting
Increased intracranial pressure
Postural hypotension accentuated by hypovolemia
Constipation
Urinary retention
Itching around nose, urticaria (more frequent with parenteral and spinal administration)

person with a dose of 60 mg of morphine, whereas in addicts maximally tolerant to opioids as much as 2000 mg of morphine taken over a 2- or 3-hour period may not produce significant respiratory depression. Tolerance also develops to the antidiuretic, emetic, and hypotensive effects but not to the miotic, convulsant, and constipating actions (Table 31–3).

Tolerance to the sedating and respiratory effects of the opioids dissipates within a few days after the drugs are discontinued. Tolerance to the emetic effects may persist for several months after withdrawal of the drug. The rates at which tolerance appears and disappears, as well as the degree of tolerance, may also differ considerably among the different opioid analgesics and among individuals using the same drug. For instance, tolerance to methadone develops more slowly and to a lesser degree than to morphine.

Tolerance also develops to analgesics with mixed receptor effects but to a lesser extent than to the agonists. Such effects as hallucinations, sedation, hypothermia, and respiratory depression are reduced after repeated administration of the mixed receptor drugs. However, tolerance to the latter agents does not generally include cross-tolerance to the agonist opioids. It is also important to note that tolerance does not develop to the antagonist actions of the mixed agents or to those of the pure antagonists.

Cross-tolerance is an extremely important characteristic of the opioids, ie, patients tolerant to morphine often show a reduction in analgesic response to other agonist opioids. This is particularly true of those agents with primarily μ-receptor agonist activity. Morphine and its congeners exhibit cross-tolerance not only with respect to their analgesic actions but also to their euphoriant, sedative, and respiratory effects. However, the cross-tolerance existing among the μ-receptor agonists can often be partial or incomplete. This clinical observation has led to the concept of "opioid rotation," which has been used in the treatment of cancer pain for many years. A patient who is experiencing decreasing effectiveness of one opioid analgesic regimen is "rotated" to a different opioid analgesic (eg, morphine to hydromorphone; hydromorphone to methadone) and typically experiences significantly improved analgesia at a reduced overall equivalent dosage. Another approach is to "recouple" opioid receptor function through the use of adjunctive nonopioid agents. NMDA-receptor antagonists (eg, ketamine) have shown promise in preventing or reversing opioid-induced tolerance in animals and humans. Use of ketamine is increasing because well-controlled studies have shown clinical efficacy in reducing postoperative pain and opioid requirements in opioid-tolerant patients. Agents that independently enhance μ-receptor recycling may also hold promise to improve analgesia in the opioid-tolerant patient.

The novel use of δ-receptor antagonists with μ-receptor agonists is also emerging as a strategy to avoid the development of tolerance. This idea has developed around the observation that mice lacking the δ-opioid receptor fail to develop tolerance to morphine.

2. Dependence—The development of physical dependence is an invariable accompaniment of tolerance to repeated administration of an opioid of the μ type. Failure to continue administering the drug results in a characteristic withdrawal or abstinence syndrome that reflects an exaggerated rebound from the acute pharmacologic effects of the opioid.

The signs and symptoms of withdrawal include rhinorrhea, lacrimation, yawning, chills, gooseflesh (piloerection), hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, and hostility. The number and intensity of the signs and symptoms are largely dependent on the degree of physical dependence that has developed. Administration of an opioid at this time suppresses abstinence signs and symptoms almost immediately.

The time of onset, intensity, and duration of abstinence syndrome depend on the drug previously used and may be related to its biologic half-life. With morphine or heroin, withdrawal signs usually start within 6–10 hours after the last dose. Peak effects are seen at 36–48 hours, after which most of the signs and symptoms gradually subside. By 5 days, most of the effects have disappeared, but some may persist for months. In the case of meperidine, the withdrawal syndrome largely subsides within 24 hours, whereas with methadone several days are required to reach the peak of the abstinence syndrome, and it may last as long as 2 weeks. The slower subsidence of methadone effects is associated with a less intense immediate syndrome, and this is the basis for its use in the detoxification of heroin addicts. However, despite the loss of physical dependence on the opioid, craving for it may persist. In addition to methadone, buprenorphine and clonidine (an α_2-noradrenergic receptor agonist) are FDA-approved treatments for opioid analgesic detoxification (see Chapter 32).

A transient, explosive abstinence syndrome—**antagonist-precipitated withdrawal**—can be induced in a subject physically dependent on opioids by administering naloxone or another antagonist. Within 3 minutes after injection of the antagonist, signs and symptoms similar to those seen after abrupt discontinuance appear, peaking in 10–20 minutes and largely subsiding after 1 hour. Even in the case of methadone, withdrawal of which results in a relatively mild abstinence syndrome, the antagonist-precipitated abstinence syndrome may be very severe.

In the case of agents with mixed effects, withdrawal signs and symptoms can be induced after repeated administration followed by abrupt discontinuance of pentazocine, cyclazocine, or nalorphine, but the syndrome appears to be somewhat different from that produced by morphine and other agonists. Anxiety, loss of appetite and body weight, tachycardia, chills, increase in body temperature, and abdominal cramps have been noted.

3. Addiction—The euphoria, indifference to stimuli, and sedation usually caused by the opioid analgesics, especially when injected intravenously, tend to promote their compulsive use. In addition, the addict experiences abdominal effects that have been likened to an intense sexual orgasm. These factors constitute the primary reasons for opioid abuse liability and are strongly reinforced by the development of physical dependence. This disorder has been linked to dysregulation of brain regions mediating reward and stress (see Chapter 32).

Obviously, the risk of causing dependence is an important consideration in the therapeutic use of these drugs. *Despite that risk, under no circumstances should adequate pain relief ever be withheld simply because an opioid exhibits potential for abuse or because legislative controls complicate the process of prescribing narcotics.* Furthermore, certain principles can be observed by the clinician to

minimize problems presented by tolerance and dependence when using opioid analgesics:

- Establish therapeutic goals before starting opioid therapy. This tends to limit the potential for physical dependence. The patient and his or her family should be included in this process.
- Once an effective dose is established, attempt to limit dosage to this level. This goal is facilitated by use of a written treatment contract that specifically prohibits early refills and having multiple prescribing physicians.
- Instead of opioid analgesics—especially in chronic management—consider using other types of analgesics or compounds exhibiting less pronounced withdrawal symptoms on discontinuance.
- Frequently evaluate continuing analgesic therapy and the patient's need for opioids.

B. Diagnosis and Treatment of Opioid Overdosage

Intravenous injection of naloxone dramatically reverses coma due to opioid overdose but not that due to other CNS depressants. Use of the antagonist should not, of course, delay the institution of other therapeutic measures, especially respiratory support.

See also the Antagonists section below and Chapter 58.

C. Contraindications and Cautions in Therapy

1. Use of pure agonists with weak partial agonists—When a weak partial agonist such as pentazocine is given to a patient also receiving a full agonist (eg, morphine), there is a risk of diminishing analgesia or even inducing a state of withdrawal; combining full agonist with partial agonist opioids should be avoided.

2. Use in patients with head injuries—Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation. In patients with elevated intracranial pressure, this may lead to lethal alterations in brain function.

3. Use during pregnancy—In pregnant women who are chronically using opioids, the fetus may become physically dependent in utero and manifest withdrawal symptoms in the early postpartum period. A daily dose as small as 6 mg of heroin (or equivalent) taken by the mother can result in a mild withdrawal syndrome in the infant, and twice that much may result in severe signs and symptoms, including irritability, shrill crying, diarrhea, or even seizures. Recognition of the problem is aided by a careful history and physical examination. When withdrawal symptoms are judged to be relatively mild, treatment is aimed at control of these symptoms using such drugs as diazepam; with more severe withdrawal, camphorated tincture of opium (paregoric; 0.4 mg of morphine/mL) in an oral dose of 0.12–0.24 mL/kg is used. Oral doses of methadone (0.1–0.5 mg/kg) have also been used.

4. Use in patients with impaired pulmonary function—In patients with borderline respiratory reserve, the depressant properties of the opioid analgesics may lead to acute respiratory failure.

5. Use in patients with impaired hepatic or renal function—Because morphine and its congeners are metabolized primarily in the liver, their use in patients in prehepatic coma may be questioned. Half-life is prolonged in patients with impaired renal function, and morphine and its active glucuronide metabolite may accumulate; dosage can often be reduced in such patients.

6. Use in patients with endocrine disease—Patients with adrenal insufficiency (Addison's disease) and those with hypothyroidism (myxedema) may have prolonged and exaggerated responses to opioids.

TABLE 31–5 Opioid drug interactions.

Drug Group	Interaction with Opioids
Sedative-hypnotics	Increased central nervous system depression, particularly respiratory depression.
Antipsychotic tranquilizers	Increased sedation. Variable effects on respiratory depression. Accentuation of cardiovascular effects (antimuscarinic and α-blocking actions).
Monoamine oxidase inhibitors	Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexic coma; hypertension has also been reported.

Drug Interactions

Because seriously ill or hospitalized patients may require a large number of drugs, there is always a possibility of drug interactions when the opioid analgesics are administered. Table 31–5 lists some of these drug interactions and the reasons for not combining the named drugs with opioids.

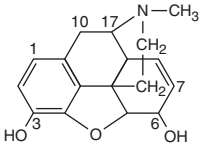
SPECIFIC AGENTS

The following section describes the most important and widely used opioid analgesics, along with features peculiar to specific agents. Data about doses approximately equivalent to 10 mg of intramuscular morphine, oral versus parenteral efficacy, duration of analgesia, and intrinsic activity (maximum efficacy) are presented in Table 31–2.

STRONG AGONISTS

Phenanthrenes

Morphine, hydromorphone, and **oxymorphone** are strong agonists useful in treating severe pain. These prototypic agents have been described in detail above.

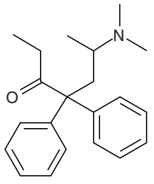


Morphine

Heroin (diamorphine, diacetylmorphine) is potent and fast-acting, but its use is prohibited in the USA and Canada. In recent years, there has been considerable agitation to revive its use. However, double-blind studies have not supported the claim that heroin is more effective than morphine in relieving severe chronic pain, at least when given by the intramuscular route.

Phenylheptylamines

Methadone has undergone a dramatic revival as a potent and clinically useful analgesic. It can be administered by the oral, intravenous, subcutaneous, spinal, and rectal routes. It is well absorbed from the gastrointestinal tract and its bioavailability far exceeds that of oral morphine.



Methadone

Methadone is not only a potent μ-receptor agonist but its racemic mixture of D- and L-methadone isomers can also block both NMDA receptors and monoaminergic reuptake transporters. These nonopioid receptor properties may help explain its ability to relieve difficult-to-treat pain (neuropathic, cancer pain), especially when a previous trial of morphine has failed. In this regard, when analgesic tolerance or intolerable side effects have developed with the use of increasing doses of morphine or hydromorphone, "opioid rotation" to methadone has provided superior analgesia at 10–20% of the morphine-equivalent daily dose. In contrast to its use in suppressing symptoms of opioid withdrawal, use of methadone as an analgesic typically requires administration at intervals of no more than 8 hours. However, given methadone's highly variable pharmacokinetics and long half-life (25–52 hours), initial administration should be closely monitored to avoid potentially harmful adverse effects, especially respiratory depression. Because methadone is metabolized by CYP3A4 and CYP2B6 isoforms in the liver, inhibition of its metabolic pathway or hepatic dysfunction has also been associated with overdose effects, including respiratory depression or, more rarely, prolonged QT-based cardiac arrhythmias.

Methadone is widely used in the treatment of opioid abuse. Tolerance and physical dependence develop more slowly with methadone than with morphine. The withdrawal signs and symptoms occurring after abrupt discontinuance of methadone are milder, although more prolonged, than those of morphine. These properties make methadone a useful drug for detoxification and for maintenance of the chronic relapsing heroin addict.

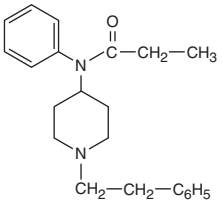
For detoxification of a heroin-dependent addict, low doses of methadone (5–10 mg orally) are given two or three times daily for 2 or 3 days. Upon discontinuing methadone, the addict experiences a mild but endurable withdrawal syndrome.

For maintenance therapy of the opioid recidivist, tolerance to 50–100 mg/d of oral methadone may be deliberately produced; in this state, the addict experiences cross-tolerance to heroin, which prevents most of the addiction-reinforcing effects of heroin. One rationale of maintenance programs is that blocking the reinforcement obtained from abuse of illicit opioids removes the drive to obtain them, thereby reducing criminal activity and making the addict more amenable to psychiatric and rehabilitative therapy. The pharmacologic basis for the use of methadone in maintenance programs is sound and the sociologic basis is rational, but some methadone programs fail because nonpharmacologic management is inadequate.

The concurrent administration of methadone to heroin addicts known to be recidivists has been questioned because of the increased risk of overdose death secondary to respiratory arrest. Not only has the number of patients prescribed methadone for persistent pain increased, but the incidence of accidental overdose and complications related to respiratory depression have also increased. Buprenorphine, a partial μ-receptor agonist with long-acting properties, has been found to be effective in opioid detoxification and maintenance programs and is presumably associated with a lower risk of such overdose fatalities.

Phenylpiperidines

Fentanyl is one of the most widely used agents in the family of synthetic opioids. The fentanyl subgroup now includes **sufentanil, alfentanil,** and **remifentanil** in addition to the parent compound, fentanyl.



Fentanyl

These opioids differ mainly in their potency and biodisposition. Sufentanil is five to seven times more potent than fentanyl. Alfentanil is considerably less potent than fentanyl, but acts more rapidly and has a markedly shorter duration of action. Remifentanil is metabolized very rapidly by blood and nonspecific tissue esterases, making its pharmacokinetic and pharmacodynamic half-lives extremely short. Such properties are useful when these compounds are used in anesthesia practice. Although fentanyl is now the predominant analgesic in the phenylpiperidine class, **meperidine** continues to be used. This older opioid has significant antimuscarinic effects, which may be a contraindication if tachycardia would be a problem. Meperidine is also reported to have a negative inotropic action on the heart. In addition, it has the potential for producing seizures secondary to accumulation of its metabolite, normeperidine, in patients receiving high doses or with concurrent renal failure. Given this undesirable profile, use of meperidine as a first-line analgesic is becoming increasingly rare.

Morphinans

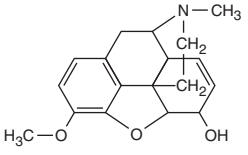
Levorphanol is a synthetic opioid analgesic closely resembling morphine in its action.

MILD TO MODERATE AGONISTS

Phenanthrenes

Codeine, dihydrocodeine, and **hydrocodone** are all somewhat less efficacious than morphine and often have adverse effects that limit the maximum tolerated dose when one attempts to achieve analgesia comparable to that of morphine. **Oxycodone** is more potent and is prescribed alone in higher doses as immediate-release or controlled-release forms for the treatment of moderate to severe pain. Combinations of hydrocodone or oxycodone with acetaminophen are the predominant formulations of orally administered analgesics for the treatment of mild to moderate pain. However, there has been a large increase in the use of controlled-release oxycodone at the highest dose range.

Since each controlled-release tablet of oxycodone contains a large quantity of oxycodone to allow for prolonged action, those intent on abusing the old formulation have modified the tablets, achieving high levels instantly, resulting in abuse and possible fatal overdose. The FDA recently approved a new formulation of the controlled-release form of oxycodone that reportedly prevents the tablets from being cut, broken, chewed, crushed, or dissolved to release more oxycodone. This new formulation will hopefully lead to less abuse by snorting or injection. Approximately half a million people used a controlled-release form of oxycodone for the first time in 2008, which prompted the FDA to require the manufacturer to collect data on abuse or misuse of the drug. The FDA is also requiring a Risk Evaluation and Mitigation Strategy (REMS) that will include the issuance of a medication guide to patients and a requirement for prescriber education regarding the appropriate use of opioid analgesics in the treatment of pain. (See Box: Educating Opioid Prescribers.)



Codeine

Phenylheptylamines

Propoxyphene is chemically related to methadone but has extremely low analgesic activity. Its low efficacy makes it unsuitable, even in combination with aspirin, for severe pain. The increasing incidence of deaths associated with its use and misuse caused it to be withdrawn in the United States.

Phenylpiperidines

Diphenoxylate and its metabolite, **difenoxin,** are not used for analgesia but for the treatment of diarrhea. They are scheduled for minimal control (difenoxin is Schedule IV, diphenoxylate Schedule V; see inside front cover) because the likelihood of their abuse is remote. The poor solubility of the compounds limits their use for parenteral injection. As antidiarrheal drugs, they are used in combination with atropine. The atropine is added in a concentration too low to have a significant antidiarrheal effect but is presumed to further reduce the likelihood of abuse.

Loperamide is a phenylpiperidine derivative used to control diarrhea. However, due to action on peripheral μ-opioid receptors and lack of effect on CNS receptors, there is renewed interest in its potential for the treatment of neuropathic pain. Its potential for abuse is considered very low because of its limited access to the brain. It is therefore available without a prescription.

The usual dose with all of these antidiarrheal agents is two tablets to start and then one tablet after each diarrheal stool.

Educating Opioid Prescribers

The treatment of pain is a difficult clinical-pharmacologic problem, and prescribers of opioids have often failed to appreciate this difficulty. As a result, there have been large increases of drug abuse cases in the USA and a nearly fourfold increase in overdose deaths due to prescription opioids between 1999 and 2009. These statistics have prompted the Food and Drug Administration to formulate plans for opioid manufacturers to provide training for all opioid prescribers. The FDA is working to devise methods by which this training would be mandatory for all prescribers and would emphasize the thorough understanding of opioid clinical pharmacology with special education about long-acting and extended-release formulations. The educational emphasis on the long-acting and sustained-release formulations (eg, methadone, oxycodone) reflects their association with skyrocketing morbidity and mortality.

OPIOIDS WITH MIXED RECEPTOR ACTIONS

Care should be taken not to administer any partial agonist or drug with mixed opioid receptor actions to patients receiving pure agonist drugs because of the unpredictability of both drugs' effects; reduction of analgesia or precipitation of an explosive abstinence syndrome may result.

Phenanthrenes

Nalbuphine is a strong κ-receptor *agonist* and a μ-receptor *antagonist;* it is given parenterally. At higher doses there seems to be a definite ceiling—not noted with morphine—to the respiratory depressant effect. Unfortunately, when respiratory depression does occur, it may be relatively resistant to naloxone reversal.

Buprenorphine is a potent and long-acting phenanthrene derivative that is a partial μ-receptor agonist and a κ–receptor antagonist. Administration by the sublingual route is preferred to avoid significant first-pass effect. Its long duration of action is due to its slow dissociation from μ receptors. This property renders its

effects resistant to naloxone reversal. Its clinical applications are much like those of nalbuphine. In addition, studies continue to suggest that buprenorphine is as effective as methadone in the detoxification and maintenance of heroin abusers. Buprenorphine was approved by the FDA in 2002 for the management of opioid dependence. In contrast to methadone, high-dose administration of buprenorphine results in a μ-opioid *antagonist* action, limiting its properties of analgesia and respiratory depression. Moreover, buprenorphine is also available combined with a pure μ-opioid antagonist (Suboxone) to help prevent its diversion for illicit intravenous abuse. A slow-release transdermal patch preparation that releases drug over a 1-week period is also available.

Morphinans

Butorphanol produces analgesia equivalent to nalbuphine and buprenorphine but appears to produce more sedation at equianalgesic doses. Butorphanol is considered to be predominantly a κ agonist. However, it may also act as a partial agonist or antagonist at the μ receptor.

Benzomorphans

Pentazocine is a κ agonist with weak μ-antagonist or partial agonist properties. It is the oldest mixed agent available. It may be used orally or parenterally. However, because of its irritant properties, the injection of pentazocine subcutaneously is not recommended.

MISCELLANEOUS

Tramadol is a centrally acting analgesic whose mechanism of action is predominantly based on blockade of serotonin reuptake. Tramadol has also been found to inhibit norepinephrine transporter function. Because it is only partially antagonized by naloxone, it is believed to be only a weak μ-receptor agonist. The recommended dosage is 50–100 mg orally four times daily. Toxicity includes association with seizures; the drug is relatively contraindicated in patients with a history of epilepsy and for use with other drugs that lower the seizure threshold. Another serious risk is the development of serotonin syndrome, especially if selective serotonin reuptake inhibitor (SSRI) antidepressants are being administered (see Chapter 16). Other side effects include nausea and dizziness, but these symptoms typically abate after several days of therapy. It is surprising that no clinically significant effects on respiration or the cardiovascular system have thus far been reported. Given the fact that the analgesic action of tramadol is largely independent of μ-receptor action, tramadol may serve as an adjunct with pure opioid agonists in the treatment of chronic neuropathic pain.

Tapentadol is a newer analgesic with modest μ-opioid receptor affinity and significant norepinephrine reuptake-inhibiting action. In animal models, its analgesic effects were only moderately reduced by naloxone but strongly reduced by an α_2-adrenoceptor antagonist. Furthermore, its binding to the norepinephrine transporter (NET, see Chapter 6) was stronger than that of tramadol, whereas its binding to the serotonin transporter (SERT) was less than that of tramadol. Tapentadol was approved in 2008 and has been shown to be as effective as oxycodone in the treatment of moderate to severe pain but with a reduced profile of gastrointestinal complaints such as nausea. Tapentadol carries risk for seizures in patients with seizure disorders and for the development of serotonin syndrome. It is unknown how tapentadol compares in clinical utility to tramadol or other analgesics whose mechanism of action is not based primarily on opioid receptor pharmacology.

ANTITUSSIVES

The opioid analgesics are among the most effective drugs available for the suppression of cough. This effect is often achieved at doses below those necessary to produce analgesia. The receptors involved in the antitussive effect appear to differ from those associated with the other actions of opioids. For example, the antitussive effect is also produced by stereoisomers of opioid molecules that are devoid of analgesic effects and addiction liability (see below).

The physiologic mechanism of cough is complex, and little is known about the specific mechanism of action of the opioid antitussive drugs. It appears likely that both central and peripheral effects play a role.

The opioid derivatives most commonly used as antitussives are **dextromethorphan, codeine, levopropoxyphene,** and **noscapine** (levopropoxyphene and noscapine are not available in the USA). They should be used with caution in patients taking monoamine oxidase inhibitors (see Table 31–5). Antitussive preparations usually also contain expectorants to thin and liquefy respiratory secretions. Importantly, due to increasing reports of death in young children taking dextromethorphan in formulations of over-the-counter "cold/cough" medications, its use in children less than 6 years of age has been banned by the FDA. Moreover, because of variations in the metabolism of codeine, its use for any purpose in young children is being reconsidered.

Dextromethorphan is the dextrorotatory stereoisomer of a methylated derivative of levorphanol. It is purported to be free of addictive properties and produces less constipation than codeine. The usual antitussive dose is 15–30 mg three or four times daily. It is available in many over-the-counter products. Dextromethorphan has also been found to enhance the analgesic action of morphine and presumably other μ-receptor agonists. However, abuse of its purified (powdered) form has been reported to lead to serious adverse events including death.

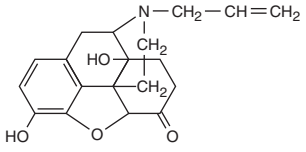
Codeine, as noted, has a useful antitussive action at doses lower than those required for analgesia. Thus, 15 mg is usually sufficient to relieve cough.

Levopropoxyphene is the stereoisomer of the weak opioid agonist dextropropoxyphene. It is devoid of opioid effects, although sedation has been described as a side effect. The usual antitussive dose is 50–100 mg every 4 hours.

THE OPIOID ANTAGONISTS

The pure opioid antagonist drugs **naloxone, naltrexone,** and **nalmefene** are morphine derivatives with bulkier substituents at the N_{17} position. These agents have a relatively high affinity for

μ-opioid binding sites. They have lower affinity for the other receptors but can also reverse agonists at δ and κ sites.



Naloxone

Pharmacokinetics

Naloxone is usually given by injection and has a short duration of action (1–2 hours) when given by this route. Metabolic disposition is chiefly by glucuronide conjugation like that of the agonist opioids with free hydroxyl groups. Naltrexone is well absorbed after oral administration but may undergo rapid first-pass metabolism. It has a half-life of 10 hours, and a single oral dose of 100 mg blocks the effects of injected heroin for up to 48 hours. Nalmefene, the newest of these agents, is a derivative of naltrexone but is available only for intravenous administration. Like naloxone, nalmefene is used for opioid overdose but has a longer half-life (8–10 hours).

Pharmacodynamics

When given in the absence of an agonist drug, these antagonists are almost inert at doses that produce marked antagonism of agonist opioid effects.

When given intravenously to a morphine-treated subject, the antagonist completely and dramatically reverses the opioid effects within 1–3 minutes. In individuals who are acutely depressed by an overdose of an opioid, the antagonist effectively normalizes respiration, level of consciousness, pupil size, bowel activity, and awareness of pain. In dependent subjects who appear normal while taking opioids, naloxone or naltrexone almost instantaneously precipitates an abstinence syndrome.

There is no tolerance to the antagonistic action of these agents, nor does withdrawal after chronic administration precipitate an abstinence syndrome.

Clinical Use

Naloxone is a pure antagonist and is preferred over older weak agonist-antagonist agents that had been used primarily as antagonists, eg, nalorphine and levallorphan.

The major application of naloxone is in the treatment of acute opioid overdose (see also Chapter 58). *It is very important that the relatively short duration of action of naloxone be borne in mind, because a severely depressed patient may recover after a single dose of naloxone and appear normal, only to relapse into coma after 1–2 hours.*

The usual initial dose of naloxone is 0.1–0.4 mg intravenously for life-threatening respiratory and CNS depression. Maintenance is with the same drug, 0.4–0.8 mg given intravenously, and repeated whenever necessary. In using naloxone in the severely opioid-depressed newborn, it is important to start with doses of 5–10 mcg/kg and to consider a second dose of up to a total of 25 mcg/kg if no response is noted.

Low-dose naloxone (0.04 mg) has an increasing role in the treatment of adverse effects that are commonly associated with intravenous or epidural opioids. Careful titration of the naloxone dosage can often eliminate the itching, nausea, and vomiting while sparing the analgesia. For this purpose, oral naloxone, and more recently modified analogs of naloxone and naltrexone, have been approved by the FDA. These include **methylnaltrexone bromide** (Relistor) for the treatment of constipation in patients with late-stage advanced illness and **alvimopan** (Entereg) for the treatment of postoperative ileus following bowel resection surgery. The principal mechanism for this selective therapeutic effect is believed to be inhibition of peripheral μ receptors in the gut with minimal CNS penetration.

Because of its long duration of action, naltrexone has been proposed as a maintenance drug for addicts in treatment programs. A single dose given on alternate days blocks virtually all of the effects of a dose of heroin. It might be predicted that this approach to rehabilitation would not be popular with a large percentage of drug users unless they are motivated to become drug-free. A related use is in combination with morphine sulfate in a controlled-release formulation (Embeda) in which 20–100 mg of morphine is slowly released over 8–12 hours or longer for the control of prolonged postoperative pain. Naltrexone, 0.4–4 mg, is sequestered in the center of the formulation pellets and is present to prevent the abuse of the morphine (by grinding and extraction of the morphine from the capsules).

There is evidence that naltrexone decreases the craving for alcohol in chronic alcoholics by increasing baseline β-endorphin release, and it has been approved by the FDA for this purpose (see Chapter 23). Naltrexone also facilitates abstinence from nicotine (cigarette smoking) with reduced weight gain. In fact, a combination of naltrexone plus bupropion (Chapter 30) may also offer an effective and synergistic strategy for weight loss. If current trials demonstrate cardiovascular safety during prolonged use, this and other weight-loss medications compounded with naltrexone may eventually win FDA approval.

SUMMARY Opioids, Opioid Substitutes, and Opioid Antagonists

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
STRONG OPIOID AGONISTS				
• Morphine • Methadone • Fentanyl	Strong μ-receptor agonists • variable affinity for δ and κ receptors	Analgesia • relief of anxiety • sedation • slowed gastrointestinal transit	Severe pain • adjunct in anesthesia (fentanyl, morphine) • pulmonary edema (morphine only) • maintenance in rehabilitation programs (methadone only)	First-pass effect • duration 1–4 h except methadone, 4–6 h • *Toxicity:* Respiratory depression • severe constipation • addiction liability • convulsions
• *Hydromorphone, oxymorphone: Like morphine in efficacy, but higher potency* • *Meperidine: Strong agonist with anticholinergic effects* • *Oxycodone: Dose-dependent analgesia* • *Sufentanil, alfentanil, remifentanil: Like fentanyl but shorter durations of action*				
PARTIAL AGONISTS				
• Codeine • Hydrocodone	Less efficacious than morphine • can antagonize strong agonists	Like strong agonists • weaker effects	Mild-moderate pain • cough (codeine)	Like strong agonists, toxicity dependent on genetic variation of metabolism
MIXED OPIOID AGONIST-ANTAGONISTS				
• Buprenorphine	Partial μ agonist • κ antagonist	Like strong agonists but can antagonize their effects • also reduces craving for alcohol	Moderate pain • some maintenance rehabilitation programs	Long duration of action 4–8 h • may precipitate abstinence syndrome
• Nalbuphine	κ Agonist • μ antagonist	Similar to buprenorphine	Moderate pain	Like buprenorphine
ANTITUSSIVES				
• Dextromethorphan	Poorly understood but strong and partial μ agonists are also effective antitussives	Reduces cough reflex	Acute debilitating cough	30–60 min duration • *Toxicity:* Minimal when taken as directed
• *Codeine, levopropoxyphene: Similar to dextromethorphan*				
OPIOID ANTAGONISTS				
• Naloxone	Antagonist at μ, δ, and κ receptors	Rapidly antagonizes all opioid effects	Opioid overdose	Duration 1–2 h (may have to be repeated when treating overdose) • *Toxicity:* Precipitates abstinence syndrome in dependent users
• *Naltrexone, nalmefene: Like naloxone but longer durations of action (10+ h); naltrexone is used in maintenance programs and can block heroin effects for up to 48 h; naltrexone is also used for alcohol and nicotine dependence; when combined with bupropion, may be effective in weight loss programs* • *Alvimopan, methylnaltrexone bromide: Potent μ antagonists with poor entry into the central nervous system; can be used to treat severe opioid-induced constipation without precipitating an abstinence syndrome*				
OTHER ANALGESICS USED IN MODERATE PAIN				
• Tapentadol	Moderate μ agonist, strong NET inhibitor	Analgesia	Moderate pain	Duration 4–6 h • *Toxicity:* Headache; nausea and vomiting; possible dependence
• Tramadol	Mixed effects: weak μ agonist, moderate SERT inhibitor, weak NET inhibitor	Analgesia	Moderate pain • adjunct to opioids in chronic pain syndromes	Duration 4–6 h • *Toxicity:* Seizures • risk of serotonin syndrome

NET, norepinephrine reuptake transporter; SERT, serotonin reuptake transporter.

PREPARATIONS AVAILABLE[1]

ANALGESIC OPIOIDS

Alfentanil (generic, Alfenta)
Parenteral: 0.5 mg/mL for injection

Buprenorphine (Buprenex, others)
Oral: 2, 8 mg sublingual tablets
Transdermal (Butrans): 5, 10, 20 mcg/h release rate for 1 week/patch
Parenteral: 0.3 mg/mL for injection

Butorphanol (generic, Stadol)
Parenteral: 1, 2 mg/mL for injection
Nasal (generic, Stadol NS): 10 mg/mL nasal spray

Codeine (sulfate or phosphate) (generic)
Oral: 15, 30, 60 mg tablets; 15 mg/5 mL solution
Parenteral: 15, 30 mg/mL for injection

Fentanyl (generic, other)
Parenteral (generic, Sublimaze): 50 mcg/mL for injection
Fentanyl Transdermal System (Duragesic): 12.5, 25, 50, 75, 100 mcg/h delivery
Fentanyl Buccal: 100, 200, 400, 600, 800 mcg oral lozenge
Fentanyl Actiq: 200, 400, 600, 800, 1200, 1600 mcg lozenge on a stick
Patient Controlled Transdermal Iontophoretic Fentanyl System: 40 mcg per dose for delivery

Hydromorphone (generic, Dilaudid)
Oral: 2, 8 mg tablets; 1 mg/mL liquid
Parenteral: 1, 2, 4, 10 mg/mL for injection

Levomethadyl acetate (Orlaam)
Oral: 10 mg/mL solution. Note: Orphan drug approved only for the treatment of narcotic addiction.

Levorphanol (generic, Levo-Dromoran)
Oral: 2 mg tablets
Parenteral: 2 mg/mL for injection

Meperidine (generic, Demerol)
Oral: 50, 100 mg tablets; 50 mg/5 mL syrup
Parenteral: 10, 25, 50, 75, 100 mg per dose for injection

Methadone (generic, Dolophine)
Oral: 5, 10 mg tablets; 40 mg dispersible tablets; 1, 2, 10 mg/mL solutions
Parenteral: 10 mg/mL for injection

Morphine sulfate (generic, others)
Oral: 15, 30 mg tablets; 15, 30 mg capsules; 10, 20, 100 mg/5 mL solution
Oral sustained-release tablets (MS Contin, others): 15, 30, 60, 100, 200 mg tablets
Oral sustained-release capsules (Avinza, Kadian): 20, 30, 50, 60, 90, 100, 120 mg capsules
Oral extended-release capsules (Embeda) (morphine sulfate/naltrexone HCl): 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, 100/4 mg
Parenteral: 0.5, 1, 2, 4, 5, 8, 10, 15, 25, 50 mg/mL for injection
Rectal: 5, 10, 20, 30 mg suppositories

Nalbuphine (generic, Nubain)
Parenteral: 10, 20 mg/mL for injection

Oxycodone (generic)
Oral: 5, 10, 15, 20, 30 mg tablets, capsules; 1, 20 mg/mL solutions
Oral sustained-release (generic, Oxy Contin): 10, 20, 40, 80 mg tablets

Oxymorphone (Numorphan)
Parenteral: 1, 1.5 mg/mL for injection
Rectal: 5 mg suppositories

Pentazocine (Talwin)
Oral: See combinations
Parenteral: 30 mg/mL for injection

Remifentanil (Ultiva)
Parenteral: 1, 2, 5 mg powder for reconstitution for injection

Sufentanil (generic, Sufenta)
Parenteral: 50 mcg/mL for injection

OTHER ANALGESICS

Tapentadol (Nucynta)
Oral: 50, 75, 100 mg tablets

Tramadol (generic, Ultram)
Oral: 50 mg tablets; 100, 200, 300 mg extended-release tablets

Ziconotide (Prialt)
Intrathecal: 25, 100 mcg/mL for programmable pump

ANALGESIC COMBINATIONS[2]

Codeine/acetaminophen (generic, Tylenol with Codeine, others)
Oral: 15, 30, 60 mg codeine plus 300 or 325 mg acetaminophen tablets or capsules; 12 mg codeine plus 120 mg acetaminophen tablets

Codeine/aspirin (generic, Empirin Compound, others)
Oral: 30, 60 mg codeine plus 325 mg aspirin tablets

Hydrocodone/acetaminophen (generic, Norco, Vicodin, Lortab, others)
Oral: 2.5, 5, 7.5, 10 mg hydrocodone plus 500 or 650 mg acetaminophen tablets

Hydrocodone/ibuprofen (Vicoprofen)
Oral: 7.5 mg hydrocodone plus 200 mg ibuprofen

Oxycodone/acetaminophen (generic, Percocet, Tylox, others)
Oral: 5 mg oxycodone plus 325 or 500 mg acetaminophen tablets
Note: High-dose acetaminophen has potential for hepatic toxicity with repeated use.

Oxycodone/aspirin (generic, Percodan)
Oral: 4.9 mg oxycodone plus 325 mg aspirin

OPIOID ANTAGONISTS

Alvimopan (Entereg)
Oral: 12 mg capsules

Methylnaltrexone (Relistor)
Parenteral: 12 mg/0.6 mL for injection

Nalmefene (Revex)
Parenteral: 0.1, 1 mg/mL for injection

Naloxone (generic, Narcan)
Parenteral: 0.4, 1 mg/mL; 0.02 mg/mL (for neonatal use) for injection

Naltrexone (generic, ReVia, Depade)
Oral: 50 mg tablets
Parenteral: 380 mg suspension for injection

ANTITUSSIVES

Codeine (generic)
Oral: 15, 30, 60 mg tablets; constituent of many proprietary syrups[2]

Dextromethorphan (generic, Benylin DM, Delsym, others)
Oral: 5, 7.5 mg lozenges; 7.5, 10, 15, 30 mg/5 mL syrup; 30 mg sustained-action liquid; constituent of many proprietary syrups[2]

[1]Antidiarrheal opioid preparations are listed in Chapter 62.

[2]Dozens of combination products are available; only a few of the most commonly prescribed are listed here. Codeine combination products available in several strengths are usually denoted No. 2 (15 mg codeine), No. 3 (30 mg codeine), and No. 4 (60 mg codeine). Prescribers should be aware of the possible danger of renal and hepatic injury with acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs contained in these analgesic combinations.

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CASE STUDY ANSWER

In this case, the treatment of severe pain should be managed with the administration of a potent intravenous opioid analgesic such as morphine, hydromorphone, or fentanyl. It is expected that he will require frequent reevaluation of both the severity of his pain and the presence of potential side effects before an additional dose of an opioid analgesic is administered. Given his history of pulmonary disease, he is also at increased risk of developing respiratory depression. Frequent reevaluation of his level of consciousness, respiratory rate, fractional oxygen saturation, and other vital parameters can help achieve the goal of pain relief and minimize respiratory depression. Concurrent use of sedative agents such as benzodiazepines should be avoided if possible and used only with great caution.

CHAPTER 32

Drugs of Abuse

Christian Lüscher, MD

CASE STUDY

A retired accountant developed a tremor and slowing of movements and was diagnosed with Parkinson's disease at age 67. At that time, his neurologist prescribed levodopa to restore dopamine levels. Two years later, motor symptoms start to fluctuate and the dopamine receptor agonist ropinirole is added to his treatment.* A few months later, he developed a strong interest in gambling, first buying lottery tickets and then visiting a casino almost every day. He concealed his gambling activity until he had lost more than $100,000. When he came for a consultation 5 weeks ago, ropinirole was replaced with monoamine oxidase inhibitor therapy. He now reports that his interest in gambling has disappeared. Is there a link between the dopamine agonist treatment and gambling addiction?

Drugs are abused (used in ways that are not medically approved) because they cause strong feelings of euphoria or alter perception. However, repetitive exposure induces widespread adaptive changes in the brain. As a consequence, drug use may become compulsive—the hallmark of addiction.

BASIC NEUROBIOLOGY OF DRUG ABUSE

DEPENDENCE VERSUS ADDICTION

Recent neurobiologic research has led to the conceptual and mechanistic separation of "dependence" and "addiction." The older term "physical dependence" is now denoted as **dependence,** whereas "psychological dependence" is more simply called **addiction.**

Every addictive drug causes its own characteristic spectrum of acute effects, but all have in common that they induce strong feelings of euphoria and reward. With repetitive exposure, addictive drugs induce adaptive changes such as tolerance (ie, escalation of dose to maintain effect). Once the abused drug is no longer available, signs of withdrawal become apparent. A combination of such signs, referred to as the **withdrawal syndrome,** defines *dependence*. Dependence is not always a correlate of drug abuse—it can also occur with many classes of nonpsychoactive drugs, eg, sympathomimetic vasoconstrictors and bronchodilators, and organic nitrate vasodilators. *Addiction*, on the other hand, consists of compulsive, relapsing drug use despite negative consequences, at times triggered by cravings that occur in response to contextual cues (see Box: Animal Models in Addiction Research). Although dependence invariably occurs with chronic exposure, only a small percentage of subjects develop a habit, lose control, and become addicted. For example, very few patients who receive opioids as analgesics desire the drug after withdrawal. And only one person out of six becomes addicted within 10 years of first use of cocaine. Conversely, relapse is very common in addicts after a successful withdrawal when, by definition, they are no longer dependent.

ADDICTIVE DRUGS INCREASE THE LEVEL OF DOPAMINE: REINFORCEMENT

To understand the long-term changes induced by drugs of abuse, their initial molecular and cellular targets must be identified. A combination of approaches in animals and humans, including functional imaging, has revealed the mesolimbic dopamine system as the prime target of addictive drugs. This system originates in the **ventral tegmental area (VTA),** a tiny structure at the tip of the brainstem, which projects to the **nucleus accumbens,** the amygdala, the hippocampus,

*The treatment of Parkinson's disease is discussed in Chapter 28.

Animal Models in Addiction Research

Many of the recent advances in addiction research have been made possible by the use of animal models. Since drugs of abuse are not only rewarding but also reinforcing, an animal will learn a behavior (eg, press a lever) when paired with drug administration. In such a self-administration paradigm, the number of times an animal is willing to press the lever in order to obtain a single dose reflects the strength of reinforcement and is therefore a measure of the rewarding properties of a drug. Observing withdrawal signs specific for rodents (eg, escape jumps or "wet-dog" shakes after abrupt termination of chronic morphine administration) allows the quantification of dependence. Behavioral tests for addiction in the rodent have proven difficult to develop, and so far no test fully captures the complexity of the disease. However it is possible to model core components of addiction, for example by monitoring behavioral sensitization and conditioned place preference. In the first test, an increase in locomotor activity is observed with intermittent drug exposure. The latter tests for the preference of a particular environment associated with drug exposure by measuring the time an animal spends in the compartment where a drug was received compared with the compartment where only saline was injected (conditioned place preference). Both tests have in common that they are sensitive to cue-conditioned effects of addictive drugs. Subsequent exposures to the environment without the drug lead to extinction of the place preference, which can be reinstated with a low dose of the drug or the presentation of a conditioned stimulus. These persistent changes serve as a model of relapse and have been linked to synaptic plasticity of excitatory transmission in the ventral tegmental area, nucleus accumbens and prefrontal cortex (see also Box: The Dopamine Hypothesis of Addiction). Recent findings suggest that prolonged self-administration of cocaine leads to behaviors in rats that closely resemble human addiction. Such "addicted rats" are very strongly motivated to seek cocaine, continue looking for the drug even when no longer available, and self-administer cocaine in spite of negative consequences, such as an electric foot shock. These findings suggest that addiction is a disease that does not respect species boundaries.

and the prefrontal cortex (Figure 32–1). Most projection neurons of the VTA are dopamine-producing neurons. When the dopamine neurons of the VTA begin to fire in bursts, large quantities of dopamine are released in the nucleus accumbens and the prefrontal cortex. Early animal studies pairing electrical stimulation of the VTA with operant responses (eg, lever pressing) that result in strong reinforcement established the central role of the mesolimbic dopamine system in reward processing. Direct application of drugs into the VTA also acts as a strong reinforcer, and systemic administration of drugs of abuse causes release of dopamine. Even selective activation of dopamine neurons is sufficient to elicit behavioral changes typically observed with addictive drugs. These very selective interventions use optogenetic methods. Blue light is delivered in a freely moving mouse through light guides to activate channelrhodopsin, a light-gated cation channel that is artificially expressed in dopamine neurons.

As a general rule, all addictive drugs activate the mesolimbic dopamine system. The behavioral significance of this increase of dopamine is still debated. An appealing hypothesis is that mesolimbic dopamine codes for the difference between expected and actual reward and thus constitutes a strong learning signal (see Box: The Dopamine Hypothesis of Addiction).

Since each addictive drug has a specific molecular target that engages distinct cellular mechanisms to activate the mesolimbic system, three classes can be distinguished: A first group binds to **G_{io} protein-coupled receptors,** a second group interacts with **ionotropic receptors or ion channels,** and a third group targets the **dopamine transporter** (Table 32–1 and Figure 32–2). G protein-coupled receptors (GPCRs) of the G_{io} family inhibit neurons through postsynaptic hyperpolarization and presynaptic regulation of transmitter release. In the VTA, the action of these drugs is preferentially on the γ-aminobutyric acid (GABA) neurons that act as local inhibitory interneurons. Addictive drugs that bind to ionotropic receptors and ion channels can have combined effects on dopamine neurons and GABA neurons, eventually leading to enhanced release of dopamine. Finally, addictive drugs that interfere with monoamine transporters block reuptake or stimulate nonvesicular release of dopamine, causing an accumulation of extracellular dopamine in target structures. Since neurons of the VTA also express somatodendritic transporters, which normally clear dopamine released by the dendrites, class III drugs also increase dopamine level in the VTA. Although drugs of this class also affect transporters of other monoamines (norepinephrine, serotonin), action on the dopamine transporter remains central for addiction. This is consistent with the observations that antidepressants that block serotonin and norepinephrine uptake, but not dopamine uptake, do not cause addiction even after prolonged use.

DEPENDENCE: TOLERANCE & WITHDRAWAL

With chronic exposure to addictive drugs, the brain shows signs of adaptation. For example, if morphine is used at short intervals, the dose has to be progressively increased over the course of several days to maintain rewarding or analgesic effects. This phenomenon is called tolerance. It may become a serious problem because of increasing side effects—eg, respiratory depression—that do not show much tolerance and may lead to fatalities associated with overdose.

Tolerance to opioids may be due to a reduction of the concentration of a drug or a shorter duration of action in a target system

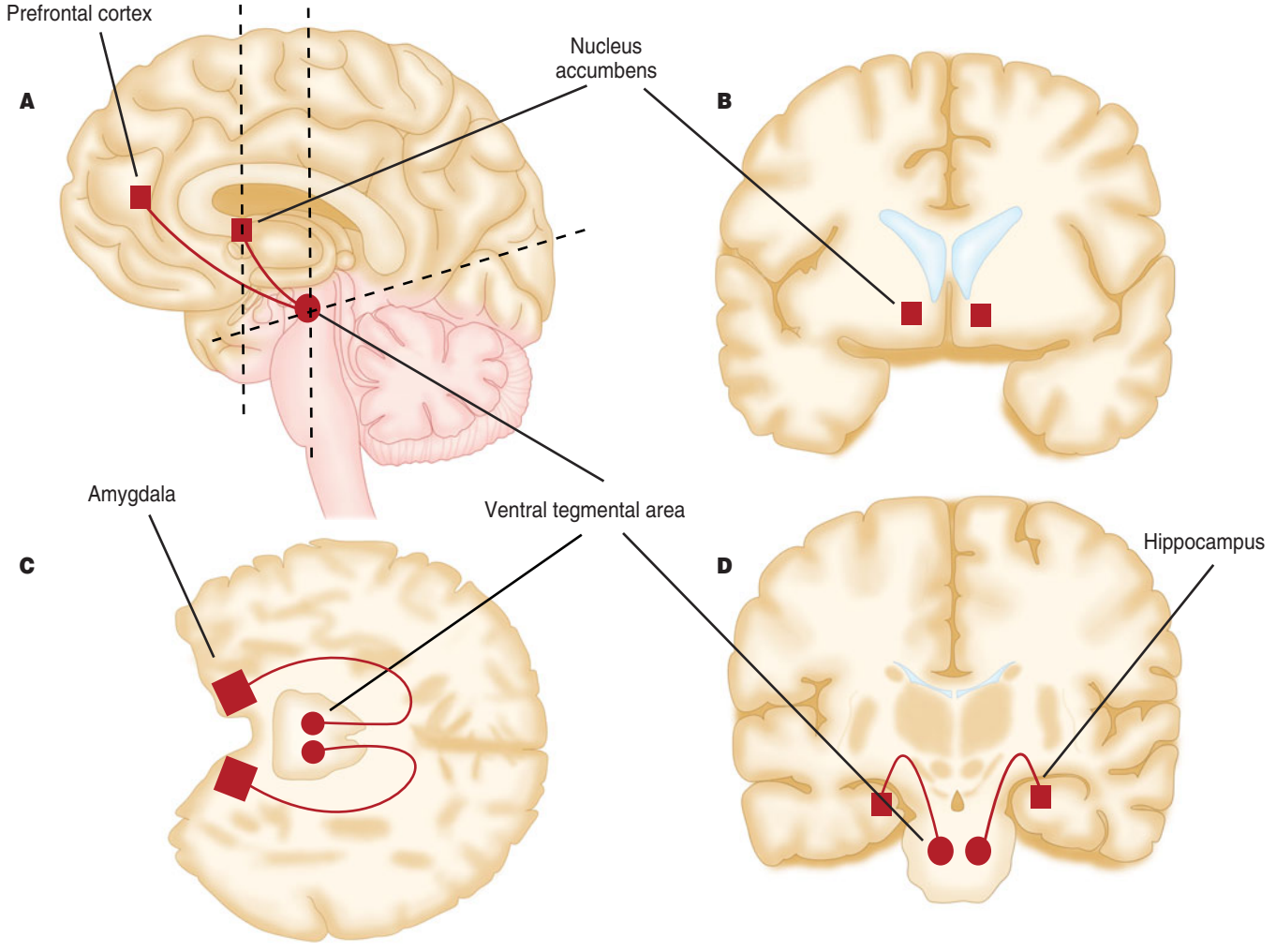

FIGURE 32–1 Major connections of the mesolimbic dopamine system in the brain. Schematic diagram of brain sections illustrating that the dopamine projections originate in the ventral tegmental area and target the nucleus accumbens, prefrontal cortex, amygdala, and hippocampus. The dashed lines on the sagittal section indicate where the horizontal and coronal sections were made.

(pharmacokinetic tolerance). Alternatively, it may involve changes of μ-opioid receptor function (pharmacodynamic tolerance). In fact, many μ-opioid receptor agonists promote strong receptor phosphorylation that triggers the recruitment of the adaptor protein β-arrestin, causing G proteins to uncouple from the receptor and to internalize within minutes (see Chapter 2). Since this decreases signaling, it is tempting to explain tolerance by such a mechanism. However, morphine, which strongly induces tolerance, does not recruit β-arrestins and fails to promote receptor internalization. Conversely, other agonists that drive receptor internalization very efficiently induce only modest tolerance. Based on these observations, it has been hypothesized that desensitization and receptor internalization actually protect the cell from overstimulation. In this model, morphine, by failing to trigger receptor endocytosis, disproportionally stimulates adaptive processes, which eventually cause tolerance. Although the molecular identity of these processes is still under investigation, they may be similar to the ones involved in withdrawal (see below).

Adaptive changes become fully apparent once drug exposure is terminated. This state is called **withdrawal** and is observed to varying degrees after chronic exposure to most drugs of abuse. Withdrawal from opioids in humans is particularly strong (described below). Studies in rodents have added significantly to our understanding of the neural and molecular mechanisms that underlie dependence. For example, signs of dependence, as well as analgesia and reward, are abolished in knockout mice lacking the μ-opioid receptor, but not in mice lacking other opioid receptors (δ, κ). Although activation of the μ-opioid receptor initially strongly inhibits adenylyl cyclase, this inhibition becomes weaker after several days of repeated exposure. The reduction of the

The Dopamine Hypothesis of Addiction

In the earliest version of the hypothesis described in this chapter, mesolimbic dopamine was believed to be the neurochemical correlate of pleasure and reward. However, during the past decade, experimental evidence has led to several revisions. Phasic dopamine release may actually code for the *prediction error* of reward rather than the reward itself. This distinction is based on pioneering observations in monkeys that dopamine neurons in the ventral tegmental area (VTA) are most efficiently activated by a reward (eg, a few drops of fruit juice) that is not anticipated. When the animal learns to predict the occurrence of a reward (eg, by pairing it with a stimulus such as a sound), dopamine neurons stop responding to the reward itself (juice), but increase their firing rate when the conditioned stimulus (sound) occurs. Finally, if reward is predicted but not delivered (sound but no juice), dopamine neurons are inhibited below their baseline activity and become silent. In other words, the mesolimbic system continuously scans the reward situation. It increases its activity when reward is larger than expected, and shuts down in the opposite case, thus coding for the prediction error of reward.

Under physiologic conditions the mesolimbic dopamine signal could represent a learning signal responsible for reinforcing constructive behavioral adaptation (eg, learning to press a lever for food). Addictive drugs, by directly increasing dopamine, would generate a strong but inappropriate learning signal, thus hijacking the reward system and leading to pathologic reinforcement. As a consequence, behavior becomes compulsive; that is decisions are no longer planned and under control, but automatic, which is the hallmark of addiction.

This appealing hypothesis has been challenged based on the observation that some reward and drug-related learning is still possible in the absence of dopamine. Another intriguing observation is that mice genetically modified to lack the primary molecular target of cocaine, the dopamine transporter DAT, still self-administer the drug. Only when transporters of other biogenic amines are also knocked out does cocaine completely lose its rewarding properties. However, in $DAT^{-/-}$ mice, in which basal synaptic dopamine levels are high, cocaine still leads to increased dopamine release, presumably because other cocaine-sensitive monoamine transporters (NET, SERT) are able to clear some dopamine. When cocaine is given, these transporters are also inhibited and dopamine is again increased. As a consequence of this substitution among monoamine transporters, fluoxetine (a selective serotonin reuptake inhibitor, see Chapter 30) becomes addictive in $DAT^{-/-}$ mice. This concept is supported by newer evidence showing that deletion of the cocaine binding site on DAT leaves basal dopamine levels unchanged but abolishes the rewarding effect of cocaine.

The dopamine hypothesis of addiction has also been challenged by the observation that salient stimuli that are not rewarding (they may actually even be aversive and therefore negative reinforcers) also activate a subpopulation of dopamine neurons in the VTA. Some of the neurons that are activated by aversive stimuli do in fact release dopamine, while the majority of dopamine neurons are actually inhibited by aversive stimuli. These recent findings suggest that in parallel to the reward system, a system for aversion-learning originates in the VTA.

Regardless of the many roles of dopamine under physiologic conditions, all addictive drugs significantly increase its concentration in target structures of the mesolimbic projection. This suggests that high levels of dopamine may actually be at the origin of the adaptive changes that underlie dependence and addiction, a concept that is now supported by novel techniques that allow controlling the activity of dopamine neurons in vivo. In fact manipulations that drive sustained activity of VTA dopamine neurons cause the same cellular adaptations and behavioral changes typically observed with addictive drug exposure.

inhibition of adenylyl cyclase is due to a counter-adaptation of the enzyme system during exposure to the drug, which results in overproduction of cAMP during subsequent withdrawal. Several mechanisms exist for this adenylyl cyclase compensatory response, including up-regulation of transcription of the enzyme. Increased cAMP concentrations in turn strongly activate the transcription factor cyclic AMP response element binding protein (CREB), leading to the regulation of downstream genes. Of the few such genes identified to date, one of the most interesting is the gene for the endogenous κ-opioid ligand dynorphin. During withdrawal, neurons of the nucleus accumbens produce high levels of dynorphin, which is then co-released with GABA onto the projection neurons of the VTA (Figure 32–3). These cells express κ-opioid receptors on their synaptic terminals and on the dendrites. As a consequence, they are inhibited and dopamine release is reduced. This mechanism exemplifies the adaptive processes engaged during dependence and may underlie the intense dysphoria typically observed during withdrawal.

ADDICTION: A DISEASE OF MALADAPTIVE LEARNING

Addiction is characterized by a high motivation to obtain and use a drug despite negative consequences. With time, drug use becomes compulsive ("wanting without liking"). Addiction is a recalcitrant, chronic, and stubbornly relapsing disease that is very difficult to treat.

TABLE 32–1 The mechanistic classification of drugs of abuse.[1]

Name	Main Molecular Target	Pharmacology	Effect on Dopamine (DA) Neurons	RR[2]
Drugs That Activate G Protein-Coupled Receptors				
Opioids	μ-OR (G_{io})	Agonist	Disinhibition	4
Cannabinoids	CB_1R (G_{io})	Agonist	Disinhibition	2
γ-Hydroxybutyric acid (GHB)	$GABA_BR$ (G_{io})	Weak agonist	Disinhibition	?
LSD, mescaline, psilocybin	$5\text{-}HT_{2A}R$ (G_q)	Partial agonist	…	1
Drugs That Bind to Ionotropic Receptors and Ion Channels				
Nicotine	nAChR ($\alpha_2\beta_2$)	Agonist	Excitation	4
Alcohol	$GABA_AR$, $5\text{-}HT_3R$, nAChR, NMDAR, Kir3 channels		Excitation, disinhibition (?)	3
Benzodiazepines	$GABA_AR$	Positive modulator	Disinhibition	3
Phencyclidine, ketamine	NMDAR	Antagonist	…	1
Drugs That Bind to Transporters of Biogenic Amines				
Cocaine	DAT, SERT, NET	Inhibitor	Blocks DA uptake	5
Amphetamine	DAT, NET, SERT, VMAT	Reverses transport	Blocks DA uptake , synaptic depletion	5
Ecstasy	SERT > DAT, NET	Reverses transport	Blocks DA uptake, synaptic depletion	?

$5\text{-}HT_xR$, serotonin receptor; CB_1R, cannabinoid-1; DAT, dopamine transporter; GABA, γ-aminobutyric acid; Kir3 channels, G protein-coupled inwardly rectifying potassium channels; LSD, lysergic acid diethylamide; μ-OR, μ-opioid receptor; nAChR, nicotinic acetylcholine receptor; NET, norepinephrine transporter; NMDAR, *N*-methyl-D-aspartate receptor; SERT, serotonin transporter; VMAT, vesicular monoamine transporter; ? indicates data not available.

[1]Drugs fall into one of three categories, targeting either G protein-coupled receptors, ionotropic receptors or ion channels, or biogenic amine transporters.

[2]RR, relative risk of addiction; 1 = nonaddictive; 5 = highly addictive.

The central problem is that even after successful withdrawal and prolonged drug-free periods, addicted individuals have a high risk of relapsing. Relapse is typically triggered by one of the following three conditions: reexposure to the addictive drug, stress, or a context that recalls prior drug use. It appears that when paired with drug use, a neutral stimulus may undergo a switch and motivate ("trigger") addiction-related behavior. This phenomenon may involve synaptic plasticity in the target nuclei of the mesolimbic projection (eg, nucleus accumbens). Several recent studies suggest that the recruitment of the dorsal striatum is responsible for the

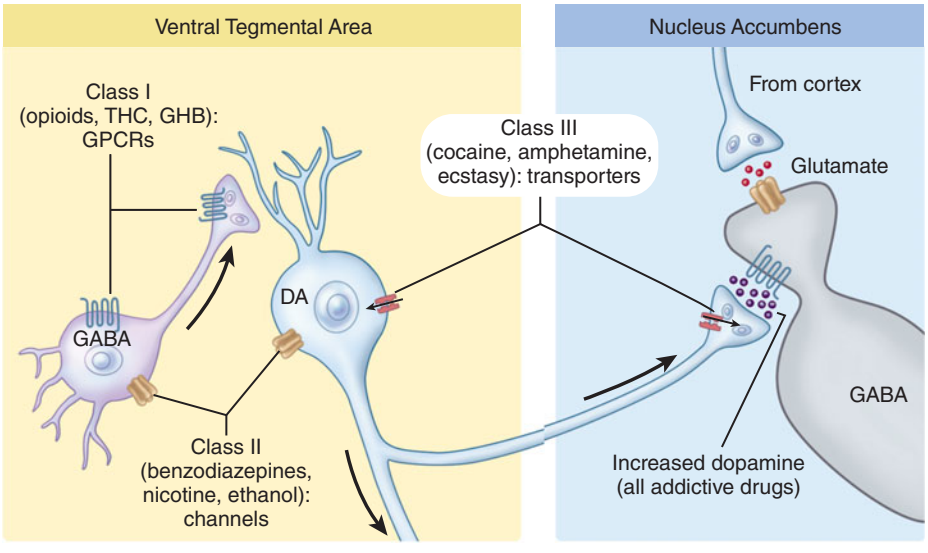

FIGURE 32–2 Neuropharmacologic classification of addictive drugs by primary target (see text and Table 32–1). DA, dopamine; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric acid; GPCRs, G protein-coupled receptors; THC, Δ^9-tetrahydrocannabinol.

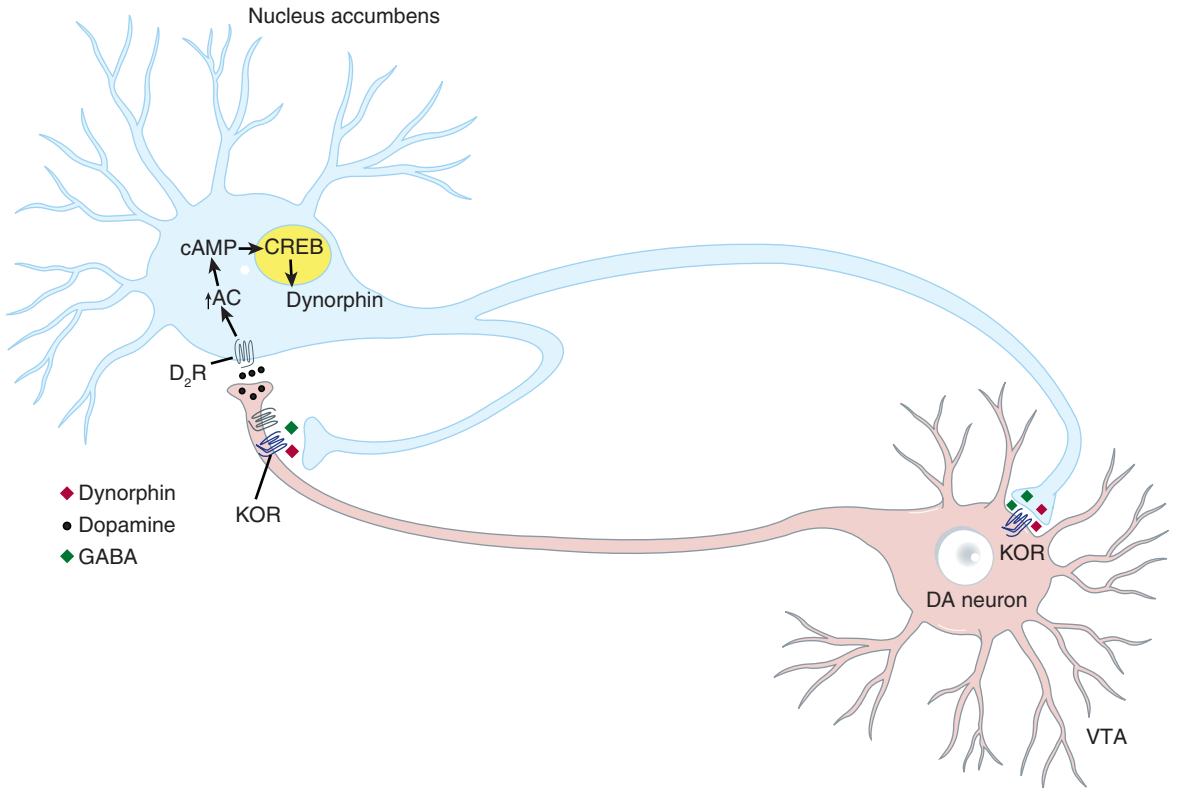

FIGURE 32–3 CREB-mediated up-regulation of dynorphin during withdrawal from dependence. Supersensitization of adenylyl cyclase (AC) leads to an increase of cAMP concentration in medium spiny neurons of the accumbens. This activates the transcription factor CREB, which turns on several genes, including that for dynorphin. Dynorphin is then co-released with γ-aminobutyric acid (GABA), activating the κ-opioid receptor (KOR) located on dopamine neurons of the ventral tegmental area (VTA), thereby leading to pre- and postsynaptic inhibition. D_2R, dopamine D_2 receptor.

compulsion. This switch may depend on synaptic plasticity in the nucleus accumbens of the ventral striatum, where mesolimbic dopamine afferents and cortical glutamatergic afferents converge. If dopamine release codes for the prediction error of reward (see Box: The Dopamine Hypothesis of Addiction), pharmacologic stimulation of the mesolimbic dopamine systems will generate an unusually strong learning signal. Unlike natural rewards, addictive drugs continue to increase dopamine even when reward is expected. Such overriding of the prediction error signal may eventually be responsible for the usurping of memory processes by addictive drugs.

The involvement of learning and memory systems in addiction is also suggested by clinical studies. For example, the role of context in relapse is supported by the report that soldiers who became addicted to heroin during the Vietnam War had significantly better outcomes when treated after their return home, compared with addicts who remained in the environment where they had taken the drug. In other words, cravings may recur at the presentation of contextual cues (eg, people, places, or drug paraphernalia). Current research therefore focuses on the effects of drugs on associative forms of synaptic plasticity, such as long-term potentiation (LTP), which underlie learning and memory (see Box: Synaptic Plasticity & Addiction).

Non-substance-dependent disorders, such as pathologic gambling and compulsive shopping, share many clinical features of addiction. Several lines of arguments suggest that they also share the underlying neurobiologic mechanisms. This conclusion is supported by the clinical observation that, as an adverse effect of dopamine agonist medication, patients with Parkinson's disease may become pathologic gamblers (see Case Study). Other patients may develop a habit for recreational activities, such as shopping, eating compulsively, or becoming excessively involved in sexual activity (hypersexuality). Although large-scale studies are not yet available, an estimated 1 of 7 parkinsonian patients develops an addiction-like behavior when receiving dopamine agonists.

Large individual differences exist also in vulnerability to substance-related addiction. Whereas one person may become "hooked" after a few doses, others may be able to use a drug occasionally during their entire lives without ever having difficulty in stopping. Even when dependence is induced with chronic exposure, only a small percentage of dependent users progress to addiction. Recent studies in rats suggest that impulsivity or excessive anxiety may be crucial traits that represent a risk for addiction. The transition to addiction is determined by a combination

Synaptic Plasticity & Addiction

Long-term potentiation (LTP) is a form of experience-dependent synaptic plasticity that is induced by activating glutamate receptors of the *N*-methyl-D-aspartate (NMDA) type. Since NMDA receptors are blocked by magnesium at negative potentials, their activation requires the concomitant release of glutamate (presynaptic activity) onto a receiving neuron that is depolarized (postsynaptic activity). Correlated pre- and postsynaptic activity durably enhances synaptic efficacy and triggers the formation of new connections. Because associativity is a critical component, LTP has become a leading candidate mechanism underlying learning and memory. LTP can be elicited at glutamatergic synapses of the mesolimbic reward system and is modulated by dopamine. Drugs of abuse could therefore interfere with LTP at sites of convergence of dopamine and glutamate projections (eg, ventral tegmental area [VTA], nucleus accumbens, or prefrontal cortex). Interestingly, exposure to an addictive drug triggers a specific form of synaptic plasticity at excitatory afferents (drug-evoked synaptic plasticity) and reduces $GABA_A$ receptor-mediated inhibition of the VTA. As a consequence, the excitability of dopamine neurons is increased, the synaptic calcium sources altered, and the rules for subsequent LTP inverted. Genetic manipulations in mice that prevent drug-evoked plasticity at this synapse also have effects on persistent changes of drug-associated behavioral paradigms such as reinstatement of conditioned place preference, further supporting the idea that synaptic plasticity is involved in context-dependent components of relapse.

of environmental and genetic factors. Heritability of addiction, as determined by comparing monozygotic with dizygotic twins, is relatively modest for cannabinoids but very high for cocaine. It is of interest that the relative risk for addiction (addiction liability) of a drug (Table 32–1) correlates with its heritability, suggesting that the neurobiologic basis of addiction common to all drugs is what is being inherited. Further genomic analysis indicates that only a few alleles (or perhaps even a single recessive allele) need to function in combination to produce the phenotype. However, identification of the genes involved remains elusive. Although some substance-specific candidate genes have been identified (eg, alcohol dehydrogenase), future research will also focus on genes implicated in the neurobiologic mechanisms common to all addictive drugs.

NONADDICTIVE DRUGS OF ABUSE

Some drugs of abuse do not lead to addiction. This is the case for substances that alter perception without causing sensations of reward and euphoria, such as the hallucinogens and the dissociative anesthetics (Table 32–1). Unlike addictive drugs, which primarily target the mesolimbic dopamine system, these agents primarily target cortical and thalamic circuits. Lysergic acid diethylamide (LSD), for example, activates the serotonin $5\text{-}HT_{2A}$ receptor in the prefrontal cortex, enhancing glutamatergic transmission onto pyramidal neurons. These excitatory afferents mainly come from the thalamus and carry sensory information of varied modalities, which may constitute a link to enhanced perception. Phencyclidine (PCP) and ketamine produce a feeling of separation of mind and body (which is why they are called dissociative anesthetics) and, at higher doses, stupor and coma. The principal mechanism of action is a use-dependent inhibition of glutamate receptors of the *N*-methyl-D-aspartate (NMDA) type.

The classification of NMDA antagonists as nonaddictive drugs was based on early assessments, which, in the case of PCP, have recently been questioned. In fact, animal research shows that PCP can increase mesolimbic dopamine concentrations and has some reinforcing properties in rodents. Concurrent effects on both thalamocortical and mesolimbic systems also exist for other addictive drugs. Psychosis-like symptoms can be observed with cannabinoids, amphetamines, and cocaine, which may reflect their effects on thalamocortical structures. For example, cannabinoids, in addition to their documented effects on the mesolimbic dopamine system, also enhance excitation in cortical circuits through presynaptic inhibition of GABA release.

Hallucinogens and NMDA antagonists, even if they do not produce dependence or addiction, can still have long-term effects. Flashbacks of altered perception can occur years after LSD use. Moreover, chronic use of PCP may lead to an irreversible schizophrenia-like psychosis.

BASIC PHARMACOLOGY OF DRUGS OF ABUSE

Since all addictive drugs increase dopamine concentrations in target structures of the mesolimbic projections, we classify them on the basis of their molecular targets and the underlying mechanisms (Table 32–1 and Figure 32–2). The first group contains the **opioids, cannabinoids, γ-hydroxybutyric acid (GHB),** and the **hallucinogens,** which all exert their action through G_{io} protein-coupled receptors. The second group includes **nicotine, alcohol, the benzodiazepines, dissociative anesthetics,** and some **inhalants,** which interact with ionotropic receptors or ion channels. The last group comprises **cocaine, amphetamines,** and **ecstasy,** which all bind to monoamine transporters. The nonaddictive drugs are classified using the same criteria.

DRUGS THAT ACTIVATE G_{IO}-COUPLED RECEPTORS

OPIOIDS

Opioids may have been the first drugs to be abused (preceding stimulants), and are still among the most commonly used for nonmedical purposes.

Pharmacology & Clinical Aspects

As described in Chapter 31, opioids comprise a large family of endogenous and exogenous agonists at three G protein-coupled receptors: the μ-, κ-, and δ-opioid receptors. Although all three receptors couple to inhibitory G proteins (ie, they all inhibit adenylyl cyclase), they have distinct, sometimes even opposing effects, mainly because of the cell type-specific expression throughout the brain. In the VTA, for example, μ-opioid receptors are selectively expressed on GABA neurons (which they inhibit), whereas κ-opioid receptors are expressed on and inhibit dopamine neurons. This may explain why μ-opioid agonists cause euphoria, whereas κ agonists induce dysphoria.

In line with the latter observations, the rewarding effects of morphine are absent in knockout mice lacking μ receptors but persist when either of the other opioid receptors are ablated. In the VTA, μ opioids cause an inhibition of GABAergic inhibitory interneurons, which leads eventually to a disinhibition of dopamine neurons.

The most commonly abused μ opioids include **morphine, heroin** (diacetylmorphine, which is rapidly metabolized to morphine), **codeine,** and **oxycodone. Meperidine** abuse is common among health professionals. All of these drugs induce strong tolerance and dependence. The withdrawal syndrome may be very severe (except for codeine) and includes intense dysphoria, nausea or vomiting, muscle aches, lacrimation, rhinorrhea, mydriasis, piloerection, sweating, diarrhea, yawning, and fever. Beyond the withdrawal syndrome, which usually lasts no longer than a few days, individuals who have received opioids as analgesics only rarely develop addiction. In contrast, when taken for recreational purposes, opioids are highly addictive. The relative risk of addiction is 4 out of 5 on a scale of 1 = nonaddictive, 5 = highly addictive.

Treatment

The opioid antagonist **naloxone** reverses the effects of a dose of morphine or heroin within minutes. This may be life-saving in the case of a massive overdose (see Chapters 31 and 58). Naloxone administration also provokes an acute withdrawal (precipitated abstinence) syndrome in a dependent person who has recently taken an opioid.

In the treatment of opioid addiction, a long-acting opioid (eg, **methadone, buprenorphine)** is often substituted for the shorter-acting, more rewarding, opioid (eg, heroin). For substitution therapy, methadone is given orally once daily, facilitating supervised intake. Using a partial agonist (buprenorphine) and the much longer half-life (methadone and buprenorphine) may also have some beneficial effects (eg, weaker drug sensitization, which typically requires intermittent exposures), but it is important to realize that abrupt termination of methadone administration invariably precipitates a withdrawal syndrome; that is, the subject on substitution therapy remains dependent. Some countries (eg, Switzerland, Netherlands) even allow substitution of heroin by heroin. A follow-up of a cohort of addicts who receive heroin injections in a controlled setting and have access to counseling indicates that addicts under heroin substitution have an improved health status and are better integrated in society.

CANNABINOIDS

Endogenous cannabinoids that act as neurotransmitters include 2-arachidonyl glycerol (2-AG) and anandamide, both of which bind to CB_1 receptors. These very lipid-soluble compounds are released at the postsynaptic somatodendritic membrane, and diffuse through the extracellular space to bind at presynaptic CB_1 receptors, where they inhibit the release of either glutamate or GABA. Because of such backward signaling, endocannabinoids are called retrograde messengers. In the hippocampus, release of endocannabinoids from pyramidal neurons selectively affects inhibitory transmission and may contribute to the induction of synaptic plasticity during learning and memory formation.

Exogenous cannabinoids, eg in **marijuana,** include several pharmacologically active substances including **Δ^9-tetrahydrocannabinol (THC),** a powerful psychoactive substance. Like opioids, THC causes disinhibition of dopamine neurons, mainly by presynaptic inhibition of GABA neurons in the VTA. The half-life of THC is about 4 hours. The onset of effects of THC after smoking marijuana occurs within minutes and reaches a maximum after 1–2 hours. The most prominent effects are euphoria and relaxation. Users also report feelings of well-being, grandiosity, and altered perception of passage of time. Dose-dependent perceptual changes (eg, visual distortions), drowsiness, diminished coordination, and memory impairment may occur. Cannabinoids can also create a dysphoric state and, in rare cases following the use of very high doses, eg, in **hashish,** result in visual hallucinations, depersonalization, and frank psychotic episodes. Additional effects of THC, eg, increased appetite, attenuation of nausea, decreased intraocular pressure, and relief of chronic pain, have led to the use of cannabinoids in medical therapeutics. The justification of medicinal use of marijuana was comprehensively examined by the Institute of Medicine (IOM) of the National Academy of Sciences in its 1999 report, *Marijuana & Medicine*. This continues to be a controversial issue, mainly because of the fear that cannabinoids may serve as a gateway to the consumption of "hard" drugs or cause schizophrenia in individuals with a predisposition.

Chronic exposure to marijuana leads to dependence, which is revealed by a distinctive, but mild and short-lived, withdrawal syndrome that includes restlessness, irritability, mild agitation, insomnia, nausea, and cramping. The relative risk for addiction is 2.

The synthetic Δ^9-THC analog **dronabinol** is a Food and Drug Administration (FDA)-approved cannabinoid agonist currently marketed in the USA and some European countries. **Nabilone,** an

older commercial Δ^9-THC analog, was recently reintroduced in the USA for adjunctive therapy in chronic pain management. The cannabinoid system is likely to emerge as an important drug target in the future because of its apparent involvement in several therapeutically desirable effects.

GAMMA-HYDROXYBUTYRIC ACID

Gamma-hydroxybutyric acid (GHB) is produced during the metabolism of GABA, but the function of this endogenous agent is unknown at present. The pharmacology of GHB is complex because there are two distinct binding sites. The protein that contains a high-affinity binding site (1 μM) for GHB has been cloned, but its involvement in the cellular effects of GHB at pharmacologic concentrations remains unclear. The low-affinity binding site (1 mM) has been identified as the $GABA_B$ receptor. In mice that lack $GABA_B$ receptors, even very high doses of GHB have no effect; this suggests that $GABA_B$ receptors are the sole mediators of GHB's pharmacologic action.

GHB was first synthesized in 1960 and introduced as a general anesthetic. Because of its narrow safety margin and its addictive potential, it is not available in the USA for this purpose at present. It can however be prescribed (under restricted access rules) to treat narcolepsy, because GHB decreases daytime sleepiness and episodes of cataplexy through a mechanism unrelated to the reward system. Before causing sedation and coma, GHB causes euphoria, enhanced sensory perceptions, a feeling of social closeness, and amnesia. These properties have made it a popular "club drug" that goes by colorful street names such as "liquid ecstasy," "grievous bodily harm," or "date rape drug." As the latter name suggests, GHB has been used in date rapes because it is odorless and can be readily dissolved in beverages. It is rapidly absorbed after ingestion and reaches a maximal plasma concentration 20–30 minutes after ingestion of a 10–20 mg/kg dose. The elimination half-life is about 30 minutes.

Although $GABA_B$ receptors are expressed on all neurons of the VTA, GABA neurons are much more sensitive to GHB than are dopamine neurons (Figure 32–4). This is reflected by the EC_{50}s, which differ by about one order of magnitude, and indicates the difference in coupling efficiency of the $GABA_B$ receptor and the potassium channels responsible for the hyperpolarization. Because GHB is a weak agonist, only GABA neurons are inhibited at the concentrations typically obtained with recreational use. This feature may underlie the reinforcing effects of GHB and the basis for addiction to the drug. At higher doses, however, GHB also hyperpolarizes dopamine neurons, eventually completely inhibiting dopamine release. Such an inhibition of the VTA may in turn preclude its activation by other addictive drugs and may explain why GHB might have some usefulness as an "anticraving" compound.

LSD, MESCALINE, & PSILOCYBIN

LSD, mescaline, and psilocybin are commonly called hallucinogens because of their ability to alter consciousness such that the individual senses things that are not present. They induce, often in an unpredictable way, perceptual symptoms, including shape and color distortion. Psychosis-like manifestations (depersonalization, hallucinations, distorted time perception) have led some to classify these drugs as psychotomimetics. They also produce somatic symptoms (dizziness, nausea, paresthesias, and blurred vision). Some users have reported intense reexperiencing of perceptual effects (flashbacks) up to several years after the last drug exposure.

Hallucinogens differ from most other drugs described in this chapter in that they induce neither dependence nor addiction. However, repetitive exposure still leads to rapid tolerance (also called tachyphylaxis). Animals do not self-administer hallucinogens, suggesting that they are not rewarding to them. Additional studies show that these drugs also fail to stimulate dopamine release, further supporting the idea that only drugs that activate the mesolimbic dopamine system are addictive. Instead, hallucinogens increase glutamate release in the cortex, presumably by enhancing excitatory afferent input via presynaptic serotonin receptors (eg, $5HT_{2A}$) from the thalamus.

LSD is an ergot alkaloid. After synthesis, blotter paper or sugar cubes are sprinkled with the liquid and allowed to dry. When LSD is swallowed, psychoactive effects typically appear after 30 minutes and last 6–12 hours. During this time, subjects have impaired ability to make rational judgments and understand common dangers, which puts them at risk for accidents and personal injury.

In an adult, a typical dose is 20–30 mcg. LSD is considered neurotoxic and like most ergot alkaloids, may lead to strong contractions of the uterus that can induce abortion (see Chapter 16).

The main molecular target of LSD and other hallucinogens is the $5\text{-}HT_{2A}$ receptor. This receptor couples to G proteins of the G_q type and generates inositol trisphosphate (IP_3), leading to a release of intracellular calcium. Although hallucinogens, and LSD in particular, have been proposed for several therapeutic indications, efficacy has never been demonstrated.

DRUGS THAT MEDIATE THEIR EFFECTS VIA IONOTROPIC RECEPTORS

NICOTINE

In terms of numbers affected, addiction to nicotine exceeds all other forms of addiction, touching more than 50% of all adults in some countries. Nicotine exposure occurs primarily through smoking of tobacco, which causes associated diseases that are responsible for many preventable deaths. The chronic use of chewing tobacco and snuff tobacco is also addictive.

Nicotine is a selective agonist of the nicotinic acetylcholine receptor (nAChR) that is normally activated by acetylcholine (see Chapters 6 and 7). Based on nicotine's enhancement of cognitive performance and the association of Alzheimer's dementia with a loss of ACh-releasing neurons from the nucleus basalis of Meynert, nAChRs are believed to play an important role in many cognitive processes. The rewarding effect of nicotine requires involvement of

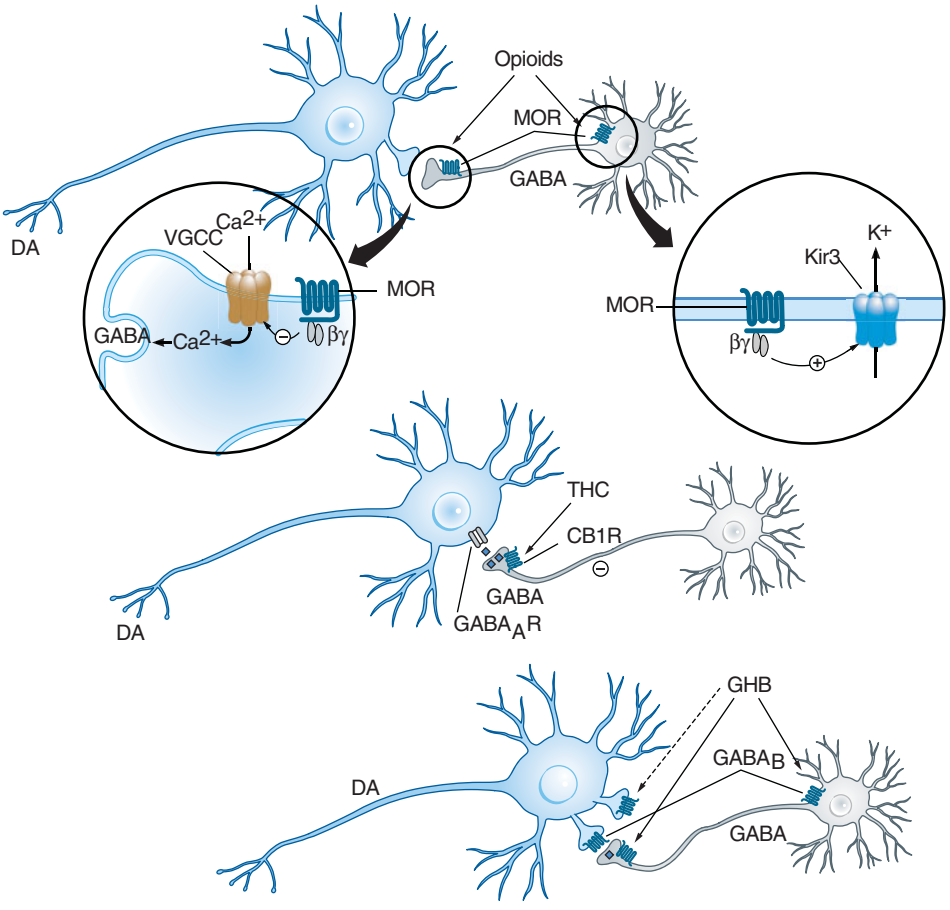

FIGURE 32–4 Disinhibition of dopamine (DA) neurons in the ventral tegmental area (VTA) through drugs that act via G_{i_o}-coupled receptors. **Top:** Opioids target μ-opioid receptors (MORs) that in the VTA are located exclusively on γ-aminobutyric acid (GABA) neurons. MORs are expressed on the presynaptic terminal of these cells and the somatodendritic compartment of the postsynaptic cells. Each compartment has distinct effectors (*insets*). G protein-βγ-mediated inhibition of voltage-gated calcium channels (VGCC) is the major mechanism in the presynaptic terminal. Conversely, in dendrites MORs activate K channels. **Middle:** Δ^9-tetrahydrocannabinol (THC) and other cannabinoids mainly act through presynaptic inhibition. **Bottom:** Gama-hydroxybutyric acid (GHB) targets $GABA_B$ receptors, which are located on both cell types. However, GABA neurons are more sensitive to GHB than are DA neurons, leading to disinhibition at concentrations typically obtained with recreational use. CB_1R, cannabinoid receptors.

the VTA, in which nAChRs are expressed on dopamine neurons. When nicotine excites projection neurons, dopamine is released in the nucleus accumbens and the prefrontal cortex, thus fulfilling the dopamine requirement of addictive drugs. Recent work has identified α4β2-containing channels in the VTA as the nAChRs that are required for the rewarding effects of nicotine. This statement is based on the observation that knockout mice deficient for the β2 subunit lose interest in self-administering nicotine, and that in these mice, this behavior can be restored through an in vivo transfection of the β2 subunit in neurons of the VTA. Electrophysiologic evidence suggests that homomeric nAChRs made exclusively of α7 subunits also contribute to the reinforcing effects of nicotine. These receptors are mainly expressed on synaptic terminals of excitatory afferents projecting onto the dopamine neurons. They also contribute to nicotine-evoked dopamine release and the long-term changes induced by the drugs related to addiction (eg, long-term synaptic potentiation of excitatory inputs).

Nicotine withdrawal is mild compared with opioid withdrawal and involves irritability and sleep problems. However, nicotine is among the most addictive drugs (relative risk 4), and relapse after attempted cessation is very common.

Treatment

Treatments for nicotine addiction include nicotine itself in forms that are slowly absorbed and several other drugs. Nicotine that is chewed, inhaled, or transdermally delivered can be substituted for the nicotine in cigarettes, thus slowing the pharmacokinetics and eliminating the many complications associated with the toxic substances found in tobacco smoke. Recently, two partial agonists of α4β2-containing nAChRs have been characterized; the plant-extract **cytisine** and its synthetic derivative **varenicline.** Both work by occupying nAChRs on dopamine neurons of the VTA, thus preventing nicotine from exerting its action. Varenicline may

impair the capacity to drive and has been associated with suicidal ideation. The antidepressant **bupropion** is approved for nicotine cessation therapy. It is most effective when combined with behavioral therapies.

Many countries have banned smoking in public places to create smoke-free environments. This important step not only reduces passive smoking and the hazards of secondhand smoke, but also the risk that ex-smokers will be exposed to smoke, which as a contextual cue, may trigger relapse.

BENZODIAZEPINES

Benzodiazepines are commonly prescribed as anxiolytics and sleep medications. They represent a moderate risk for abuse, which has to be weighed against their beneficial effects. Benzodiazepines are abused by some persons for their euphoriant effects, but most often abuse occurs concomitant with other drugs, eg, to attenuate anxiety during withdrawal from opioids.

Barbiturates, which preceded benzodiazepines as the most commonly abused sedative hypnotics (after ethanol), are now rarely prescribed to outpatients and therefore constitute a less common prescription drug problem than they did in the past. Street sales of barbiturates, however, continue. Management of barbiturate withdrawal and addiction is similar to that of benzodiazepines.

Benzodiazepine dependence is very common, and diagnosis of addiction probably often missed. Withdrawal from benzodiazepines occurs within days of stopping the medication and varies as a function of the half-life of elimination. Symptoms include irritability, insomnia, phonophobia and photophobia, depression, muscle cramps, and even seizures. Typically, these symptoms taper off within 1–2 weeks.

Benzodiazepines are positive modulators of the $GABA_A$ receptor, increasing both single-channel conductance and open-channel probability. $GABA_A$ receptors are pentameric structures consisting of α, β, and γ subunits (see Chapter 22). GABA receptors on dopamine neurons of the VTA lack α1, a subunit isoform that is present in GABA neurons nearby (ie, interneurons). Because of this difference, unitary synaptic currents in interneurons are larger than those in dopamine neurons, and when this difference is amplified by benzodiazepines, interneurons fall silent. GABA is no longer released, and benzodiazepines lose their effect on dopamine neurons, ultimately leading to disinhibition of the dopamine neurons. The rewarding effects of benzodiazepines are, therefore, mediated by α1-containing $GABA_A$ receptors expressed on VTA neurons. Receptors containing α5 subunits seem to be required for tolerance to the sedative effects of benzodiazepines, and studies in humans link α2β3-containing receptors to alcohol dependence (the $GABA_A$ receptor is also a target of alcohol, see following text). Taken together, a picture is emerging linking $GABA_A$ receptors that contain the α1 subunit isoform to their addiction liability. By extension, α1-sparing compounds, which at present remain experimental and are not approved for human use, may eventually be preferred to treat anxiety disorders because of their reduced risk to induced addiction.

ALCOHOL

Alcohol (ethanol, see Chapter 23) is regularly used by a majority of the population in many Western countries. Although only a minority becomes dependent and addicted, abuse is a very serious public health problem because of the many diseases associated with alcoholism.

Pharmacology

The pharmacology of alcohol is complex, and no single receptor mediates all of its effects. On the contrary, alcohol alters the function of several receptors and cellular functions, including $GABA_A$ receptors, Kir3/GIRK channels, adenosine reuptake (through the equilibrative nucleoside transporter, ENT1), glycine receptor, NMDA receptor, and $5\text{-}HT_3$ receptor. They are all, with the exception of ENT1, either ionotropic receptors or ion channels. It is not clear which of these targets is responsible for the increase of dopamine release from the mesolimbic reward system. The inhibition of ENT1 is probably not responsible for the rewarding effects (ENT1 knockout mice drink more than controls) but seems to be involved in alcohol dependence through an accumulation of adenosine, stimulation of adenosine A_2 receptors, and ensuing enhanced CREB signaling.

Dependence becomes apparent 6–12 hours after cessation of heavy drinking as a withdrawal syndrome that may include tremor (mainly of the hands), nausea and vomiting, excessive sweating, agitation, and anxiety. In some individuals, this is followed by visual, tactile, and auditory hallucinations 12–24 hours after cessation. Generalized seizures may manifest after 24–48 hours. Finally, 48–72 hours after cessation, an alcohol withdrawal delirium (delirium tremens) may become apparent in which the person hallucinates, is disoriented, and shows evidence of autonomic instability. Delirium tremens is associated with 5–15% mortality.

Treatment

Treatment of ethanol withdrawal is supportive and relies on **benzodiazepines,** taking care to use compounds such as oxazepam and lorazepam, which are not as dependent on hepatic metabolism as most other benzodiazepines. In patients in whom monitoring is not reliable and liver function is adequate, a longer-acting benzodiazepine such as chlordiazepoxide is preferred.

As in the treatment of all chronic drug abuse problems, heavy reliance is placed on psychosocial approaches to alcohol addiction. This is perhaps even more important for the alcoholic patient because of the ubiquitous presence of alcohol in many social contexts.

The pharmacologic treatment of alcohol addiction is limited, although several compounds, with different goals, have been used. Therapy is discussed in Chapter 23.

KETAMINE & PHENCYCLIDINE (PCP)

Ketamine and PCP were developed as general anesthetics (see Chapter 25), but only ketamine is still used for this application. Both drugs, along with others, are now classified as "club drugs" and sold

under names such as "angel dust," "Hog," and "Special K." They owe their effects to their use-dependent, noncompetitive antagonism of the NMDA receptor. The effects of these substances became apparent when patients undergoing surgery reported unpleasant vivid dreams and hallucinations after anesthesia. Ketamine and PCP are white crystalline powders in their pure forms, but on the street they are also sold as liquids, capsules, or pills, which can be snorted, ingested, injected, or smoked. Psychedelic effects last for about 1 hour and also include increased blood pressure, impaired memory function, and visual alterations. At high doses, unpleasant out-of-body and near-death experiences have been reported. Although ketamine and phencyclidine do not cause dependence and addiction (relative risk = 1), chronic exposure, particularly to PCP, may lead to long-lasting psychosis closely resembling schizophrenia, which may persist beyond drug exposure.

INHALANTS

Inhalant abuse is defined as recreational exposure to chemical vapors, such as **nitrates, ketones,** and aliphatic and aromatic **hydrocarbons.** These substances are present in a variety of household and industrial products that are inhaled by "sniffing," "huffing," or "bagging." Sniffing refers to inhalation from an open container, huffing to the soaking of a cloth in the volatile substance before inhalation, and bagging to breathing in and out of a paper or plastic bag filled with fumes. It is common for novices to start with sniffing and progress to huffing and bagging as addiction develops. Inhalant abuse is particularly prevalent in children and young adults.

The exact mechanism of action of most volatile substances remains unknown. Altered function of ionotropic receptors and ion channels throughout the central nervous system has been demonstrated for a few. Nitrous oxide, for example, binds to NMDA receptors and fuel additives enhance $GABA_A$ receptor function. Most inhalants produce euphoria; increased excitability of the VTA has been documented for toluene and may underlie its addiction risk. Other substances, such as amyl nitrite ("poppers"), primarily produce smooth muscle relaxation and enhance erection, but are not addictive. With chronic exposure to the aromatic hydrocarbons (eg, benzene, toluene), toxic effects can be observed in many organs, including white matter lesions in the central nervous system. Management of overdose remains supportive.

DRUGS THAT BIND TO TRANSPORTERS OF BIOGENIC AMINES

Cocaine

The prevalence of cocaine abuse has increased greatly over the last decade and now represents a major public health problem worldwide. Cocaine is highly addictive (relative risk = 5), and its use is associated with a number of complications.

Cocaine is an alkaloid found in the leaves of *Erythroxylon coca*, a shrub indigenous to the Andes. For more than 100 years, it has been extracted and used in clinical medicine, mainly as a local anesthetic and to dilate pupils in ophthalmology. Sigmund Freud famously proposed its use to treat depression and alcohol dependence, but addiction quickly brought an end to this idea.

Cocaine hydrochloride is a water-soluble salt that can be injected or absorbed by any mucosal membrane (eg, nasal snorting). When heated in an alkaline solution, it is transformed into the free base, "crack cocaine," which can then be smoked. Inhaled crack cocaine is rapidly absorbed in the lungs and penetrates swiftly into the brain, producing an almost instantaneous "rush."

In the peripheral nervous system, cocaine inhibits voltage-gated sodium channels, thus blocking initiation and conduction of action potentials (see Chapter 26). This effect, however, seems responsible for neither the acute rewarding nor the addictive effects. In the central nervous system, cocaine blocks the uptake of dopamine, noradrenaline, and serotonin through their respective transporters. The block of the **dopamine transporter (DAT),** by increasing dopamine concentrations in the nucleus accumbens, has been implicated in the rewarding effects of cocaine (Figure 32–5). In fact, the rewarding effects of cocaine are abolished in mice with a cocaine-insensitive DAT. The activation of the sympathetic nervous system results mainly from blockage of the norepinephrine transporter (NET) and leads to an acute increase in arterial pressure, tachycardia, and often, ventricular arrhythmias. Users typically lose their appetite, are hyperactive, and sleep little. Cocaine exposure increases the risk for intracranial hemorrhage, ischemic stroke, myocardial infarction, and seizures. Cocaine overdose may lead to hyperthermia, coma, and death.

Susceptible individuals may become dependent and addicted after only a few exposures to cocaine. Although a withdrawal syndrome is reported, it is not as strong as that observed with opioids. Tolerance may develop, but in some users a reverse tolerance is observed; that is, they become sensitized to small doses of cocaine. This behavioral sensitization is in part context-dependent. Cravings are very strong and underline the very high addiction liability of cocaine. To date, no specific antagonist is available, and the management of intoxication remains supportive. Developing a pharmacologic treatment for cocaine addiction is a top priority.

AMPHETAMINES

Amphetamines are a group of synthetic, indirect-acting sympathomimetic drugs that cause the release of endogenous biogenic amines, such as dopamine and noradrenaline (see Chapters 6 and 9). Amphetamine, methamphetamine, and their many derivatives exert their effects by reversing the action of biogenic amine transporters at the plasma membrane. Amphetamines are substrates of these transporters and are taken up into the cell (Figure 32–5). Once in the cell, amphetamines interfere with the vesicular monoamine transporter (VMAT; see Figure 6–4), depleting synaptic vesicles of their neurotransmitter content. As a consequence, levels of dopamine (or other transmitter amine) in the cytoplasm increase and quickly become sufficient to cause release into the

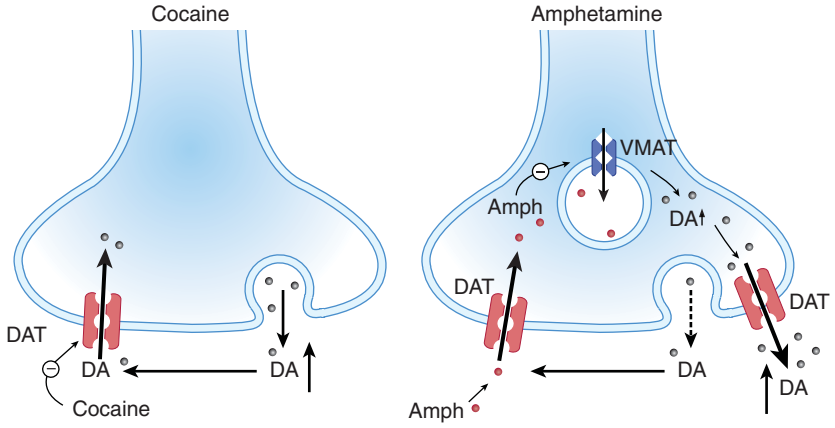

FIGURE 32–5 Mechanism of action of cocaine and amphetamine on synaptic terminal of dopamine (DA) neurons. **Left:** Cocaine inhibits the dopamine transporter (DAT), decreasing DA clearance from the synaptic cleft and causing an increase in extracellular DA concentration. **Right:** Since amphetamine (Amph) is a substrate of the DAT, it competitively inhibits DA transport. In addition, once in the cell, amphetamine interferes with the vesicular monoamine transporter (VMAT) and impedes the filling of synaptic vesicles. As a consequence, vesicles are depleted and cytoplasmic DA increases. This leads to a reversal of DAT direction, strongly increasing nonvesicular release of DA, and further increasing extracellular DA concentrations.

synapse by reversal of the plasma membrane DAT. Normal vesicular release of dopamine consequently decreases (because synaptic vesicles contain less transmitter), whereas nonvesicular release increases. Similar mechanisms apply for other biogenic amines (serotonin and norepinephrine).

Together with GHB and ecstasy, amphetamines are often referred to as "club drugs," because they are increasingly popular in the club scene. They are often produced in small clandestine laboratories, which makes their precise chemical identification difficult. They differ from ecstasy chiefly in the context of use: intravenous administration and "hard core" addiction is far more common with amphetamines, especially methamphetamine. In general, amphetamines lead to elevated catecholamine levels that increase arousal and reduce sleep, whereas the effects on the dopamine system mediate euphoria but may also cause abnormal movements and precipitate psychotic episodes. Effects on serotonin transmission may play a role in the hallucinogenic and anorexigenic functions as well as in the hyperthermia often caused by amphetamines.

Unlike many other abused drugs, amphetamines are neurotoxic. The exact mechanism is not known, but neurotoxicity depends on the NMDA receptor and affects mainly serotonin and dopamine neurons.

Amphetamines are typically taken initially in pill form by abusers, but can also be smoked or injected. Heavy users often progress rapidly to intravenous administration. Within hours after oral ingestion, amphetamines increase alertness and cause euphoria, agitation, and confusion. Bruxism (tooth grinding) and skin flushing may occur. Effects on heart rate may be minimal with some compounds (eg, methamphetamine), but with increasing dosage these agents often lead to tachycardia and dysrhythmias. Hypertensive crisis and vasoconstriction may lead to stroke. Spread of HIV and hepatitis infection in inner cities has been closely associated with needle sharing by intravenous users of methamphetamine.

With chronic use, amphetamine tolerance may develop, leading to dose escalation. Withdrawal consists of dysphoria, drowsiness (in some cases, insomnia), and general irritability.

ECSTASY (MDMA)

Ecstasy is the name of a class of drugs that includes a large variety of derivatives of the amphetamine-related compound methylenedioxymethamphetamine (MDMA). MDMA was originally used in some forms of psychotherapy, but no medically useful effects were documented. This is perhaps not surprising, because the main effect of ecstasy appears to be to foster feelings of intimacy and empathy without impairing intellectual capacities. Today, MDMA and its many derivatives are often produced in small quantities in ad hoc laboratories and distributed at parties or "raves," where it is taken orally. Ecstasy therefore is the prototypical designer drug and, as such, is increasingly popular.

Similar to the amphetamines, MDMA causes release of biogenic amines by reversing the action of their respective transporters. It has a preferential affinity for the **serotonin transporter (SERT)** and therefore most strongly increases the extracellular concentration of serotonin. This release is so profound that there is a marked intracellular depletion for 24 hours after a single dose. With repetitive administration, serotonin depletion may become permanent, which has triggered a debate on its neurotoxicity. Although direct proof from animal models for neurotoxicity remains weak, several studies report long-term cognitive impairment in heavy users of MDMA.

In contrast, there is a wide consensus that MDMA has several acute toxic effects, in particular hyperthermia, which along with dehydration (eg, caused by an all-night dance party) may be fatal. Other complications include serotonin syndrome (mental status change, autonomic hyperactivity, and neuromuscular abnormalities,

see Chapter 16) and seizures. Following warnings about the dangers of MDMA, some users have attempted to compensate for hyperthermia by drinking excessive amounts of water, causing water intoxication involving severe hyponatremia, seizures, and even death.

Withdrawal is marked by a mood "offset" characterized by depression lasting up to several weeks. There have also been reports of increased aggression during periods of abstinence in chronic MDMA users.

Taken together, the evidence for irreversible damage to the brain, although not completely convincing, implies that even occasional recreational use of MDMA cannot be considered safe.

CLINICAL PHARMACOLOGY OF DEPENDENCE & ADDICTION

To date no single pharmacologic treatment (even in combination with behavioral interventions) efficiently eliminates addiction. This is not to say that addiction is irreversible. Pharmacologic interventions may in fact be useful at all stages of the disease. This is particularly true in the case of a massive overdose, in which reversal of drug action may be a life-saving measure. However, in this regard, FDA-approved antagonists are available only for opioids and benzodiazepines.

Pharmacologic interventions may also aim to alleviate the withdrawal syndrome, particularly after opioid exposure. On the assumption that withdrawal reflects at least in part a hyperactivity of central adrenergic systems, the α_2-adrenoceptor agonist clonidine (also used as a centrally active antihypertensive drug, see Chapter 11) has been used with some success to attenuate withdrawal. Today, most clinicians prefer to manage opioid withdrawal by very slowly tapering the administration of long-acting opioids.

Another widely accepted treatment is substitution of a legally available agonist that acts at the same receptor as the abused drug. This approach has been approved for opioids and nicotine. For example, heroin addicts may receive methadone to replace heroin; smoking addicts may receive nicotine continuously via a transdermal patch system to replace smoking. In general, a rapid-acting substance is replaced with one that acts or is absorbed more slowly. Substitution treatments are largely justified by the benefits of reducing associated health risks, the reduction of drug-associated crime, and better social integration. Although dependence persists, it may be possible, with the support of behavioral interventions, to motivate drug users to gradually reduce the dose and become abstinent.

The biggest challenge is the treatment of addiction itself. Several approaches have been proposed, but all remain experimental. One approach is to pharmacologically reduce cravings. The μ-opioid receptor antagonist and partial agonist **naltrexone** is FDA-approved for this indication in opioid and alcohol addiction. Its effect is modest and may involve a modulation of endogenous opioid systems.

Clinical trials are currently being conducted with a number of drugs, including the high-affinity $GABA_B$-receptor agonist **baclofen,** and initial results have shown a significant reduction of craving. This effect may be mediated by the inhibition of the dopamine neurons of the VTA, which is possible at baclofen concentrations obtained by oral administration because of its very high affinity for the $GABA_B$ receptor.

Rimonabant is an inverse agonist of the CB_1 receptor that behaves like an antagonist of cannabinoids. It was developed for smoking cessation and to facilitate weight loss. Because of frequent adverse effects—most notably severe depression carrying a substantial risk of suicide—this drug is no longer used clinically. It was initially used in conjunction with diet and exercise for patients with a body mass index above 30 kg/m^2 (27 kg/m^2 if associated risk factors, such as type 2 diabetes or dyslipidemia are present). Although a recent large-scale study confirmed that rimonabant is effective for smoking cessation and the prevention of weight gain in smokers who quit, this indication has never been approved. Although the cellular mechanism of rimonabant remains to be elucidated, data in rodents convincingly demonstrate that this compound can reduce self-administration in naive as well as drug-experienced animals.

SUMMARY Drugs Used to Treat Dependence and Addiction

Subclass	Mechanism of Action	Effects	Clinical Application	Pharmacokinetics, Toxicities, Interactions
OPIOID RECEPTOR ANTAGONIST				
• Naloxone	Nonselective antagonist of opioid receptors	Reverses the acute effects of opioids; can precipitate severe abstinence syndrome	Opioid overdose	Effect much shorter than morphine (1–2 h); therefore several injections required
• Naltrexone	Antagonist of opioid receptors	Blocks effects of illicit opioids	Treatment of alcoholism	Half-life ~ 4 h
SYNTHETIC OPIOID				
• Methadone	Slow-acting agonist of μ-opioid receptor	Acute effects similar to morphine (see text)	Substitution therapy for opioid addicts	High oral bioavailability • half-life highly variable among individuals (range 4–130 h) • *Toxicity:* Respiratory depression, constipation, miosis, tolerance, dependence, and withdrawal symptoms
PARTIAL μ-OPIOID RECEPTOR AGONIST				
• Buprenorphine	Partial agonist at μ-opioid receptors	Attenuates acute effects of morphine	Oral substitution therapy for opioid addicts	Long half-life (40 h) • formulated together with naloxone to avoid illicit IV injections
NICOTINIC RECEPTOR PARTIAL AGONIST				
• Varenicline	Partial agonist of nicotinic acetylcholine receptor of the α4β2-type	Occludes "rewarding" effects of smoking • heightened awareness of colors	Smoking cessation	*Toxicity:* Nausea and vomiting, convulsions, psychiatric changes
• *Cytisine: Natural analog (extracted from laburnum flowers) of varenicline*				
BENZODIAZEPINES				
• Oxazepam, others	Positive modulators of the $GABA_A$ receptors, increase frequency of channel opening	Enhances GABAergic synaptic transmission; attenuates withdrawal symptoms (tremor, hallucinations, anxiety) in alcoholics • prevents withdrawal seizures	Delirium tremens	Half-life 4–15 h • pharmacokinetics not affected by decreased liver function
• *Lorazepam: Alternate to oxazepam with similar properties*				
***N*-METHYL-D-ASPARTATE (NMDA)**				
• Acamprosate	Antagonist of NMDA glutamate receptors	May interfere with forms of synaptic plasticity that depend on NMDA receptors	Treatment of alcoholism • effective only in combination with counseling	Allergic reactions, arrhythmia, and low or high blood pressure, headaches, insomnia, and impotence • hallucinations, particularly in elderly patients
CANNABINOID RECEPTOR AGONIST				
• Rimonabant	CB_1 receptor inverse agonist	Decreases neurotransmitter release at GABAergic and glutamatergic synapses	Approved in Europe from 2006 to 2008 to treat obesity, then withdrawn because of major side effects • Smoking cessation has never been approved, but remains an off-label indication	Major depression, including increased risk of suicide

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CASE STUDY ANSWER

The patient was diagnosed with pathologic gambling secondary to the dopamine agonist prescription. Compulsive behavior including gambling, binge eating, or hypersexuality is observed in about 15% of patients who receive dopamine agonist treatment. The condition is not related to Parkinson's disease, as compulsive behaviors also occur in patients with restless legs syndrome who are treated with the same medication. The incidence with levodopa is lower, and compulsive behavior is sometimes preceded by dose escalation.

SECTION VI DRUGS USED TO TREAT DISEASES OF THE BLOOD, INFLAMMATION, & GOUT

CHAPTER 33

Agents Used in Anemias; Hematopoietic Growth Factors

Susan B. Masters, PhD

CASE STUDY

A 65-year-old woman with a long-standing history of poorly controlled type 2 diabetes mellitus presents with increasing numbness and paresthesias in her extremities, generalized weakness, a sore tongue, and gastrointestinal discomfort. Physical examination reveals a frail-looking, pale woman with diminished vibration sensation, diminished spinal reflexes, and a positive Babinski sign. Examination of her oral cavity reveals Hunter's glossitis, in which the tongue appears deep red in color and abnormally smooth and shiny due to atrophy of the lingual papillae. Laboratory testing reveals a macrocytic anemia based on a hematocrit of 30% (normal for women, 37–48%), a hemoglobin concentration of 9.4 g/dL (normal for elderly women, 11.7–13.8 g/dL), an erythrocyte mean cell volume (MCV) of 123 fL (normal, 84–99 fL), an erythrocyte mean cell hemoglobin concentration (MCHC) of 34% (normal, 31–36%), and a low reticulocyte count. Further laboratory testing reveals a normal serum folate concentration and a serum vitamin B_{12} (cobalamin) concentration of 98 pg/mL (normal, 250–1100 pg/mL). Results of a Schilling test indicate a diagnosis of pernicious anemia. Once megaloblastic anemia was identified, why was it important to measure serum concentrations of both folic acid and cobalamin? Should this patient be treated with oral or parenteral vitamin B_{12}?

Hematopoiesis, the production from undifferentiated stem cells of circulating erythrocytes, platelets, and leukocytes, is a remarkable process that produces over 200 billion new blood cells per day in the normal person and even greater numbers of cells in people with conditions that cause loss or destruction of blood cells. The hematopoietic machinery resides primarily in the bone marrow in adults and requires a constant supply of three essential nutrients—**iron, vitamin B_{12},** and **folic acid**—as well as the presence of **hematopoietic growth factors,** proteins that regulate the proliferation and differentiation of hematopoietic cells. Inadequate supplies of either the essential nutrients or the growth factors result in deficiency of functional blood cells. **Anemia,** a deficiency in

Sickle Cell Disease and Hydroxyurea

Sickle cell disease is an important genetic cause of hemolytic anemia, a form of anemia due to increased erythrocyte destruction, instead of the reduced mature erythrocyte production seen with iron, folic acid, and vitamin B_{12} deficiency. Patients with sickle cell disease are homozygous for the aberrant β-hemoglobin S (HbS) allele or heterozygous for HbS and a second mutated β-hemoglobin gene such as hemoglobin C (*HbC*) or β-thalassemia. Sickle cell disease has an increased prevalence in individuals of African descent because the heterozygous trait confers resistance to malaria.

In the majority of patients with sickle cell disease, anemia is not the major problem; the anemia is generally well compensated even though such individuals have a chronically low hematocrit (20–30%), a low serum hemoglobin level (7–10 g/dL), and an elevated reticulocyte count. Instead, the primary problem is that deoxygenated HbS chains form polymeric structures that dramatically change erythrocyte shape, reduce deformability, and elicit membrane permeability changes that further promote hemoglobin polymerization. Abnormal erythrocytes aggregate in the microvasculature—where oxygen tension is low and hemoglobin is deoxygenated—and cause veno-occlusive damage. The clinical manifestations of sickle cell disease reflect organ damage by veno-occlusive events. In the musculoskeletal system, this results in characteristic, extremely painful bone and joint pain. In the cerebral vascular system, it causes ischemic stroke. Damage to the spleen increases the risk of infection, particularly by encapsulated bacteria such as *Streptococcus pneumoniae*. In the pulmonary system, there is an increased risk of infection and, in adults, an increase in embolism and pulmonary hypertension. Supportive treatment includes analgesics, antibiotics, pneumococcal vaccination, and blood transfusions. In addition, the cancer chemotherapeutic drug **hydroxyurea** (hydroxycarbamide) reduces veno-occlusive events. It is approved in the United States for treatment of adults with recurrent sickle cell crises and approved in Europe in adults and children with recurrent vaso-occlusive events. As an anticancer drug used in the treatment of chronic and acute myelogenous leukemia, hydroxyurea inhibits ribonucleotide reductase and thereby depletes deoxynucleoside triphosphate and arrests cells in the S phase of the cell cycle (see Chapter 54). In the treatment of sickle cell disease, hydroxyurea acts through poorly defined pathways to increase the production of fetal hemoglobin γ (HbF), which interferes with the polymerization of HbS. Clinical trials have shown that hydroxyurea decreases painful crises in adults and children with severe sickle cell disease. Its adverse effects include hematopoietic depression, gastrointestinal effects, and teratogenicity in pregnant women.

oxygen-carrying erythrocytes, is the most common and several forms are easily treated. Sickle cell anemia, a condition resulting from a genetic alteration in the hemoglobin molecule, is common but is not easily treated. It is discussed in the Box: Sickle Cell Disease and Hydroxyurea. **Thrombocytopenia** and **neutropenia** are not rare, and some forms are amenable to drug therapy. In this chapter, we first consider treatment of anemia due to deficiency of iron, vitamin B_{12}, or folic acid and then turn to the medical use of hematopoietic growth factors to combat anemia, thrombocytopenia, and neutropenia, and to support stem cell transplantation.

AGENTS USED IN ANEMIAS

IRON

Basic Pharmacology

Iron deficiency is the most common cause of chronic anemia. Like other forms of chronic anemia, iron deficiency anemia leads to pallor, fatigue, dizziness, exertional dyspnea, and other generalized symptoms of tissue hypoxia. The cardiovascular adaptations to chronic anemia—tachycardia, increased cardiac output, vasodilation—can worsen the condition of patients with underlying cardiovascular disease.

Iron forms the nucleus of the iron-porphyrin heme ring, which together with globin chains forms hemoglobin. Hemoglobin reversibly binds oxygen and provides the critical mechanism for oxygen delivery from the lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed, giving rise to **microcytic hypochromic anemia.** Iron-containing heme is also an essential component of myoglobin, cytochromes, and other proteins with diverse biologic functions.

Pharmacokinetics

Free inorganic iron is extremely toxic, but iron is required for essential proteins such as hemoglobin; therefore, evolution has provided an elaborate system for regulating iron absorption, transport, and storage (Figure 33–1). The system uses specialized transport, storage, ferrireductase, and ferroxidase proteins whose concentrations are controlled by the body's demand for hemoglobin synthesis and adequate iron stores (Table 33–1). A peptide called hepcidin, produced primarily by liver cells, serves as a key central regulator of the system. Nearly all of the iron used to support hematopoiesis is reclaimed from catalysis of the hemoglobin in senescent or damaged erythrocytes. Normally, only a small amount of iron is lost from the body each day, so dietary

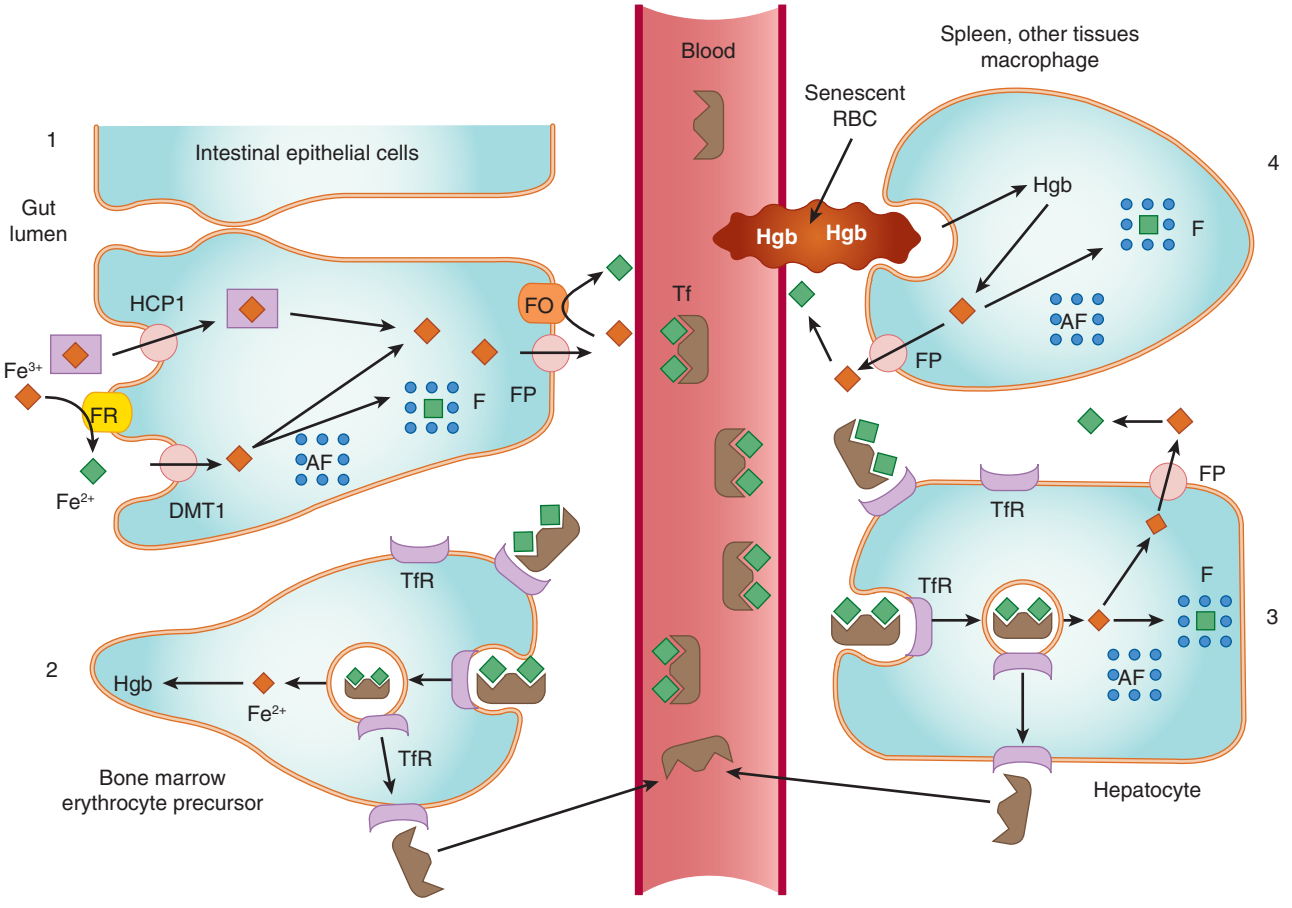

FIGURE 33–1 Absorption, transport, and storage of iron. Intestinal epithelial cells actively absorb inorganic iron via the divalent metal transporter 1 (DMT1) and heme iron via the heme carrier protein 1 (HCP1). Iron that is absorbed or released from absorbed heme iron in the intestine (**1**) is actively transported into the blood by ferroportin (FP) or complexed with apoferritin (AF) and stored as ferritin (F). In the blood, iron is transported by transferrin (Tf) to erythroid precursors in the bone marrow for synthesis of hemoglobin (Hgb) (**2**) or to hepatocytes for storage as ferritin (**3**). The transferrin-iron complex binds to transferrin receptors (TfR) in erythroid precursors and hepatocytes and is internalized. After release of iron, the TfR-Tf complex is recycled to the plasma membrane and Tf is released. Macrophages that phagocytize senescent erythrocytes (RBC) reclaim the iron from the RBC hemoglobin and either export it or store it as ferritin (**4**). Hepatocytes use several mechanisms to take up iron and store the iron as ferritin. FO, ferroxidase. (Modified and reproduced, with permission, from Trevor A et al: *Pharmacology Examination & Board Review*, 9th ed. McGraw-Hill, 2010.)

TABLE 33–1 Iron distribution in normal adults.[1]

	Iron Content (mg)	
	Men	***Women***
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin and other forms)	750	300
Total	4248	2314

[1]Values are based on data from various sources and assume that normal men weigh 80 kg and have a hemoglobin level of 16 g/dL and that normal women weigh 55 kg and have a hemoglobin level of 14 g/dL.

Adapted, with permission, from Brown EB: Iron deficiency anemia. In: Wyngaarden JB, Smith LH (editors). *Cecil Textbook of Medicine*, 16th ed. Saunders, 1982.

requirements are small and easily fulfilled by the iron available in a wide variety of foods. However, in special populations with either increased iron requirements (eg, growing children, pregnant women) or increased losses of iron (eg, menstruating women), iron requirements can exceed normal dietary supplies and iron deficiency can develop.

A. Absorption

The average American diet contains 10–15 mg of elemental iron daily. A normal individual absorbs 5–10% of this iron, or about 0.5–1 mg daily. Iron is absorbed in the duodenum and proximal jejunum, although the more distal small intestine can absorb iron if necessary. Iron absorption increases in response to low iron stores or increased iron requirements. Total iron absorption increases to 1–2 mg/d in menstruating women and may be as high as 3–4 mg/d in pregnant women.

Iron is available in a wide variety of foods but is especially abundant in meat. The iron in meat protein can be efficiently absorbed, because heme iron in meat hemoglobin and myoglobin can be absorbed intact without first having to be dissociated into elemental iron (Figure 33–1). Iron in other foods, especially vegetables and grains, is often tightly bound to organic compounds and is much less available for absorption. Nonheme iron in foods and iron in inorganic iron salts and complexes must be reduced by a ferrireductase to ferrous iron (Fe^{2+}) before it can be absorbed by intestinal mucosal cells.

Iron crosses the luminal membrane of the intestinal mucosal cell by two mechanisms: active transport of ferrous iron by the divalent metal transporter DMT1, and absorption of iron complexed with heme (Figure 33–1). Together with iron split from absorbed heme, the newly absorbed iron can be actively transported into the blood across the basolateral membrane by a transporter known as ferroportin and oxidized to ferric iron (Fe^{3+}) by the ferroxidase hephaestin. The liver-derived hepcidin inhibits intestinal cell iron release by binding to ferroportin and triggering its internalization and destruction. Excess iron is stored in intestinal epithelial cells as ferritin, a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of a specialized storage protein called apoferritin.

B. Transport

Iron is transported in the plasma bound to **transferrin,** a β-globulin that can bind two molecules of ferric iron (Figure 33–1). The transferrin-iron complex enters maturing erythroid cells by a specific receptor mechanism. Transferrin receptors—integral membrane glycoproteins present in large numbers on proliferating erythroid cells—bind and internalize the transferrin-iron complex through the process of receptor-mediated endocytosis. In endosomes, the ferric iron is released, reduced to ferrous iron, and transported by DMT1 into the cytoplasm, where it is funneled into hemoglobin synthesis or stored as ferritin. The transferrin-transferrin receptor complex is recycled to the cell membrane, where the transferrin dissociates and returns to the plasma. This process provides an efficient mechanism for supplying the iron required by developing red blood cells.

Increased erythropoiesis is associated with an increase in the number of transferrin receptors on developing erythroid cells and a reduction in hepatic hepcidin release. Iron store depletion and iron deficiency anemia are associated with an increased concentration of serum transferrin.

C. Storage

In addition to the storage of iron in intestinal mucosal cells, iron is also stored, primarily as ferritin, in macrophages in the liver, spleen, and bone, and in parenchymal liver cells (Figure 33–1). The mobilization of iron from macrophages and hepatocytes is primarily controlled by hepcidin regulation of ferroportin activity. Low hepcidin concentrations result in iron release from these storage sites; high hepcidin concentrations inhibit iron release. Ferritin is detectable in serum. Since the ferritin present in serum is in equilibrium with storage ferritin in reticuloendothelial tissues, the serum ferritin level can be used to estimate total body iron stores.

D. Elimination

There is no mechanism for excretion of iron. Small amounts are lost in the feces by exfoliation of intestinal mucosal cells, and trace amounts are excreted in bile, urine, and sweat. These losses account for no more than 1 mg of iron per day. Because the body's ability to excrete iron is so limited, regulation of iron balance must be achieved by changing intestinal absorption and storage of iron, in response to the body's needs. As noted below, impaired regulation of iron absorption leads to serious pathology.

Clinical Pharmacology

A. Indications for the Use of Iron

The only clinical indication for the use of iron preparations is the treatment or prevention of iron deficiency anemia. This manifests as a hypochromic, microcytic anemia in which the erythrocyte mean cell volume (MCV) and the mean cell hemoglobin concentration are low (Table 33–2). Iron deficiency is commonly seen in populations with increased iron requirements. These include infants, especially premature infants; children during rapid growth periods; pregnant and lactating women; and patients with chronic kidney disease who lose erythrocytes at a relatively high rate during hemodialysis and also form them at a high rate as a result of treatment with the erythrocyte growth factor erythropoietin (see below). Inadequate iron absorption can also cause iron deficiency. This is seen after gastrectomy and in patients with severe small bowel disease that results in generalized malabsorption.

The most common cause of iron deficiency in adults is blood loss. Menstruating women lose about 30 mg of iron with each

TABLE 33–2 Distinguishing features of the nutritional anemias.

Nutritional Deficiency	Type of Anemia	Laboratory Abnormalities
Iron	Microcytic, hypochromic with MCV <80 fL and MCHC <30%	Low SI <30 mcg/dL with increased TIBC, resulting in a % transferrin saturation (SI/TIBC) of <10%; low serum ferritin level (<20 mcg/L)
Folic acid Vitamin B_{12}	Macrocytic, normochromic with MCV >100 fL and normal or elevated MCHC	Low serum folic acid (<4 ng/mL) Low serum cobalamin (<150 pmol/L) accompanied by increased serum homocysteine (>13 µmol/L), and increased serum (>0.4 µmol/L) and urine (>3.6 µmol/mol creatinine) methylmalonic acid

MCV, mean cell volume; MCHC, mean cell hemoglobin concentration; SI, serum iron; TIBC, transferrin iron-binding capacity.

menstrual period; women with heavy menstrual bleeding may lose much more. Thus, many premenopausal women have low iron stores or even iron deficiency. In men and postmenopausal women, the most common site of blood loss is the gastrointestinal tract. Patients with unexplained iron deficiency anemia should be evaluated for occult gastrointestinal bleeding.

B. Treatment

Iron deficiency anemia is treated with oral or parenteral iron preparations. Oral iron corrects the anemia just as rapidly and completely as parenteral iron in most cases if iron absorption from the gastrointestinal tract is normal. An exception is the high requirement for iron of patients with advanced chronic kidney disease who are undergoing hemodialysis and treatment with erythropoietin; for these patients, parenteral iron administration is preferred.

1. Oral iron therapy—A wide variety of oral iron preparations is available. Because ferrous iron is most efficiently absorbed, ferrous salts should be used. Ferrous sulfate, ferrous gluconate, and ferrous fumarate are all effective and inexpensive and are recommended for the treatment of most patients.

Different iron salts provide different amounts of elemental iron, as shown in Table 33–3. In an iron-deficient individual, about 50–100 mg of iron can be incorporated into hemoglobin daily, and about 25% of oral iron given as ferrous salt can be absorbed. Therefore, 200–400 mg of elemental iron should be given daily to correct iron deficiency most rapidly. Patients unable to tolerate such large doses of iron can be given lower daily doses of iron, which results in slower but still complete correction of iron deficiency. Treatment with oral iron should be continued for 3–6 months after correction of the cause of the iron loss. This corrects the anemia and replenishes iron stores.

Common adverse effects of oral iron therapy include nausea, epigastric discomfort, abdominal cramps, constipation, and diarrhea. These effects are usually dose-related and can often be overcome by lowering the daily dose of iron or by taking the tablets immediately after or with meals. Some patients have less severe gastrointestinal adverse effects with one iron salt than another and benefit from changing preparations. Patients taking oral iron develop black stools; this has no clinical significance in itself but may obscure the diagnosis of continued gastrointestinal blood loss.

TABLE 33–3 Some commonly used oral iron preparations.

Preparation	Tablet Size	Elemental Iron per Tablet	Usual Adult Dosage for Treatment of Iron Deficiency (Tablets per Day)
Ferrous sulfate, hydrated	325 mg	65 mg	2–4
Ferrous sulfate, desiccated	200 mg	65 mg	2–4
Ferrous gluconate	325 mg	36 mg	3–4
Ferrous fumarate	325 mg	106 mg	2–3

2. Parenteral iron therapy—Parenteral therapy should be reserved for patients with documented iron deficiency who are unable to tolerate or absorb oral iron and for patients with extensive chronic anemia who cannot be maintained with oral iron alone. This includes patients with advanced chronic renal disease requiring hemodialysis and treatment with erythropoietin, various postgastrectomy conditions and previous small bowel resection, inflammatory bowel disease involving the proximal small bowel, and malabsorption syndromes.

The challenge with parenteral iron therapy is that parenteral administration of inorganic free ferric iron produces serious dose-dependent toxicity, which severely limits the dose that can be administered. However, when the ferric iron is formulated as a colloid containing particles with a core of iron oxyhydroxide surrounded by a core of carbohydrate, bioactive iron is released slowly from the stable colloid particles. In the United States, the three available forms of parenteral iron are **iron dextran, sodium ferric gluconate complex,** and **iron sucrose.**

Iron dextran is a stable complex of ferric oxyhydroxide and dextran polymers containing 50 mg of elemental iron per milliliter of solution. It can be given by deep intramuscular injection or by intravenous infusion, although the intravenous route is used most commonly. Intravenous administration eliminates the local pain and tissue staining that often occur with the intramuscular route and allows delivery of the entire dose of iron necessary to correct the iron deficiency at one time. Adverse effects of intravenous iron dextran therapy include headache, light-headedness, fever, arthralgias, nausea and vomiting, back pain, flushing, urticaria, bronchospasm, and, rarely, anaphylaxis and death. Owing to the risk of a hypersensitivity reaction, a small test dose of iron dextran should always be given before full intramuscular or intravenous doses are given. Patients with a strong history of allergy and patients who have previously received parenteral iron dextran are more likely to have hypersensitivity reactions after treatment with parenteral iron dextran. The iron dextran formulations used clinically are distinguishable as high-molecular-weight and low-molecular-weight forms. In the United States, the InFeD preparation is a low-molecular-weight form while DexFerrum is a high-molecular-weight form. Clinical data—primarily from observational studies—indicate that the risk of anaphylaxis is largely associated with high-molecular-weight formulations.

Sodium ferric gluconate complex and **iron-sucrose complex** are alternative parenteral iron preparations. These agents can be given only by the intravenous route. They appear to be less likely than high-molecular-weight iron dextran to cause hypersensitivity reactions.

For patients treated chronically with parenteral iron, it is important to monitor iron storage levels to avoid the serious toxicity associated with iron overload. Unlike oral iron therapy, which is subject to the regulatory mechanism provided by the intestinal uptake system, parenteral administration—which bypasses this

regulatory system—can deliver more iron than can be safely stored. Iron stores can be estimated on the basis of serum concentrations of ferritin and the transferrin saturation, which is the ratio of the total serum iron concentration to the total iron-binding capacity (TIBC).

Clinical Toxicity

A. Acute Iron Toxicity

Acute iron toxicity is seen almost exclusively in young children who accidentally ingest iron tablets. As few as 10 tablets of any of the commonly available oral iron preparations can be lethal in young children. Adult patients taking oral iron preparations should be instructed to store tablets in child-proof containers out of the reach of children. Children who are poisoned with oral iron experience necrotizing gastroenteritis, with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dyspnea. Subsequently, improvement is often noted, but this may be followed by severe metabolic acidosis, coma, and death. Urgent treatment is necessary. **Whole bowel irrigation** (see Chapter 58) should be performed to flush out unabsorbed pills. **Deferoxamine,** a potent iron-chelating compound, can be given intravenously to bind iron that has already been absorbed and to promote its excretion in urine and feces. Activated charcoal, a highly effective adsorbent for most toxins, does ***not*** bind iron and thus is ineffective. Appropriate supportive therapy for gastrointestinal bleeding, metabolic acidosis, and shock must also be provided.

B. Chronic Iron Toxicity

Chronic iron toxicity (iron overload), also known as **hemochromatosis,** results when excess iron is deposited in the heart, liver, pancreas, and other organs. It can lead to organ failure and death. It most commonly occurs in patients with inherited hemochromatosis, a disorder characterized by excessive iron absorption, and in patients who receive many red cell transfusions over a long period of time (eg, individuals with β-thalassemia).

Chronic iron overload in the absence of anemia is most efficiently treated by intermittent phlebotomy. One unit of blood can be removed every week or so until all of the excess iron is removed. Iron chelation therapy using parenteral **deferoxamine** or the oral iron chelator **deferasirox** (see Chapter 57) is less efficient as well as more complicated, expensive, and hazardous, but it may be the only option for iron overload that cannot be managed by phlebotomy, as is the case for many individuals with inherited and acquired causes of refractory anemia such as thalassemia major, sickle cell anemia, aplastic anemia, etc.

VITAMIN B_{12}

Vitamin B_{12} (cobalamin) serves as a cofactor for several essential biochemical reactions in humans. Deficiency of vitamin B_{12} leads to megaloblastic anemia (Table 33–2), gastrointestinal symptoms, and neurologic abnormalities. Although deficiency of vitamin B_{12} due to an inadequate supply in the diet is unusual, deficiency of B_{12} in adults—especially older adults—due to inadequate absorption of dietary vitamin B_{12} is a relatively common and easily treated disorder.

Chemistry

Vitamin B_{12} consists of a porphyrin-like ring with a central cobalt atom attached to a nucleotide. Various organic groups may be covalently bound to the cobalt atom, forming different cobalamins. Deoxyadenosylcobalamin and methylcobalamin are the active forms of the vitamin in humans. **Cyanocobalamin** and **hydroxocobalamin** (both available for therapeutic use) and other cobalamins found in food sources are converted to the active forms. The ultimate source of vitamin B_{12} is from microbial synthesis; the vitamin is not synthesized by animals or plants. The chief dietary source of vitamin B_{12} is microbially derived vitamin B_{12} in meat (especially liver), eggs, and dairy products. Vitamin B_{12} is sometimes called **extrinsic factor** to differentiate it from **intrinsic factor,** a protein secreted by the stomach that is required for gastrointestinal uptake of dietary vitamin B_{12}.

Pharmacokinetics

The average American diet contains 5–30 mcg of vitamin B_{12} daily, 1–5 mcg of which is usually absorbed. The vitamin is avidly stored, primarily in the liver, with an average adult having a total vitamin B_{12} storage pool of 3000–5000 mcg. Only trace amounts of vitamin B_{12} are normally lost in urine and stool. Because the normal daily requirements of vitamin B_{12} are only about 2 mcg, it would take about 5 years for all of the stored vitamin B_{12} to be exhausted and for megaloblastic anemia to develop if B_{12} absorption were stopped. Vitamin B_{12} is absorbed after it complexes with intrinsic factor, a glycoprotein secreted by the parietal cells of the gastric mucosa. Intrinsic factor combines with the vitamin B_{12} that is liberated from dietary sources in the stomach and duodenum, and the intrinsic factor-vitamin B_{12} complex is subsequently absorbed in the distal ileum by a highly selective receptor-mediated transport system. Vitamin B_{12} deficiency in humans most often results from malabsorption of vitamin B_{12} due either to lack of intrinsic factor or to loss or malfunction of the absorptive mechanism in the distal ileum. Nutritional deficiency is rare but may be seen in strict vegetarians after many years without meat, eggs, or dairy products.

Once absorbed, vitamin B_{12} is transported to the various cells of the body bound to a family of specialized glycoproteins, transcobalamin I, II, and III. Excess vitamin B_{12} is stored in the liver.

Pharmacodynamics

Two essential enzymatic reactions in humans require vitamin B_{12} (Figure 33–2). In one, methylcobalamin serves as an intermediate in the transfer of a methyl group from N^5-methyltetrahydrofolate to homocysteine, forming methionine (Figure 33–2A; Figure 33–3, section 1). Without vitamin B_{12}, conversion of the major dietary and storage folate—N^5-methyltetrahydrofolate—to tetrahydrofolate, the precursor of folate cofactors, cannot occur. As a result, vitamin B_{12} deficiency leads to deficiency of folate cofactors necessary for several biochemical reactions involving the transfer of one-carbon

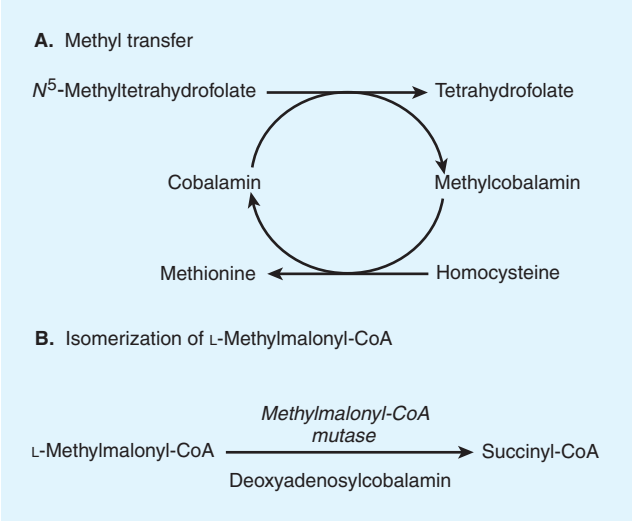

FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}. See text for details.

groups. In particular, the depletion of tetrahydrofolate prevents synthesis of adequate supplies of the deoxythymidylate (dTMP) and purines required for DNA synthesis in rapidly dividing cells, as shown in Figure 33–3, section 2. The accumulation of folate as N^5-methyltetrahydrofolate and the associated depletion of tetrahydrofolate cofactors in vitamin B_{12} deficiency have been referred to as the "methylfolate trap." This is the biochemical step whereby vitamin B_{12} and folic acid metabolism are linked, and it explains why the megaloblastic anemia of vitamin B_{12} deficiency can be partially corrected by ingestion of large amounts of folic acid. Folic acid can be reduced to dihydrofolate by the enzyme dihydrofolate reductase (Figure 33–3, section 3) and thereby serve as a source of the tetrahydrofolate required for synthesis of the purines and dTMP required for DNA synthesis.

Vitamin B_{12} deficiency causes the accumulation of homocysteine due to reduced formation of methylcobalamin, which is required for the conversion of homocysteine to methionine (Figure 33–3, section 1). The increase in serum homocysteine can be used to help establish a diagnosis of vitamin B_{12} deficiency (Table 33–2). There is evidence from observational studies that

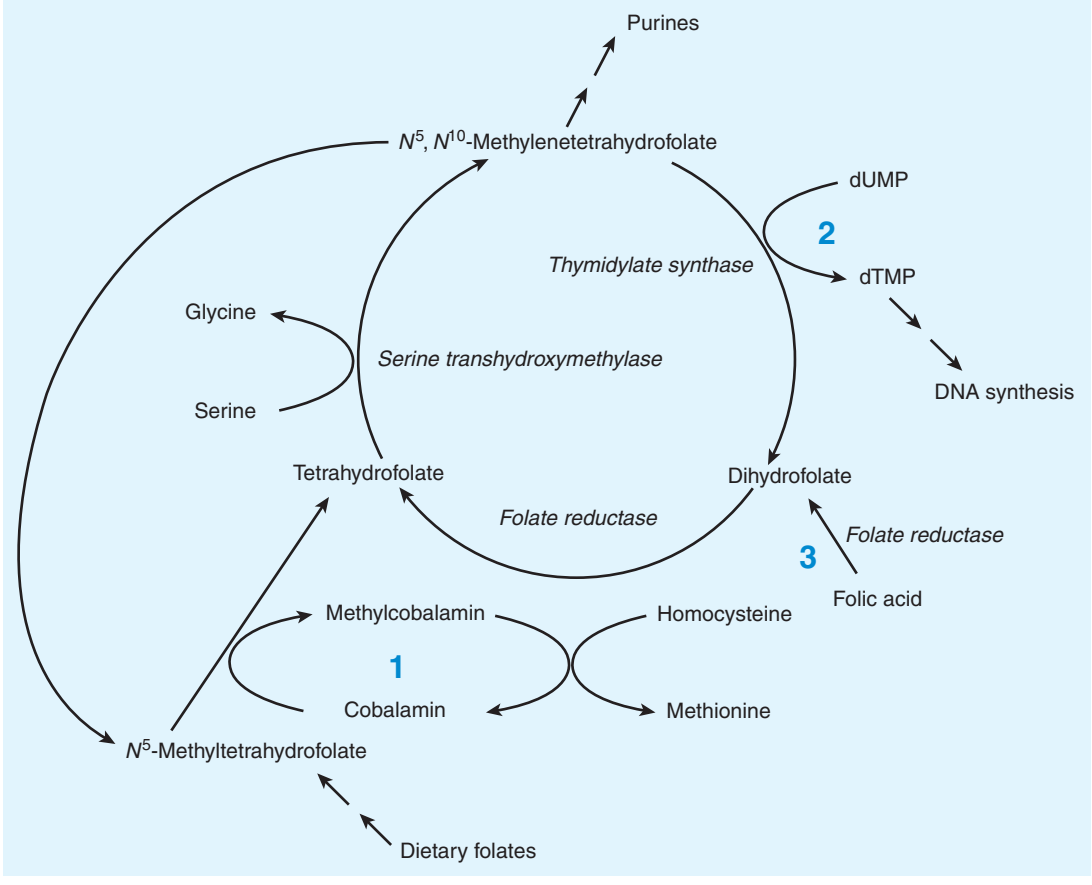

FIGURE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the dTMP cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows indicate pathways with more than one intermediate step.

elevated serum homocysteine increases the risk of atherosclerotic cardiovascular disease. However, randomized clinical trials have not shown a definitive reduction in cardiovascular events (myocardial infarction, stroke) in patients receiving vitamin supplementation that lowers serum homocysteine.

The other reaction that requires vitamin B_{12} is isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase (Figure 33–2B). In vitamin B_{12} deficiency, this conversion cannot take place and the substrate, methylmalonyl-CoA, as well as methylmalonic acid accumulate. The increase in serum and urine concentrations of methylmalonic acid can be used to support a diagnosis of vitamin B_{12} deficiency (Table 33–2). In the past, it was thought that abnormal accumulation of methylmalonyl-CoA causes the neurologic manifestations of vitamin B_{12} deficiency. However, newer evidence instead implicates the disruption of the methionine synthesis pathway as the cause of neurologic problems. Whatever the biochemical explanation for neurologic damage, the important point is that administration of folic acid in the setting of vitamin B_{12} deficiency will not prevent neurologic manifestations even though it will largely correct the anemia caused by the vitamin B_{12} deficiency.

Clinical Pharmacology

Vitamin B_{12} is used to treat or prevent deficiency. The most characteristic clinical manifestation of vitamin B_{12} deficiency is megaloblastic, macrocytic anemia (Table 33–2), often with associated mild or moderate leukopenia or thrombocytopenia (or both), and a characteristic hypercellular bone marrow with an accumulation of megaloblastic erythroid and other precursor cells. The neurologic syndrome associated with vitamin B_{12} deficiency usually begins with paresthesias in peripheral nerves and weakness and progresses to spasticity, ataxia, and other central nervous system dysfunctions. Correction of vitamin B_{12} deficiency arrests the progression of neurologic disease, but it may not fully reverse neurologic symptoms that have been present for several months. Although most patients with neurologic abnormalities caused by vitamin B_{12} deficiency have megaloblastic anemia when first seen, occasional patients have few if any hematologic abnormalities.

Once a diagnosis of megaloblastic anemia is made, it must be determined whether vitamin B_{12} or folic acid deficiency is the cause. (Other causes of megaloblastic anemia are very rare.) This can usually be accomplished by measuring serum levels of the vitamins. The Schilling test, which measures absorption and urinary excretion of radioactively labeled vitamin B_{12}, can be used to further define the mechanism of vitamin B_{12} malabsorption when this is found to be the cause of the megaloblastic anemia.

The most common causes of vitamin B_{12} deficiency are pernicious anemia, partial or total gastrectomy, and conditions that affect the distal ileum, such as malabsorption syndromes, inflammatory bowel disease, or small bowel resection.

Pernicious anemia results from defective secretion of intrinsic factor by the gastric mucosal cells. Patients with pernicious anemia have gastric atrophy and fail to secrete intrinsic factor (as well as hydrochloric acid). The Schilling test shows diminished absorption of radioactively labeled vitamin B_{12}, which is corrected when intrinsic factor is administered with radioactive B_{12}, since the vitamin can then be normally absorbed.

Vitamin B_{12} deficiency also occurs when the region of the distal ileum that absorbs the vitamin B_{12}-intrinsic factor complex is damaged, as when the ileum is involved with inflammatory bowel disease or when the ileum is surgically resected. In these situations, radioactively labeled vitamin B_{12} is not absorbed in the Schilling test, even when intrinsic factor is added. Rare cases of vitamin B_{12} deficiency in children have been found to be secondary to congenital deficiency of intrinsic factor or to defects of the receptor sites for vitamin B_{12}-intrinsic factor complex located in the distal ileum.

Almost all cases of vitamin B_{12} deficiency are caused by malabsorption of the vitamin; therefore, parenteral injections of vitamin B_{12} are required for therapy. For patients with potentially reversible diseases, the underlying disease should be treated after initial treatment with parenteral vitamin B_{12}. Most patients, however, do not have curable deficiency syndromes and require lifelong treatment with vitamin B_{12}.

Vitamin B_{12} for parenteral injection is available as cyanocobalamin or hydroxocobalamin. Hydroxocobalamin is preferred because it is more highly protein-bound and therefore remains longer in the circulation. Initial therapy should consist of 100–1000 mcg of vitamin B_{12} intramuscularly daily or every other day for 1–2 weeks to replenish body stores. Maintenance therapy consists of 100–1000 mcg intramuscularly once a month for life. If neurologic abnormalities are present, maintenance therapy injections should be given every 1–2 weeks for 6 months before switching to monthly injections. Oral vitamin B_{12}-intrinsic factor mixtures and liver extracts should not be used to treat vitamin B_{12} deficiency; however, oral doses of 1000 mcg of vitamin B_{12} daily are usually sufficient to treat patients with pernicious anemia who refuse or cannot tolerate the injections. After pernicious anemia is in remission following parenteral vitamin B_{12} therapy, the vitamin can be administered intranasally as a spray or gel.

FOLIC ACID

Reduced forms of folic acid are required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines, and DNA. Folate deficiency is relatively common, even though the deficiency is easily corrected by administration of folic acid. The consequences of folate deficiency go beyond the problem of anemia because folate deficiency is implicated as a cause of congenital malformations in newborns and may play a role in vascular disease (see Box: Folic Acid Supplementation: A Public Health Dilemma).

Chemistry

Folic acid (pteroylglutamic acid) is composed of a heterocycle (pteridine), *p*-aminobenzoic acid, and glutamic acid (Figure 33–4). Various numbers of glutamic acid moieties are attached to the pteroyl portion of the molecule, resulting in monoglutamates, triglutamates, or polyglutamates. Folic acid undergoes reduction,

Folic Acid Supplementation: A Public Health Dilemma

Starting in January 1998, all products made from enriched grains in the United States and Canada were required to be supplemented with folic acid. These rulings were issued to reduce the incidence of congenital neural tube defects (NTDs). Epidemiologic studies show a strong correlation between maternal folic acid deficiency and the incidence of NTDs such as spina bifida and anencephaly. The requirement for folic acid supplementation is a public health measure aimed at the significant number of women who do not receive prenatal care and are not aware of the importance of adequate folic acid ingestion for preventing birth defects in their infants. Observational studies from countries that supplement grains with folic acid have found that supplementation is associated with a significant (20–25%) reduction in NTD rates. Observational studies also suggest that rates of other types of congenital anomalies (heart and orofacial) have fallen since supplementation began.

There may be an added benefit for adults. N^5-Methyltetrahydrofolate is required for the conversion of homocysteine to methionine (Figure 33–2; Figure 33–3, reaction 1). Impaired synthesis of N^5-methyltetrahydrofolate results in elevated serum concentrations of homocysteine. Data from several sources suggest a positive correlation between elevated serum homocysteine and occlusive vascular diseases such as ischemic heart disease and stroke. Clinical data suggest that the folate supplementation program has improved the folate status and reduced the prevalence of hyperhomocysteinemia in a population of middle-aged and older adults who did not use vitamin supplements. There is also evidence that adequate folic acid protects against several cancers, including colorectal, breast, and cervical cancer.

Although the potential benefits of supplemental folic acid during pregnancy are compelling, the decision to require folic acid in grains was controversial. As described in the text, ingestion of folic acid can partially or totally correct the anemia caused by vitamin B_{12} deficiency. However, folic acid supplementation does not prevent the potentially irreversible neurologic damage caused by vitamin B_{12} deficiency. People with pernicious anemia and other forms of vitamin B_{12} deficiency are usually identified because of signs and symptoms of anemia, which typically occur before neurologic symptoms. Some opponents of folic acid supplementation were concerned that increased folic acid intake in the general population would mask vitamin B_{12} deficiency and increase the prevalence of neurologic disease in the elderly population. To put this in perspective, approximately 4000 pregnancies, including 2500 live births, in the United States each year are affected by NTDs. In contrast, it is estimated that over 10% of the elderly population in the United States, or several million people, are at risk for the neuropsychiatric complications of vitamin B_{12} deficiency. In acknowledgment of this controversy, the FDA kept its requirements for folic acid supplementation at a somewhat low level. There is also concern based on observational and prospective clinical trials that high folic acid levels can increase the risk of some diseases, such as colorectal cancer, for which folic acid may exhibit a bell-shaped curve. Further research is needed to more accurately define the optimal level of folic acid fortification in food and recommendations for folic acid supplementation in different populations and age groups.

catalyzed by the enzyme dihydrofolate reductase ("folate reductase"), to give dihydrofolic acid (Figure 33–3, section 3). Tetrahydrofolate is subsequently transformed to folate cofactors possessing one-carbon units attached to the 5-nitrogen, to the 10-nitrogen, or to both positions (Figure 33–3). Folate cofactors are interconvertible by various enzymatic reactions and serve the important biochemical function of donating one-carbon units at various levels of oxidation. In most of these, tetrahydrofolate is regenerated and becomes available for reutilization.

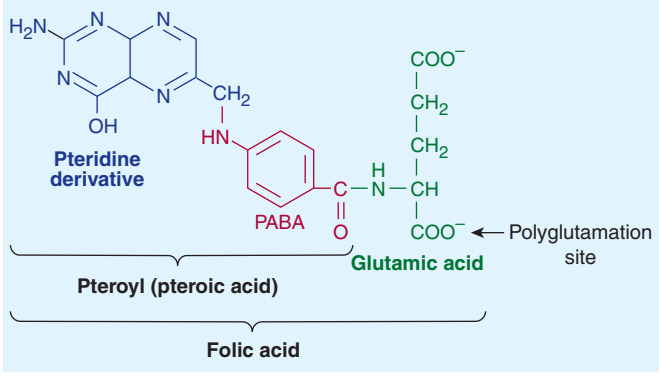

FIGURE 33–4 The structure of folic acid. (Reproduced, with permission, from Murray RK et al: *Harper's Biochemistry*, 24th ed. McGraw-Hill, 1996.)

Pharmacokinetics

The average American diet contains 500–700 mcg of folates daily, 50–200 mcg of which is usually absorbed, depending on metabolic requirements. Pregnant women may absorb as much as 300–400 mcg of folic acid daily. Various forms of folic acid are present in a wide variety of plant and animal tissues; the richest sources are yeast, liver, kidney, and green vegetables. Normally, 5–20 mg of folates is stored in the liver and other tissues. Folates are excreted in the urine and stool and are also destroyed by catabolism, so serum levels fall within a few days when intake is diminished. Because body stores of folates are relatively low and daily requirements high, folic acid deficiency and megaloblastic anemia can develop within 1–6 months after the intake of folic acid stops, depending on the patient's nutritional status and the rate of folate utilization.

Unaltered folic acid is readily and completely absorbed in the proximal jejunum. Dietary folates, however, consist primarily of

polyglutamate forms of N^5-methyltetrahydrofolate. Before absorption, all but one of the glutamyl residues of the polyglutamates must be hydrolyzed by the enzyme α-1-glutamyl transferase ("conjugase") within the brush border of the intestinal mucosa. The monoglutamate N^5-methyltetrahydrofolate is subsequently transported into the bloodstream by both active and passive transport and is then widely distributed throughout the body. Inside cells, N^5-methyltetrahydrofolate is converted to tetrahydrofolate by the demethylation reaction that requires vitamin B_{12} (Figure 33–3, section 1).

Pharmacodynamics

Tetrahydrofolate cofactors participate in one-carbon transfer reactions. As described earlier in the discussion of vitamin B_{12}, one of these essential reactions produces the dTMP needed for DNA synthesis. In this reaction, the enzyme thymidylate synthase catalyzes the transfer of the one-carbon unit of N^5, N^{10}-methylenetetrahydrofolate to deoxyuridine monophosphate (dUMP) to form dTMP (Figure 33–3, section 2). Unlike all the other enzymatic reactions that use folate cofactors, in this reaction the cofactor is oxidized to dihydrofolate, and for each mole of dTMP produced, 1 mole of tetrahydrofolate is consumed. In rapidly proliferating tissues, considerable amounts of tetrahydrofolate are consumed in this reaction, and continued DNA synthesis requires continued regeneration of tetrahydrofolate by reduction of dihydrofolate, catalyzed by the enzyme dihydrofolate reductase. The tetrahydrofolate thus produced can then reform the cofactor N^5, N^{10}-methylenetetrahydrofolate by the action of serine transhydroxymethylase and thus allow for the continued synthesis of dTMP. The combined catalytic activities of dTMP synthase, dihydrofolate reductase, and serine transhydroxymethylase are referred to as the *dTMP synthesis cycle*. Enzymes in the dTMP cycle are the targets of two anticancer drugs; methotrexate inhibits dihydrofolate reductase, and a metabolite of 5-fluorouracil inhibits thymidylate synthase (see Chapter 54).

Cofactors of tetrahydrofolate participate in several other essential reactions. N^5-Methylenetetrahydrofolate is required for the vitamin B_{12}-dependent reaction that generates methionine from homocysteine (Figure 33–2A; Figure 33–3, section 1). In addition, tetrahydrofolate cofactors donate one-carbon units during the de novo synthesis of essential purines. In these reactions, tetrahydrofolate is regenerated and can reenter the tetrahydrofolate cofactor pool.

Clinical Pharmacology

Folate deficiency results in a megaloblastic anemia that is microscopically indistinguishable from the anemia caused by vitamin B_{12} deficiency (see above). However, folate deficiency does not cause the characteristic neurologic syndrome seen in vitamin B_{12} deficiency. In patients with megaloblastic anemia, folate status is assessed with assays for serum folate or for red blood cell folate. Red blood cell folate levels are often of greater diagnostic value than serum levels, because serum folate levels tend to be labile and do not necessarily reflect tissue levels.

Folic acid deficiency is often caused by inadequate dietary intake of folates. Patients with alcohol dependence and patients with liver disease can develop folic acid deficiency because of poor diet and diminished hepatic storage of folates. Pregnant women and patients with hemolytic anemia have increased folate requirements and may become folic acid-deficient, especially if their diets are marginal. Evidence implicates maternal folic acid deficiency in the occurrence of fetal neural tube defects. (See Box: Folic Acid Supplementation: A Public Health Dilemma.) Patients with malabsorption syndromes also frequently develop folic acid deficiency. Patients who require renal dialysis are at risk of folic acid deficiency because folates are removed from the plasma during the dialysis procedure.

Folic acid deficiency can be caused by drugs. Methotrexate and, to a lesser extent, trimethoprim and pyrimethamine, inhibit dihydrofolate reductase and may result in a deficiency of folate cofactors and ultimately in megaloblastic anemia. Long-term therapy with phenytoin can also cause folate deficiency, but only rarely causes megaloblastic anemia.

Parenteral administration of folic acid is rarely necessary, since oral folic acid is well absorbed even in patients with malabsorption syndromes. A dose of 1 mg folic acid orally daily is sufficient to reverse megaloblastic anemia, restore normal serum folate levels, and replenish body stores of folates in almost all patients. Therapy should be continued until the underlying cause of the deficiency is removed or corrected. Therapy may be required indefinitely for patients with malabsorption or dietary inadequacy. Folic acid supplementation to prevent folic acid deficiency should be considered in high-risk patients, including pregnant women, patients with alcohol dependence, hemolytic anemia, liver disease, or certain skin diseases, and patients on renal dialysis.

HEMATOPOIETIC GROWTH FACTORS

The hematopoietic growth factors are glycoprotein hormones that regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow. The first growth factors to be identified were called colony-stimulating factors because they could stimulate the growth of colonies of various bone marrow progenitor cells in vitro. Many of these growth factors have been purified and cloned, and their effects on hematopoiesis have been extensively studied. Quantities of these growth factors sufficient for clinical use are produced by recombinant DNA technology.

Of the known hematopoietic growth factors, **erythropoietin (epoetin alfa and epoetin beta), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF),** and **interleukin-11 (IL-11)** are currently in clinical use. **Romiplostim** is a novel biologic agent that activates the thrombopoietin receptor.

The hematopoietic growth factors and drugs that mimic their action have complex effects on the function of a wide variety of cell types, including nonhematologic cells. Their usefulness in other areas of medicine, particularly as potential anticancer and anti-inflammatory drugs, is being investigated.

ERYTHROPOIETIN

Chemistry & Pharmacokinetics

Erythropoietin, a 34–39 kDa glycoprotein, was the first human hematopoietic growth factor to be isolated. It was originally purified from the urine of patients with severe anemia. Recombinant human erythropoietin (rHuEPO, epoetin alfa) is produced in a mammalian cell expression system. After intravenous administration, erythropoietin has a serum half-life of 4–13 hours in patients with chronic renal failure. It is not cleared by dialysis. It is measured in international units (IU). Darbepoetin alfa is a modified form of erythropoietin that is more heavily glycosylated as a result of changes in amino acids. Darbepoetin alfa has a twofold to threefold longer half-life than epoetin alfa. Methoxy polyethylene glycol-epoetin beta is an isoform of erythropoietin covalently attached to a long polyethylene glycol polymer. This long-lived recombinant product is administered as a single intravenous or subcutaneous dose at 2-week or monthly intervals, whereas epoetin alfa is generally administered three times a week and darbepoetin is administered weekly.

Pharmacodynamics

Erythropoietin stimulates erythroid proliferation and differentiation by interacting with erythropoietin receptors on red cell progenitors. The erythropoietin receptor is a member of the JAK/STAT superfamily of cytokine receptors that use protein phosphorylation and transcription factor activation to regulate cellular function (see Chapter 2). Erythropoietin also induces release of reticulocytes from the bone marrow. Endogenous erythropoietin is primarily produced in the kidney. In response to tissue hypoxia, more erythropoietin is produced through an increased rate of transcription of the erythropoietin gene. This results in correction of the anemia, provided that the bone marrow response is not impaired by red cell nutritional deficiency (especially iron deficiency), primary bone marrow disorders (see below), or bone marrow suppression from drugs or chronic diseases.

Normally, an inverse relationship exists between the hematocrit or hemoglobin level and the serum erythropoietin level. Nonanemic individuals have serum erythropoietin levels of less than 20 IU/L. As the hematocrit and hemoglobin levels fall and anemia becomes more severe, the serum erythropoietin level rises exponentially. Patients with moderately severe anemia usually have erythropoietin levels in the 100–500 IU/L range, and patients with severe anemia may have levels of thousands of IU/L. The most important exception to this inverse relationship is in the anemia of chronic renal failure. In patients with renal disease, erythropoietin levels are usually low because the kidneys cannot produce the growth factor. These are the patients most likely to respond to treatment with exogenous erythropoietin. In most primary bone marrow disorders (aplastic anemia, leukemias, myeloproliferative and myelodysplastic disorders, etc) and most nutritional and secondary anemias, endogenous erythropoietin levels are high, so there is less likelihood of a response to exogenous erythropoietin (but see below).

Clinical Pharmacology

The availability of erythropoiesis-stimulating agents (ESAs) has had a significant positive impact for patients with several types of anemia (Table 33–4). The ESAs consistently improve the

TABLE 33–4 Clinical uses of hematopoietic growth factors and agents that mimic their actions.

Hematopoietic Growth Factor	Clinical Condition Being Treated or Prevented	Recipients
Erythropoietin, darbepoetin alfa	Anemia	Patients with chronic renal failure
		HIV-infected patients treated with zidovudine
		Cancer patients treated with myelosuppressive cancer chemotherapy
		Patients scheduled to undergo elective, noncardiac, nonvascular surgery
Granulocyte colony-stimulating factor (G-CSF; filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim)	Neutropenia	Cancer patients treated with myelosuppressive cancer chemotherapy
		Patients with severe chronic neutropenia
		Patients recovering from bone marrow transplantation
	Stem cell or bone marrow transplantation	Patients with nonmyeloid malignancies or other conditions being treated with stem cell or bone marrow transplantation
	Mobilization of peripheral blood progenitor cells (PBPCs)	Donors of stem cells for allogeneic or autologous transplantation
Interleukin-11 (IL-11, oprelvekin)	Thrombocytopenia	Patients with nonmyeloid malignancies who receive myelosuppressive cancer chemotherapy
Romiplostim	Thrombocytopenia	Patients with idiopathic thrombocytopenic purpura

hematocrit and hemoglobin level, often eliminate the need for transfusions, and reliably improve quality of life indices. The ESAs are used routinely in patients with anemia secondary to chronic kidney disease. In patients treated with an ESA, an increase in reticulocyte count is usually observed in about 10 days and an increase in hematocrit and hemoglobin levels in 2–6 weeks. Dosages of ESAs are adjusted to maintain a target hemoglobin up to, but not exceeding, 10–12 g/dL. To support the increased erythropoiesis, nearly all patients with chronic kidney disease require oral or parenteral iron supplementation. Folate supplementation may also be necessary in some patients.

In selected patients, erythropoietin is also used to reduce the need for red blood cell transfusion in patients undergoing myelosuppressive cancer chemotherapy who have a hemoglobin level <10 mg/dL, and for selected patients with low-risk myelodysplastic syndromes and anemia requiring red blood cell transfusion. Patients who have disproportionately low serum erythropoietin levels for their degree of anemia are most likely to respond to treatment. Patients with endogenous erythropoietin levels of less than 100 IU/L have the best chance of response, although patients with erythropoietin levels between 100 and 500 IU/L respond occasionally. Methoxy polyethylene glycol-epoetin beta should not be used for treatment of anemia caused by cancer chemotherapy because a clinical trial found significantly more deaths among patients receiving this form of erythropoietin.

Erythropoietin has been used successfully to offset the anemia produced by zidovudine treatment in patients with HIV infection and in the treatment of the anemia of prematurity. It can also be used to reduce the need for transfusion in high-risk patients undergoing elective, non-cardiac, nonvascular surgery.

Erythropoietin is one of the drugs banned by the International Olympic Committee. The use of erythropoietin by athletes is based on their hope that increased red blood cell concentration will increase oxygen delivery to muscles and improve performance.

Toxicity

The most common adverse effects of erythropoietin are hypertension and thrombotic complications. In March 2007, the FDA issued a warning that patients with chronic renal failure or cancer whose serum hemoglobin is raised to more than 12 g/dL with an ESA face a greater risk of a thrombotic event or, in patients with advanced head and neck cancers, faster tumor growth. The warning was primarily based on clinical trial data from patients with chronic kidney disease indicating an increased rate of mortality and cardiovascular events (stroke, myocardial infarction, worsening congestive heart failure, and hypertension) in patients dosed with an ESA to a target hemoglobin level of 12–16 g/dL or dosed to maintain a normal hematocrit (42%) versus a lower target hematocrit of 30%. In addition, a meta-analysis of 51 placebo-controlled trials of ESAs in cancer patients reported an increased rate of all-cause mortality and venous thrombosis in those receiving an ESA. Based on the accumulated evidence, it is recommended that the hemoglobin level not exceed 12 g/dL in patients with chronic kidney disease receiving an ESA, and that ESAs be used conservatively in cancer patients (eg, when hemoglobin levels are <10 g/dL) and with the lowest dose needed to avoid transfusion.

Allergic reactions to ESAs have been infrequent. There have been a small number of cases of pure red cell aplasia (PRCA) accompanied by neutralizing antibodies to erythropoietin. PRCA was most commonly seen in dialysis patients treated subcutaneously for a long period with a particular form of epoetin alfa (Eprex with a polysorbate 80 stabilizer rather than human serum albumin) that is not available in the United States. After regulatory agencies required that Eprex be administered intravenously rather than subcutaneously, the rate of ESA-associated PRCA diminished. However, rare cases have still been seen with all ESAs administered subcutaneously for long periods to patients with chronic kidney disease.

MYELOID GROWTH FACTORS

Chemistry & Pharmacokinetics

G-CSF and **GM-CSF,** the two myeloid growth factors currently available for clinical use, were originally purified from cultured human cell lines (Table 33–4). Recombinant human G-CSF (**rHuG-CSF; filgrastim**) is produced in a bacterial expression system. It is a nonglycosylated peptide of 175 amino acids, with a molecular weight of 18 kDa. Recombinant human GM-CSF (**rHuGM-CSF; sargramostim**) is produced in a yeast expression system. It is a partially glycosylated peptide of 127 amino acids, with three molecular species with molecular weights of 15,500; 15,800; and 19,500. These preparations have serum half-lives of 2–7 hours after intravenous or subcutaneous administration. **Pegfilgrastim,** a covalent conjugation product of filgrastim and a form of polyethylene glycol, has a much longer serum half-life than recombinant G-CSF, and it can be injected once per myelosuppressive chemotherapy cycle instead of daily for several days. **Lenograstim,** used widely in Europe, is a glycosylated form of recombinant G-CSF.

Pharmacodynamics

The myeloid growth factors stimulate proliferation and differentiation by interacting with specific receptors found on myeloid progenitor cells. Like the erythropoietin receptor, these receptors are members of the JAK/STAT superfamily (see Chapter 2). G-CSF stimulates proliferation and differentiation of progenitors already committed to the neutrophil lineage. It also activates the phagocytic activity of mature neutrophils and prolongs their survival in the circulation. G-CSF also has a remarkable ability to mobilize hematopoietic stem cells, ie, to increase their concentration in peripheral blood. This biologic effect underlies a major advance in transplantation—the use of **peripheral blood stem cells (PBSCs)** rather than bone marrow stem cells for autologous and allogeneic hematopoietic stem cell transplantation (see below).

GM-CSF has broader biologic actions than G-CSF. It is a multipotential hematopoietic growth factor that stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors.

Like G-CSF, GM-CSF also stimulates the function of mature neutrophils. GM-CSF acts together with interleukin-2 to stimulate T-cell proliferation and appears to be a locally active factor at the site of inflammation. GM-CSF mobilizes peripheral blood stem cells, but it is significantly less efficacious and more toxic than G-CSF in this regard.

Clinical Pharmacology

A. Cancer Chemotherapy-Induced Neutropenia

Neutropenia is a common adverse effect of the cytotoxic drugs used to treat cancer and increases the risk of serious infection in patients receiving chemotherapy. Unlike the treatment of anemia and thrombocytopenia, transfusion of neutropenic patients with granulocytes collected from donors is performed rarely and with limited success. The introduction of G-CSF in 1991 represented a milestone in the treatment of chemotherapy-induced neutropenia. This growth factor dramatically accelerates the rate of neutrophil recovery after dose-intensive myelosuppressive chemotherapy (Figure 33–5). It reduces the duration of neutropenia and usually raises the nadir count, the lowest neutrophil count seen following a cycle of chemotherapy.

The ability of G-CSF to increase neutrophil counts after myelosuppressive chemotherapy is nearly universal, but its impact on clinical outcomes is more variable. Many, but not all, clinical trials and meta-analyses have shown that G-CSF reduces episodes of febrile neutropenia, requirements for broad-spectrum antibiotics, infections, and days of hospitalization. Clinical trials have not shown improved survival in cancer patients treated with G-CSF. Clinical guidelines for the use of G-CSF after cytotoxic chemotherapy recommend reserving G-CSF for patients at high risk for febrile neutropenia based on age, medical history, and disease characteristics; patients receiving dose-intensive chemotherapy regimens that carry a greater than 40% risk of causing febrile neutropenia; patients with a prior episode of febrile neutropenia after cytotoxic chemotherapy; patients at high risk for febrile neutropenia; and patients who are unlikely to survive an episode of febrile neutropenia. Pegfilgrastim is an alternative to G-CSF for prevention of chemotherapy-induced febrile neutropenia. Pegfilgrastim can be administered once per chemotherapy cycle, and it may shorten the period of severe neutropenia slightly more than G-CSF.

Like G-CSF and pegfilgrastim, GM-CSF also reduces the duration of neutropenia after cytotoxic chemotherapy. It has been more difficult to show that GM-CSF reduces the incidence of febrile neutropenia, probably because GM-CSF itself can induce fever. In the treatment of chemotherapy-induced neutropenia, G-CSF, 5 mcg/kg/d, or GM-CSF, 250 mcg/m^2/d, is usually started within 24–72 hours after completing chemotherapy and is continued until the absolute neutrophil count is greater than 10,000 cells/μL. Pegfilgrastim is given as a single dose of 6 mg.

The utility and safety of the myeloid growth factors in the postchemotherapy supportive care of patients with acute myeloid leukemia (AML) have been the subject of a number of clinical trials. Because leukemic cells arise from progenitors whose proliferation and differentiation are normally regulated by hematopoietic growth factors, including GM-CSF and G-CSF, there was concern that myeloid growth factors could stimulate leukemic cell growth and increase the rate of relapse. The results of randomized clinical trials suggest that both G-CSF and GM-CSF are safe following induction and consolidation treatment of myeloid and lymphoblastic leukemia. There has been no evidence that these growth factors reduce the rate of remission or increase relapse rate. On the contrary, the growth factors accelerate neutrophil recovery and reduce infection rates and days of hospitalization. Both G-CSF and GM-CSF have FDA approval for treatment of patients with AML.

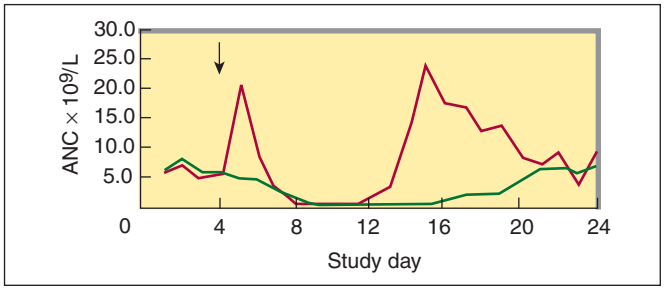

FIGURE 33–5 Effects of granulocyte colony-stimulating factor (G-CSF; *red line*) or placebo (*green line*) on absolute neutrophil count (ANC) after cytotoxic chemotherapy for lung cancer. Doses of chemotherapeutic drugs were administered on days 1 and 3. G-CSF or placebo injections were started on day 4 and continued daily through day 12 or 16. The first peak in ANC reflects the recruitment of mature cells by G-CSF. The second peak reflects a marked increase in new neutrophil production by the bone marrow under stimulation by G-CSF. (Normal ANC is 2.2–8.6 × 10^9/L.) (Modified and reproduced, with permission, from Crawford J et al: Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164.)

B. Other Applications

G-CSF and GM-CSF have also proved to be effective in treating the neutropenia associated with **congenital neutropenia, cyclic neutropenia, myelodysplasia,** and **aplastic anemia.** Many patients with these disorders respond with a prompt and sometimes dramatic increase in neutrophil count. In some cases, this results in a decrease in the frequency of infections. Because neither G-CSF nor GM-CSF stimulates the formation of erythrocytes and platelets, they are sometimes combined with other growth factors for treatment of pancytopenia.

The myeloid growth factors play an important role in **autologous stem cell transplantation** for patients undergoing high-dose chemotherapy. High-dose chemotherapy with autologous stem cell support is increasingly used to treat patients with tumors that are resistant to standard doses of chemotherapeutic drugs. The high-dose regimens produce extreme myelosuppression; the myelosuppression is then counteracted by reinfusion of the patient's own hematopoietic stem cells (which are collected prior to chemotherapy). The administration of G-CSF or GM-CSF early after autologous stem cell transplantation reduces the time to engraftment and to recovery from neutropenia in patients receiving stem cells obtained either from bone marrow or from

peripheral blood. These effects are seen in patients being treated for lymphoma or for solid tumors. G-CSF and GM-CSF are also used to support patients who have received allogeneic bone marrow transplantation for treatment of hematologic malignancies or bone marrow failure states. In this setting, the growth factors speed the recovery from neutropenia without increasing the incidence of acute graft-versus-host disease.

Perhaps the most important role of the myeloid growth factors in transplantation is for mobilization of PBSCs. Stem cells collected from peripheral blood have nearly replaced bone marrow as the hematopoietic preparation used for autologous and allogeneic transplantation. The cells can be collected in an outpatient setting with a procedure that avoids much of the risk and discomfort of bone marrow collection, including the need for general anesthesia. In addition, there is evidence that PBSC transplantation results in more rapid engraftment of all hematopoietic cell lineages and in reduced rates of graft failure or delayed platelet recovery.

G-CSF is the cytokine most commonly used for PBSC mobilization because of its increased efficacy and reduced toxicity compared with GM-CSF. To mobilize stem cells for autologous transplantation, donors are given 5–10 mcg/kg/d subcutaneously for 4 days. On the fifth day, they undergo leukapheresis. The success of PBSC transplantation depends on transfusion of adequate numbers of stem cells. CD34, an antigen present on early progenitor cells and absent from later, committed, cells, is used as a marker for the requisite stem cells. The goal is to infuse at least 5×10^6 CD34 cells/kg; this number of CD34 cells usually results in prompt and durable engraftment of all cell lineages. It may take several separate leukaphereses to collect enough CD34 cells, especially from older patients and patients who have been exposed to radiation therapy or chemotherapy.

For patients with multiple myeloma or non-Hodgkin's lymphoma who respond suboptimally to G-CSF alone, the novel hematopoietic stem cell mobilizer **plerixafor** can be added to G-CSF. Plerixafor is a bicyclam molecule originally developed as an anti-HIV drug because of its ability to inhibit the CXC chemokine receptor 4 (CXCR4), a co-receptor for HIV entry into CD4+ T lymphocytes (see Chapter 49). Early clinical trials of plerixafor revealed a remarkable ability to increase CD34 cells in peripheral blood. Plerixafor mobilizes CD34 cells by preventing chemokine stromal cell-derived factor-1α (SDF-1α) from binding to CXCR4 and directing the CD34 cells to "home" to the bone marrow. Plerixafor is administered by subcutaneous injection after four days of G-CSF treatment and 11 hours prior to leukapheresis; it can be used with G-CSF for up to four continuous days. Plerixafor is eliminated primarily by the renal route and must be dose-adjusted for patients with renal impairment. The drug is well-tolerated; the most common adverse effects associated with its use are injection site reactions, GI disturbances, dizziness, fatigue, and headache.

Toxicity

Although the three growth factors have similar effects on neutrophil counts, G-CSF and pegfilgrastim are used more frequently than GM-CSF because they are better tolerated. G-CSF and pegfilgrastim can cause bone pain, which clears when the drugs are discontinued. GM-CSF can cause more severe side effects, particularly at higher doses. These include fever, malaise, arthralgias, myalgias, and a capillary leak syndrome characterized by peripheral edema and pleural or pericardial effusions. Allergic reactions may occur but are infrequent. Splenic rupture is a rare but serious complication of the use of G-CSF for PBSC.

MEGAKARYOCYTE GROWTH FACTORS

Patients with thrombocytopenia have a high risk of hemorrhage. Although platelet transfusion is commonly used to treat thrombocytopenia, this procedure can cause adverse reactions in the recipient; furthermore, a significant number of patients fail to exhibit the expected increase in platelet count. **Thrombopoietin** and **IL-11** both appear to be key endogenous regulators of platelet production. A recombinant form of IL-11 was the first agent to gain FDA approval for treatment of thrombocytopenia. Recombinant human thrombopoietin and a pegylated form of a shortened human thrombopoietin protein underwent extensive clinical investigation in the 1990s. However, further development was abandoned after autoantibodies to the native thrombopoietin formed in healthy human subjects and caused thrombocytopenia. Efforts shifted to investigation of novel, nonimmunogenic peptide agonists of the thrombopoietin receptor, which is known as Mpl. The first of these—**romiplostim**—was approved by the FDA for idiopathic thrombocytopenic purpura in 2008.

Chemistry & Pharmacokinetics

Interleukin-11 is a 65–85 kDa protein produced by fibroblasts and stromal cells in the bone marrow. **Oprelvekin,** the recombinant form of IL-11 approved for clinical use (Table 33–4), is produced by expression in *Escherichia coli*. The half-life of IL-11 is 7–8 hours when the drug is injected subcutaneously.

Romiplostim (AMG 531) is a member of new class of therapeutics called "peptibodies," which are peptides with key biologic activities covalently linked to antibody fragments that serve to extend the peptide's half-life. Romiplostim contains two disulfide-bonded human F_c fragments, each covalently attached through a polyglycine sequence to a peptide chain containing two Mpl-binding peptides that are linked to one another by a second polyglycine sequence. The Mpl-binding peptide was selected from a peptide library based on its ability in cell assays to activate the thrombopoietin receptor. The Mpl-binding peptide has no sequence homology with human thrombopoietin and there is no evidence in animal or human studies that the Mpl-binding peptide or romiplostim induces antibodies to thrombopoietin. After subcutaneous administration, romiplostim is eliminated by the reticuloendothelial system with an average half-life of 3–4 days. Its half-life is inversely related to the serum platelet count; it has a longer half-life in patients with thrombocytopenia and a shorter half-life in patients whose platelet counts have recovered to normal levels.

Eltrombopag, an orally active small molecule agonist at the thrombopoietin receptor, was licensed in 2008 for use in patients with severe idiopathic thrombocytopenia who have failed to respond adequately to first-line treatments. Because of concerns about hepatotoxicity and hemorrhage, eltrombopag is restricted to use by registered physicians and patients and its use requires close monitoring of liver enzymes.

Pharmacodynamics

Interleukin-11 acts through a specific cell surface cytokine receptor to stimulate the growth of multiple lymphoid and myeloid cells. It acts synergistically with other growth factors to stimulate the growth of primitive megakaryocytic progenitors and, most importantly, increases the number of peripheral platelets and neutrophils.

Romiplostim has high affinity for the human Mpl receptor. It causes a dose-dependent increase in platelet count that begins on day 5 after subcutaneous administration and peaks at days 12–15.

Clinical Pharmacology

Interleukin-11 is approved for the secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of nonmyeloid cancers. Clinical trials show that it reduces the number of platelet transfusions required by patients who experience severe thrombocytopenia after a previous cycle of chemotherapy. Although IL-11 has broad stimulatory effects on hematopoietic cell lineages in vitro, it does not appear to have significant effects on the leukopenia caused by myelosuppressive chemotherapy. Interleukin-11 is given by subcutaneous injection at a dose of 50 mcg/kg/d. It is started 6–24 hours after completion of chemotherapy and continued for 14–21 days or until the platelet count passes the nadir and rises to more than 50,000 cells/μL.

In patients with chronic idiopathic thrombocytopenia (ITP) who failed to respond adequately to previous treatment with steroids, immunoglobulins, or splenectomy, romiplostim significantly increased platelet count in most patients. In a 6-week placebo-controlled study in which patients were treated weekly with 1 or 3 mcg/kg, 12 of 16 patients reached the targeted platelet range of 50,000–450,000 platelets/μL. Romiplostim does not appear to decrease the rate of platelet destruction in ITP as platelet counts returned to pretreatment levels after the drug's discontinuation. An open label trial found that many patients maintained a platelet count of 100,000 platelets/μL or higher over a 48-week period and that over half of the patients were able to discontinue other therapies. Romiplostim is initiated as a weekly subcutaneous dose of 1 mcg/kg and then continued at the lowest dose required to maintain a platelet count of at least 50,000 platelets/μL.

Toxicity

The most common adverse effects of IL-11 are fatigue, headache, dizziness, and cardiovascular effects. The cardiovascular effects include anemia (due to hemodilution), dyspnea (due to fluid accumulation in the lungs), and transient atrial arrhythmias. Hypokalemia has also been seen in some patients. All of these adverse effects appear to be reversible.

Romiplostim appears to be well tolerated except for a mild headache on the day of administration. A potential long-term concern is that two patients treated with romiplostim had an increase in bone marrow reticulin, a possible marker of myelodysplastic or myeloproliferative processes. However, neither patient had evidence of increased collagen fibrosis or of abnormal bone marrow cytogenetics.

SUMMARY Agents Used in Anemias and Hematopoietic Growth Factors

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
IRON				
• Ferrous sulfate	Required for biosynthesis of heme and heme-containing proteins, including hemoglobin and myoglobin	Adequate supplies required for normal heme synthesis • deficiency results in inadequate heme production	Iron deficiency, which manifests as microcytic anemia • oral preparation	Complicated endogenous system for absorbing, storing, and transporting iron • *Toxicity:* Acute overdose results in necrotizing gastroenteritis, abdominal pain, bloody diarrhea, shock, lethargy, and dyspnea • chronic iron overload results in hemochromatosis, with damage to the heart, liver, pancreas, and other organs • organ failure and death can ensue
• *Ferrous gluconate and ferrous fumarate: Oral iron preparations*				
• *Iron dextran, iron sucrose complex, and sodium ferric gluconate complex: Parenteral preparations; can cause pain, hypersensitivity reactions*				
IRON CHELATORS				
• Deferoxamine (see also Chapters 57 and 58)	Chelates excess iron	Reduces toxicity associated with acute or chronic iron overload	Acute iron poisoning; inherited or acquired hemochromatosis	Preferred route of administration is IM or SC • *Toxicity:* Rapid IV administration may cause hypotension • neurotoxicity and increased susceptibility to certain infections have occurred with long-term use
• *Deferasirox: Orally administered iron chelator for treatment of hemochromatosis*				
VITAMIN B_{12}				
• Cyanocobalamin • Hydroxocobalamin	Cofactor required for essential enzymatic reactions that form tetrahydrofolate, convert homocysteine to methionine, and metabolize L-methylmalonyl-CoA	Adequate supplies required for amino acid and fatty acid metabolism, and DNA synthesis	Vitamin B_{12} deficiency, which manifests as megaloblastic anemia and is the basis of pernicious anemia	Parenteral vitamin B_{12} is required for pernicious anemia and other malabsorption syndromes • *Toxicity:* No toxicity associated with excess vitamin B_{12}
FOLIC ACID				
• Folacin (pteroylglutamic acid)	Precursor of an essential donor of methyl groups used for synthesis of amino acids, purines, and deoxynucleotide	Adequate supplies required for essential biochemical reactions involving amino acid metabolism, and purine and DNA synthesis	Folic acid deficiency, which manifests as megaloblastic anemia, and prevention of congenital neural tube defects	Oral; well-absorbed; need for parenteral administration is rare • *Toxicity:* Folic acid is not toxic in overdose, but large amounts can partially compensate for vitamin B_{12} deficiency and put people with unrecognized B_{12} deficiency at risk of neurologic consequences of vitamin B_{12} deficiency, which are not compensated by folic acid

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ERYTHROCYTE-STIMULATING AGENTS				
• Epoetin alfa	Agonist of erythropoietin receptors expressed by red cell progenitors	Stimulates erythroid proliferation and differentiation, and induces the release of reticulocytes from the bone marrow	Anemia, especially anemia associated with chronic renal failure, HIV infection, cancer, and prematurity • prevention of the need for transfusion in patients undergoing certain types of elective surgery	IV or SC administration 1–3 times per week • *Toxicity:* Hypertension, thrombotic complications, and, very rarely, pure red cell aplasia • to reduce the risk of serious CV events, hemoglobin levels should be maintained <12 g/dL
• *Darbepoetin alfa: Long-acting glycosylated form administered weekly*				
• *Methoxy polyethylene glycol-epoetin beta: Long-acting form administered 1–2 times per month*				
MYELOID GROWTH FACTORS				
• Granulocyte-macrophage colony-stimulating factor (GM-CSF; filgrastim)	Stimulates G-CSF receptors expressed on mature neutrophils and their progenitors	Stimulates neutrophil progenitor proliferation and differentiation • activates phagocytic activity of mature neutrophils and extends their survival • mobilizes hematopoietic stem cells	Neutropenia associated with congenital neutropenia, cyclic neutropenia, myelodysplasia, and aplastic anemia • secondary prevention of neutropenia in patients undergoing cytotoxic chemotherapy • mobilization of peripheral blood cells in preparation for autologous and allogeneic stem cell transplantation	Daily SC administration • *Toxicity:* Bone pain • rarely, splenic rupture
• *Pegfilgrastim: Long-acting form of filgrastim that is covalently linked to a type of polyethylene glycol*				
• *GM-CSF (sargramostim): Myeloid growth factor that acts through a distinct GM-CSF receptor to stimulate proliferation and differentiation of early and late granulocytic progenitor cells, and erythroid and megakaryocyte progenitors; clinical uses are similar to those of G-CSF, but it is more likely than GM-CSF to cause fever, arthralgia, myalgia, and capillary leak syndrome*				
• *Plerixafor: Antagonist of CXCR4 used in combination with G-CSF for mobilization of peripheral blood cells prior to autologous transplantation in patients with multiple myeloma or non-Hodgkin's lymphoma who responded suboptimally to G-CSF alone*				
MEGAKARYOCYTE GROWTH FACTORS				
• Oprelvekin (interleukin-11; IL-11)	Recombinant form of an endogenous cytokine • activates IL-11 receptors	Stimulates growth of multiple lymphoid and myeloid cells, including megakaryocyte progenitors • increases the number of circulating platelets and neutrophils	Secondary prevention of thrombocytopenia in patients undergoing cytotoxic chemotherapy for nonmyeloid cancers	Daily SC injection • *Toxicity:* Fatigue, headache, dizziness, anemia, fluid accumulation in the lungs, and transient atrial arrhythmias
• *Romiplostim: Genetically engineered protein in which F_c components of a human antibody are fused to multiple copies of a peptide that stimulates the thrombopoietin receptors; approved for treatment of idiopathic thrombocytopenic purpura*				
• *Eltrombopag: Orally active, restricted use*				

PREPARATIONS AVAILABLE

Darbepoetin alfa (Aranesp)
Parenteral: 25, 40, 60, 100, 200, 300, 500 mcg/mL solution for IV or SC injection

Deferasirox (Exjade)
Oral: 125, 250, 500 mg tablets

Deferoxamine (generic, Desferal)
Parenteral: 500, 2000 mg powder for reconstitution for IM, SC, or IV injection

Eltrombopag (Promacta)
Oral: 25, 50, 75 mg tablet

Epoetin alfa (erythropoietin, EPO) (Epogen, Procrit)
Parenteral: 2000, 3000, 4000, 10,000, 20,000, 40,000 IU/mL solution for IV or SC injection

Epoetin beta (Methoxy polyethylene glycol-epoetin beta) (Mircera)
Parenteral: 50, 100, 200, 300, 400, 600, 1000 mcg/mL solution in vials and prefilled syringes for IV or SC injection

Filgrastim (G-CSF) (Neupogen)
Parenteral: 300 mcg/mL, 600 mcg/mL solution in vials and prefilled syringes for IV or SC injection

Folic acid (folacin, pteroylglutamic acid) (generic)
Oral: 0.4, 0.8, 1 mg tablets
Parenteral: 5 mg/mL solution for injection

Iron (generic)
Oral: See Table 33–3.
Parenteral (Iron dextran) (InFeD, DexFerrum): 50 mg elemental iron/mL solution for IM or IV injection
Parenteral (Sodium ferric gluconate complex) (Ferrlecit): 12.5 mg elemental iron/mL solution for IV injection
Parenteral (Iron sucrose) (Venofer): 20 mg elemental iron/mL solution for IV injection

Oprelvekin (IL-11) (Neumega)
Parenteral: 5 mg powder for reconstitution for SC injection

Pegfilgrastim (Neulasta)
Parenteral: 6 mg/0.6 mL solution in single-dose syringe

Plerixafor (Mozobil)
Parenteral: 20 mg/mL solution for SC injection

Romiplostim (Nplate)
Parenteral: 250, 500 mcg powder for reconstitution for SC injection

Sargramostim (GM-CSF) (Leukine)
Parenteral: 250 mcg powder for reconstitution; 500 mcg/mL solution

Vitamin B_{12} (generic cyanocobalamin or hydroxocobalamin)
Oral (cyanocobalamin): 50, 100, 250, 500, 1000 mcg regular tablets or lozenges; 500, 1000, 2500, 5000, 6000 mg sublingual tablets or lozenges; 1000, 1500 mg controlled-release tablets
Nasal (Nascobal, CaloMist): 500 mcg/spray
Parenteral (cyanocobalamin): 1000, 5000 mcg/mL for IM or SC injection
Parenteral (hydroxocobalamin): 1000 mcg/mL solution for IM injection; 2.5 g powder for reconstitution (antidote for cyanide poisoning) for IV injection

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CASE STUDY ANSWER

This patient's megaloblastic anemia appears to be due to vitamin B_{12} (cobalamin) deficiency secondary to impaired production of intrinsic factor resulting in insufficient absorption of vitamin B_{12} from the GI tract. It is important to measure serum concentrations of both folic acid and cobalamin because megaloblastic anemia can result from deficiency of either nutrient. It is especially important to diagnose vitamin B_{12} deficiency because this deficiency, if untreated, can lead to irreversible neurologic damage. Folate supplementation, which can compensate for vitamin B_{12}-derived anemia, does not prevent B_{12}-deficiency neurologic damage. To correct this patient's vitamin B_{12} deficiency, she would probably be treated parenterally with cobalamin because of her impaired oral absorption of vitamin B_{12}. Several weeks of daily administration would be followed with weekly doses until her hematocrit returned to normal. Monthly doses would then be given to maintain her body stores of vitamin B_{12}.

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CHAPTER 34

Drugs Used in Disorders of Coagulation

James L. Zehnder, MD

CASE STUDY

A 25-year-old woman presents to the emergency department complaining of acute onset of shortness of breath and pleuritic pain. She had been in her usual state of health until 2 days prior when she noted that her left leg was swollen and red. Her only medication was oral contraceptives. Family history was significant for a history of "blood clots" in multiple members of the maternal side of her family. Physical examination demonstrates an anxious woman with stable vital signs. The left lower extremity demonstrates erythema and edema and is tender to touch. Ultrasound reveals a deep vein thrombosis in the left lower extremity; chest computed tomography scan confirms the presence of pulmonary emboli. Laboratory blood tests indicate elevated D-dimer levels. What therapy is indicated acutely? What are the long-term therapy options? How long should she be treated? Should this individual use oral contraceptives?

Hemostasis refers to the finely regulated dynamic process of maintaining fluidity of the blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs. Either extreme—excessive bleeding or thrombosis—represents a breakdown of the hemostatic mechanism. Common causes of dysregulated hemostasis include hereditary or acquired defects in the clotting mechanism and secondary effects of infection or cancer. The drugs used to inhibit thrombosis and to limit abnormal bleeding are the subjects of this chapter.

MECHANISMS OF BLOOD COAGULATION

The vascular endothelial cell layer lining blood vessels has an anticoagulant phenotype, and circulating blood platelets and clotting factors do not normally adhere to it to an appreciable extent. In the setting of vascular injury, the endothelial cell layer rapidly undergoes a series of changes resulting in a more procoagulant phenotype. Injury exposes reactive subendothelial matrix proteins such as collagen and von Willebrand factor, which results in platelet adherence and activation, and secretion and synthesis of vasoconstrictors and platelet-recruiting and activating molecules. Thus, **thromboxane A_2 (TXA_2)** is synthesized from arachidonic acid within platelets and is a platelet activator and potent vasoconstrictor. Products secreted from platelet granules include **adenosine diphosphate (ADP),** a powerful inducer of platelet aggregation, and **serotonin (5-HT),** which stimulates aggregation and vasoconstriction. Activation of platelets results in a conformational change in the $\alpha_{IIb}\beta_{III}$ integrin (IIb/IIIa) receptor, enabling it to bind fibrinogen, which cross-links adjacent platelets, resulting in aggregation and formation of a platelet plug (Figure 34–1). Simultaneously, the coagulation system cascade is activated, resulting in thrombin generation and a fibrin clot, which stabilizes the platelet plug (see below). Knowledge of the hemostatic mechanism is important for diagnosis of bleeding disorders. Patients with defects in the formation of the primary platelet plug (defects in primary hemostasis, eg, platelet function defects, von Willebrand disease) typically bleed from surface sites (gingiva, skin, heavy menses) with injury. In contrast, patients with defects in the clotting mechanism (secondary hemostasis, eg, hemophilia A) tend to bleed into deep tissues (joints, muscle, retroperitoneum), often with no apparent inciting event, and bleeding may recur unpredictably.

The platelet is central to normal hemostasis and thromboembolic disease, and is the target of many therapies discussed in this chapter. Platelet-rich thrombi **(white thrombi)** form in the high flow rate and high shear force environment of arteries. Occlusive arterial thrombi cause serious disease by producing downstream ischemia of extremities or vital organs, and can result in limb

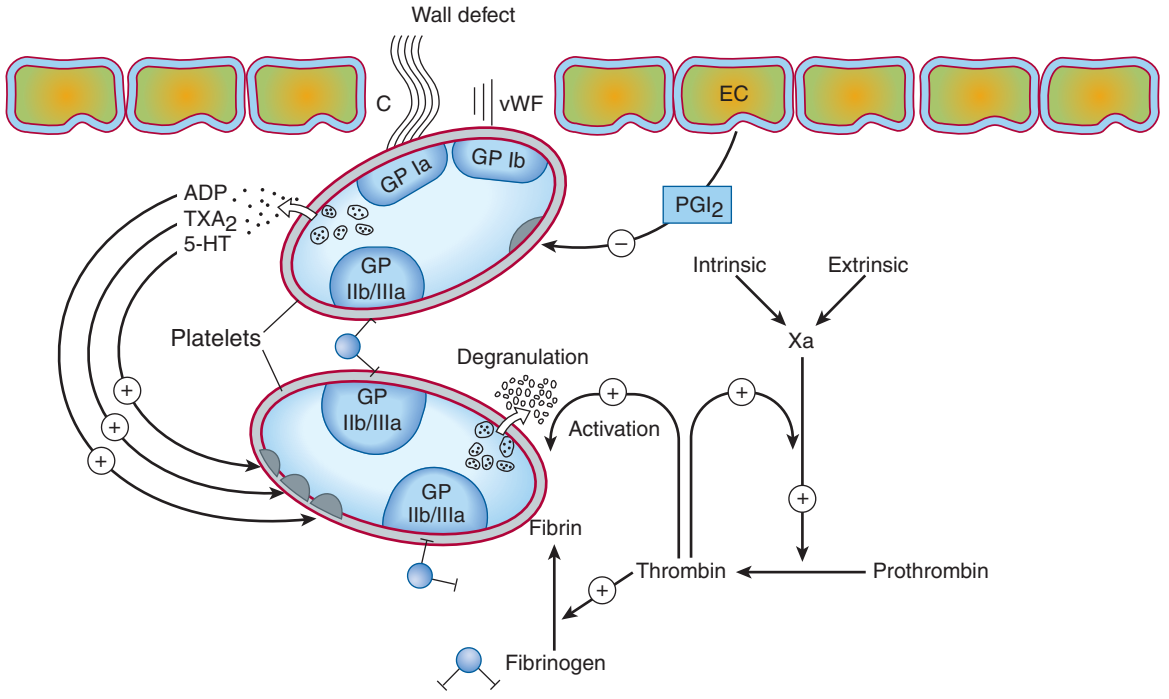

FIGURE 34–1 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI_2) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), and serotonin (5-HT). Production of factor Xa is detailed in Figure 34–2. (Redrawn and reproduced, with permission, from Simoons ML, Decker JW: New directions in anticoagulant and antiplatelet treatment. [Editorial.] Br Heart J 1995;74:337.)

amputation or organ failure. Venous clots tend to be more fibrin-rich, contain large numbers of trapped red blood cells, and are recognized pathologically as **red thrombi.** Venous thrombi can cause severe swelling and pain of the affected extremity, but the most feared consequence is pulmonary embolism. This occurs when part or all of the clot breaks off from its location in the deep venous system and travels as an embolus through the right side of the heart and into the pulmonary arterial circulation. Sudden occlusion of a large pulmonary artery can cause acute right heart failure and sudden death. In addition lung ischemia or infarction will occur distal to the occluded pulmonary arterial segment. Such emboli usually arise from the deep venous system of the proximal lower extremities or pelvis. Although all thrombi are mixed, the platelet nidus dominates the arterial thrombus and the fibrin tail dominates the venous thrombus.

BLOOD COAGULATION CASCADE

Blood coagulates due to the transformation of soluble fibrinogen into insoluble fibrin by the enzyme thrombin. Several circulating proteins interact in a cascading series of limited proteolytic reactions (Figure 34–2). At each step, a clotting factor zymogen undergoes limited proteolysis and becomes an active protease (eg, factor VII is converted to factor VIIa). Each protease factor activates the next clotting factor in the sequence, culminating in the formation of thrombin (factor IIa). Several of these factors are targets for drug therapy (Table 34–1).

Thrombin has a central role in hemostasis and has many functions. In clotting, thrombin proteolytically cleaves small peptides from fibrinogen, allowing fibrinogen to polymerize and form a fibrin clot. Thrombin also activates many upstream clotting factors, leading to more thrombin generation, and activates factor XIII, a transaminase that cross-links the fibrin polymer and stabilizes the clot. Thrombin is a potent platelet activator and mitogen. Thrombin also exerts *anti*coagulant effects by activating the protein C pathway, which attenuates the clotting response (Figure 34–2). It should therefore be apparent that the response to vascular injury is a complex and precisely modulated process that ensures that under normal circumstances, repair of vascular injury occurs without thrombosis and downstream ischemia; that is, the response is proportionate and reversible. Eventually vascular remodeling and repair occur with reversion to the quiescent resting anticoagulant endothelial cell phenotype.

Initiation of Clotting: The Tissue Factor-VIIa Complex

The main initiator of blood coagulation in vivo is the tissue factor (TF)-factor VIIa pathway (Figure 34–2). Tissue factor is a transmembrane protein ubiquitously expressed outside the vasculature, but not normally expressed in an active form within vessels.

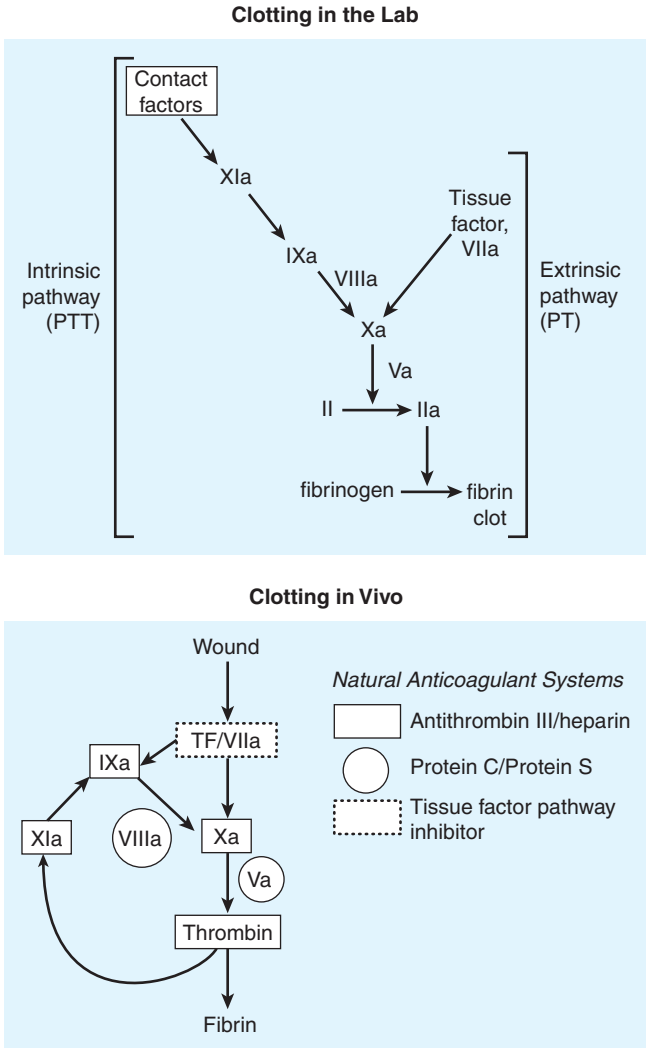

FIGURE 34–2 A model of blood coagulation. With tissue factor (TF), factor VII forms an activated complex (VIIa-TF) that catalyzes the activation of factor IX to factor IXa. Activated factor XIa also catalyzes this reaction. Tissue factor pathway inhibitor (TFPI) inhibits the catalytic action of the VIIa-TF complex. The cascade proceeds as shown, resulting ultimately in the conversion of fibrinogen to fibrin, an essential component of a functional clot. The two major anticoagulant drugs, heparin and warfarin, have very different actions. Heparin, acting in the blood, directly activates anticlotting factors, specifically antithrombin, which inactivates the factors enclosed in rectangles. Warfarin, acting in the liver, inhibits the synthesis of the factors enclosed in circles. Proteins C and S exert anticlotting effects by inactivating activated factors Va and VIIIa.

The exposure of TF on damaged endothelium or to blood that has extravasated into tissue binds TF to factor VIIa. This complex, in turn, activates factors X and IX. Factor Xa along with factor Va forms the prothrombinase complex on activated cell surfaces, which catalyzes the conversion of prothrombin (factor II) to thrombin (factor IIa). Thrombin, in turn, activates upstream clotting factors, primarily factors V, VIII, and XI, resulting in amplification of thrombin generation. The TF-factor VIIa-catalyzed activation of factor Xa is regulated by tissue factor pathway inhibitor (TFPI). Thus after initial activation of factor X to Xa by TF-VIIa, further propagation of the clot is by feedback amplification of thrombin through the intrinsic pathway factors VIII and IX (this provides an explanation of why patients with deficiency of factor VIII or IX—hemophilia A and hemophilia B, respectively—have a severe bleeding disorder).

It is also important to note that the coagulation mechanism in vivo does not occur in solution, but is localized to activated *cell surfaces* expressing anionic phospholipids such as phosphatidylserine, and is mediated by Ca^{2+} bridging between the anionic phospholipids and γ-carboxyglutamic acid residues of the clotting factors. This is the basis for using calcium chelators such as ethylenediamine tetraacetic acid (EDTA) or citrate to prevent blood from clotting in a test tube.

Antithrombin (AT) is an endogenous anticoagulant and a member of the serine protease inhibitor (serpin) family; it inactivates the serine proteases IIa, IXa, Xa, XIa, and XIIa. The endogenous anticoagulants **protein C** and **protein S** attenuate the blood clotting cascade by proteolysis of the two cofactors Va and VIIIa. From an evolutionary standpoint, it is of interest that factors V and VIII have an identical overall domain structure and considerable homology, consistent with a common ancestor gene; likewise the serine proteases are descendants of a trypsin-like common ancestor. Thus, the TF–VIIa initiating complex, serine proteases, and cofactors each have their own lineage-specific attenuation mechanism (Figure 34–2). Defects in natural anticoagulants result in an

TABLE 34–1 Blood clotting factors and drugs that affect them.[1]

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, amino-caproic acid

[1]See Figure 34–2 and text for additional details.

increased risk of venous thrombosis. The most common defect in the natural anticoagulant system is a mutation in factor V (factor V Leiden), which results in resistance to inactivation by the protein C, protein S mechanism.

Fibrinolysis

Fibrinolysis refers to the process of fibrin digestion by the fibrin-specific protease, plasmin. The fibrinolytic system is similar to the coagulation system in that the precursor form of the serine protease plasmin circulates in an inactive form as plasminogen. In response to injury, endothelial cells synthesize and release tissue plasminogen activator (t-PA), which converts plasminogen to plasmin (Figure 34–3). Plasmin remodels the thrombus and limits its extension by proteolytic digestion of fibrin.

Both plasminogen and plasmin have specialized protein domains (kringles) that bind to exposed lysines on the fibrin clot and impart clot specificity to the fibrinolytic process. It should be noted that this clot specificity is only observed at *physiologic* levels of t-PA. At the *pharmacologic* levels of t-PA used in thrombolytic therapy, clot specificity is lost and a systemic lytic state is created, with attendant increase in bleeding risk. As in the coagulation cascade, there are negative regulators of fibrinolysis: endothelial cells synthesize and release plasminogen activator inhibitor (PAI), which inhibits t-PA; in addition α_2 antiplasmin circulates in the blood at high concentrations and under physiologic conditions will rapidly inactivate any plasmin that is not clot-bound. However, this regulatory system is overwhelmed by therapeutic doses of plasminogen activators.

If the coagulation and fibrinolytic systems are pathologically activated, the hemostatic system may careen out of control, leading to generalized intravascular clotting and bleeding. This process is called **disseminated intravascular coagulation (DIC)** and may follow massive tissue injury, advanced cancers, obstetric emergencies such as abruptio placentae or retained products of conception, or bacterial sepsis. The treatment of DIC is to control the underlying disease process; if this is not possible, DIC is often fatal.

Regulation of the fibrinolytic system is useful in therapeutics. Increased fibrinolysis is effective therapy for thrombotic disease. **Tissue plasminogen activator, urokinase,** and **streptokinase** all activate the fibrinolytic system (Figure 34–3). Conversely, decreased fibrinolysis protects clots from lysis and reduces the bleeding of hemostatic failure. **Aminocaproic acid** is a clinically useful inhibitor of fibrinolysis. Heparin and the oral anticoagulant drugs do not affect the fibrinolytic mechanism.

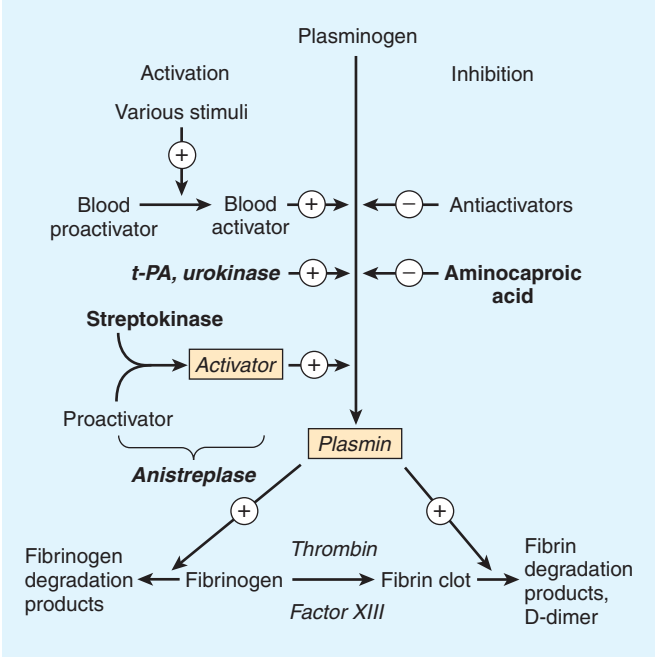

FIGURE 34–3 Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders. t-PA, tissue plasminogen activator.

BASIC PHARMACOLOGY OF THE ANTICOAGULANT DRUGS

The ideal anticoagulant drug would prevent pathologic thrombosis and limit reperfusion injury, yet allow a normal response to vascular injury and limit bleeding. Theoretically this could be accomplished by preservation of the TF-VIIa initiation phase of the clotting mechanism with attenuation of the secondary intrinsic pathway propagation phase of clot development. At this time such a drug does not exist; all anticoagulants and fibrinolytic drugs have an increased bleeding risk as their principle toxicity.

INDIRECT THROMBIN INHIBITORS

The indirect thrombin inhibitors are so-named because their antithrombotic effect is exerted by their interaction with a separate protein, antithrombin. **Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH),** and the synthetic pentasaccharide **fondaparinux** bind to antithrombin and enhance its inactivation of factor Xa (Figure 34–4). Unfractionated heparin and to a lesser extent LMWH also enhance antithrombin's inactivation of thrombin.

HEPARIN

Chemistry & Mechanism of Action

Heparin is a heterogeneous mixture of sulfated mucopolysaccharides. It binds to endothelial cell surfaces and a variety of plasma proteins. Its biologic activity is dependent upon the endogenous anticoagulant **antithrombin**. Antithrombin inhibits clotting factor proteases, especially thrombin (IIa), IXa, and Xa, by forming equimolar stable complexes with them. In the absence of heparin, these reactions are slow; in the presence of heparin, they are

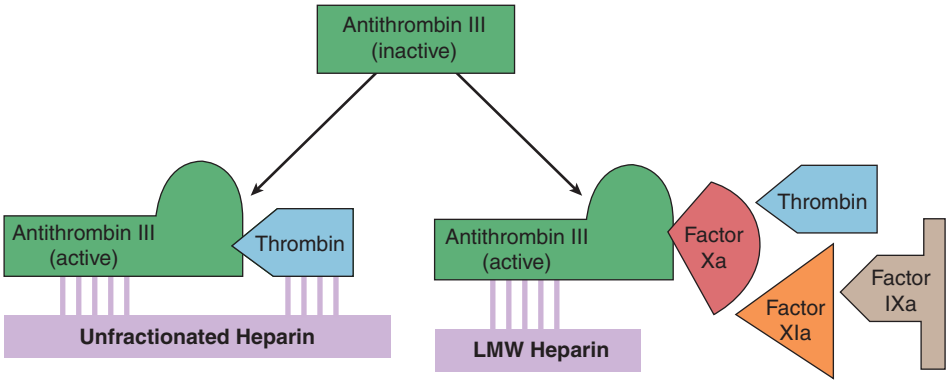

FIGURE 34–4 Cartoon illustrating differences between fondaparinux, low-molecular-weight heparins (LMWH), and high-molecular-weight heparin (HMWH, unfractionated heparin). Activated antithrombin III (AT III) degrades thrombin, factor X, and several other factors. Binding of these drugs to AT III can increase the catalytic action of AT III 1000-fold. The combination of AT III with unfractionated heparin increases degradation of both factor Xa and thrombin. Combination with fondaparinux or LMWH more selectively increases degradation of Xa.

accelerated 1000-fold. Only about a third of the molecules in commercial heparin preparations have an accelerating effect because the remainder lack the unique pentasaccharide sequence needed for high-affinity binding to antithrombin. The active heparin molecules bind tightly to antithrombin and cause a conformational change in this inhibitor. The conformational change of antithrombin exposes its active site for more rapid interaction with the proteases (the activated clotting factors). Heparin functions as a cofactor for the antithrombin-protease reaction without being consumed. Once the antithrombin-protease complex is formed, heparin is released intact for renewed binding to more antithrombin.

The antithrombin binding region of commercial unfractionated heparin consists of repeating sulfated disaccharide units composed of D-glucosamine-L-iduronic acid and D-glucosamine-D-glucuronic acid. High-molecular-weight (HMW), also known as UFH, fractions of heparin with high affinity for antithrombin markedly inhibit blood coagulation by inhibiting all three factors, especially thrombin and factor Xa. Unfractionated heparin has a molecular weight range of 5000–30,000. In contrast, the shorter-chain low-molecular-weight (LMW) fractions of heparin inhibit activated factor X but have less effect on thrombin than the HMW species. Nevertheless, numerous studies have demonstrated that LMW heparins such as **enoxaparin, dalteparin,** and **tinzaparin** are effective in several thromboembolic conditions. In fact, these LMW heparins—in comparison with UFH—have equal efficacy, increased bioavailability from the subcutaneous site of injection, and less frequent dosing requirements (once or twice daily is sufficient).

Because commercial heparin consists of a family of molecules of different molecular weights extracted from porcine intestinal mucosa and bovine lung, the correlation between the concentration of a given heparin preparation and its effect on coagulation often is poor. Therefore, UFH is standardized by bioassay. Heparin was reformulated in 2009 in response to heparin contamination events in 2007 and 2008. The contaminant was identified as over-sulfated chondroitin sulfate and linked to more than150 adverse events in patients, most commonly hypotension, nausea, and dyspnea within 30 minutes of infusion. In response to this event, heparin sodium was reformulated with stricter quality control measures and bioassays to make detection of contaminants easier. This reformulation led to a decrease in potency of approximately 10% from the previous formulation. USP heparin is now harmonized to the World Health Organization International Standard (IS) unit dose. Enoxaparin is obtained from the same sources as regular unfractionated heparin, but doses are specified in milligrams. Dalteparin, tinzaparin, and danaparoid (an LMW heparanoid containing heparan sulfate, dermatan sulfate, and chondroitin sulfate), on the other hand, are specified in anti-factor Xa units.

Monitoring of Heparin Effect

Close monitoring of the **activated partial thromboplastin time (aPTT** or **PTT)** is necessary in patients receiving UFH. Levels of UFH may also be determined by protamine titration (therapeutic levels 0.2–0.4 unit/mL) or anti-Xa units (therapeutic levels 0.3–0.7 unit/mL). Weight-based dosing of the LMW heparins results in predictable pharmacokinetics and plasma levels in patients with normal renal function. Therefore, LMW heparin levels are not generally measured except in the setting of renal insufficiency, obesity, and pregnancy. LMW heparin levels can be determined by anti-Xa units. Peak therapeutic levels should be 0.5–1 unit/mL for twice-daily dosing, determined 4 hours after administration, and approximately 1.5 units/mL for once-daily dosing.

Toxicity

A. Bleeding and Miscellaneous Effects

The major adverse effect of heparin is bleeding. This risk can be decreased by scrupulous patient selection, careful control of dosage, and close monitoring. Elderly women and patients with renal failure are more prone to hemorrhage. Heparin is of animal origin and should be used cautiously in patients with allergy. Increased loss of hair and reversible alopecia have been reported. Long-term heparin therapy is associated with osteoporosis and spontaneous fractures. Heparin accelerates the clearing of postprandial lipemia

by causing the release of lipoprotein lipase from tissues, and long-term use is associated with mineralocorticoid deficiency.

B. Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a systemic hypercoagulable state that occurs in 1–4% of individuals treated with UFH for a minimum of 7 days. Surgical patients are at greatest risk. The reported incidence of HIT is lower in pediatric populations outside the critical care setting and is relatively rare in pregnant women. The risk of HIT may be higher in individuals treated with UFH of bovine origin compared with porcine heparin and is lower in those treated exclusively with LMWH.

Morbidity and mortality in HIT are related to thrombotic events. Venous thrombosis occurs most commonly, but occlusion of peripheral or central arteries is not infrequent. If an indwelling catheter is present, the risk of thrombosis is increased in that extremity. Skin necrosis has been described, particularly in individuals treated with warfarin in the absence of a direct thrombin inhibitor, presumably due to acute depletion of the vitamin K-dependent anticoagulant protein C occurring in the presence of high levels of procoagulant proteins and an active hypercoagulable state.

The following points should be considered in all patients receiving heparin: Platelet counts should be performed frequently; thrombocytopenia appearing in a time frame consistent with an immune response to heparin should be considered suspicious for HIT; and any new thrombus occurring in a patient receiving heparin therapy should raise suspicion of HIT. Patients who develop HIT are treated by discontinuance of heparin and administration of a direct thrombin inhibitor.

Contraindications

Heparin is contraindicated in patients with HIT, hypersensitivity to the drug, active bleeding, hemophilia, significant thrombocytopenia, purpura, severe hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, ulcerative lesions of the gastrointestinal tract, threatened abortion, visceral carcinoma, or advanced hepatic or renal disease. Heparin should be avoided in patients who have recently had surgery of the brain, spinal cord, or eye, and in patients who are undergoing lumbar puncture or regional anesthetic block. Despite the apparent lack of placental transfer, heparin should be used in pregnant women only when clearly indicated.

Administration & Dosage

The indications for the use of heparin are described in the section on clinical pharmacology. A plasma concentration of heparin of 0.2–0.4 unit/mL (by protamine titration) or 0.3–0.7 unit/mL (anti-Xa units) usually prevents pulmonary emboli in patients with established venous thrombosis. This concentration generally corresponds to a PTT of 2–3 times baseline. However, the use of the PTT for heparin monitoring is problematic. There is no standardization scheme for the PTT as there is for the prothrombin time (PT) and its international normalized ratio (INR). Currently more than 300 reagent-instrument combinations are in use, and the actual ratios required to obtain an anti-Xa activity of 0.3–0.7 units/mL are variable, ranging from 1.6 to 6 times control PTT. Thus, if the PTT is used for monitoring, the laboratory should determine the clotting time that corresponds to the therapeutic range by protamine titration or anti-Xa activity, as listed above.

In addition, some patients have a prolonged baseline PTT due to factor deficiency or inhibitors (which could increase bleeding risk) or lupus anticoagulant (which is not associated with bleeding risk but may be associated with thrombosis risk). Using the PTT to assess heparin effect in such patients is very difficult. An alternative is to use anti-Xa activity to assess heparin concentration, a test now widely available on automated coagulation instruments. This approach more accurately measures the heparin concentration; however, it does not provide the global assessment of intrinsic pathway integrity of the PTT.

The following strategy is recommended: prior to initiating anticoagulant therapy of any type, the integrity of the patient's hemostatic system should be assessed by a careful history of prior bleeding events, and baseline PT and PTT. If there is a prolonged clotting time, the cause of this (deficiency or inhibitor) should be determined prior to initiating therapy, and treatment goals stratified to a risk-benefit assessment. In high-risk patients measuring both the PTT and anti-Xa activity may be useful. When *intermittent* heparin administration is used, the aPTT or anti-Xa activity should be measured 6 hours after the administered dose to maintain prolongation of the aPTT to 2–2.5 times that of the control value. However, LMW heparin therapy is the preferred option in this case, as no monitoring is required in most patients.

Continuous intravenous administration of heparin is accomplished via an infusion pump. After an initial bolus injection of 80–100 units/kg, a continuous infusion of about 15–22 units/kg/h is required to maintain the anti-Xa activity in the range of 0.3–0.7 units/mL. Low-dose prophylaxis is achieved with subcutaneous administration of heparin, 5000 units every 8–12 hours. Because of the danger of hematoma formation at the injection site, heparin must never be administered intramuscularly.

Prophylactic enoxaparin is given subcutaneously in a dosage of 30 mg twice daily or 40 mg once daily. Full-dose enoxaparin therapy is 1 mg/kg subcutaneously every 12 hours. This corresponds to a therapeutic anti-factor Xa level of 0.5–1 unit/mL. Selected patients may be treated with enoxaparin 1.5 mg/kg once a day, with a target anti-Xa level of 1.5 units/mL. The prophylactic dose of dalteparin is 5000 units subcutaneously once a day; therapeutic dosing is 200 units/kg once a day for venous disease or 120 units/kg every 12 hours for acute coronary syndrome. LMWH should be used with caution in patients with renal insufficiency or body weight greater than 150 kg. Measurement of the anti-Xa level is useful to guide dosing in these individuals.

The synthetic pentasaccharide molecule **fondaparinux** (Figure 34–4) avidly binds antithrombin with high specific activity, resulting in efficient inactivation of factor Xa. Fondaparinux has a long half-life of 15 hours, allowing for once-daily dosing by subcutaneous administration. Fondaparinux is effective in the

prevention and treatment of venous thromboembolism, and appears to not cross-react with pathologic HIT antibodies in most individuals. The use of fondaparinux as an alternative anticoagulant in HIT is currently being tested in clinical trials.

A major focus of drug development has been to develop orally active anticoagulants that do not require monitoring. **Rivaroxaban** is the first oral factor Xa inhibitor to reach phase III clinical trials. The safety and efficacy of rivaroxaban appears to be at least equivalent, and possibly superior, to LMW heparins (see below).

Reversal of Heparin Action

Excessive anticoagulant action of heparin is treated by discontinuance of the drug. If bleeding occurs, administration of a specific antagonist such as **protamine sulfate** is indicated. Protamine is a highly basic, positively charged peptide that combines with negatively charged heparin as an ion pair to form a stable complex devoid of anticoagulant activity. For every 100 units of heparin remaining in the patient, 1 mg of protamine sulfate is given intravenously; the rate of infusion should not exceed 50 mg in any 10-minute period. Excess protamine must be avoided; it also has an anticoagulant effect. Neutralization of LMW heparin by protamine is incomplete. Limited experience suggests that 1 mg of protamine sulfate may be used to partially neutralize 1 mg of enoxaparin. Protamine will not reverse the activity of fondaparinux. Excess danaparoid can be removed by plasmapheresis.

ORAL DIRECT FACTOR XA INHIBITORS

Oral Xa inhibitors, including rivaroxaban and apixaban, are approved or in advanced stages of development and along with oral thrombin inhibitors (discussed below) are likely to have a major impact on antithrombotic pharmacotherapy. These drugs inhibit factor Xa, in the final common pathway of clotting (see Figure 34–2). These drugs are given as fixed doses and do not require monitoring. They have a rapid onset of action and shorter half-lives than warfarin (approximately 10 hours but half-life may be prolonged in elderly patients or those with renal impairment).

Rivaroxaban is approved for prevention of venous thromboembolism following hip or knee surgery. The prophylactic dose is 10 mg orally per day. A recent large randomized clinical trial of DVT treatment compared a higher dose of rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg daily) to a standard treatment regimen of enoxaparin followed by warfarin. This trial demonstrated non-inferiority of rivaroxaban in preventing recurrent venous thromboembolism and showed no difference in bleeding risk. Another trial reported non-inferiority of rivaroxaban to warfarin for prevention of stroke in patients with atrial fibrillation.

Apixaban is currently in clinical development. A recent study of patients undergoing total hip replacement compared apixaban 2.5 mg orally once per day with enoxaparin 40 mg subcutaneously once per day. This trial demonstrated the apixaban arm had lower rates of venous thromboembolism and similar bleeding rates. Another multicenter study randomized patients with recent myocardial infarction to apixaban 5 mg or placebo. This trial was stopped early because of an increase in bleeding risk without a significant decrease in ischemic events. Another trial comparing apixaban to aspirin for stroke prevention in atrial fibrillation was stopped early because of evidence of increased efficacy in the apixaban arm.

Thus, it appears that the primary target populations for development of both rivaroxaban and apixaban will be prevention and treatment of patients with venous thromboembolism and stroke prevention in patients with atrial fibrillation. Both of these drugs are excreted in part by the kidneys; therefore, the dosage may need to be reduced in patients with renal impairment. In such patients, use of a hepatically metabolized drug such as warfarin may be a better alternative. No antidotes exist for direct Xa inhibitors.

DIRECT THROMBIN INHIBITORS

The direct thrombin inhibitors (DTIs) exert their anticoagulant effect by directly binding to the active site of thrombin, thereby inhibiting thrombin's downstream effects. This is in contrast to indirect thrombin inhibitors such as heparin and LMWH (see above), which act through antithrombin. **Hirudin** and **bivalirudin** are bivalent DTIs in that they bind at both the catalytic or active site of thrombin as well as at a substrate recognition site. **Argatroban** and **melagatran** are small molecules that bind only at the thrombin active site.

PARENTERAL DIRECT THROMBIN INHIBITORS

Leeches have been used for bloodletting since the age of Hippocrates. More recently, surgeons have used medicinal leeches (*Hirudo medicinalis*) to prevent thrombosis in the fine vessels of reattached digits. **Hirudin** is a specific, irreversible thrombin inhibitor from leech saliva that is now available in recombinant form as **lepirudin.** Its action is independent of antithrombin, which means it can reach and inactivate fibrin-bound thrombin in thrombi. Lepirudin has little effect on platelets or the bleeding time. Like heparin, it must be administered parenterally and is monitored by the aPTT. Lepirudin is approved by the FDA for use in patients with thrombosis related to heparin-induced thrombocytopenia. Lepirudin is excreted by the kidney and should be used with great caution in patients with renal insufficiency as no antidote exists. Up to 40% of patients who receive long-term infusions develop an antibody directed against the thrombin-lepirudin complex. These antigen-antibody complexes are not cleared by the kidney and may result in an enhanced anticoagulant effect. Some patients re-exposed to the drug have developed life-threatening anaphylactic reactions.

Bivalirudin, another bivalent inhibitor of thrombin, is administered intravenously, with a rapid onset and offset of action. The drug has a short half-life with clearance that is 20% renal and the

remainder metabolic. Bivalirudin also inhibits platelet activation and has been FDA-approved for use in percutaneous coronary angioplasty.

Argatroban is a small molecule thrombin inhibitor that is FDA-approved for use in patients with HIT with or without thrombosis and coronary angioplasty in patients with HIT. It, too, has a short half-life, is given by continuous intravenous infusion, and is monitored by aPTT. Its clearance is not affected by renal disease but is dependent on liver function; dose reduction is required in patients with liver disease. Patients on argatroban will demonstrate elevated INRs, rendering the transition to warfarin difficult (ie, the INR will reflect contributions from both warfarin and argatroban). (INR is discussed in detail in the discussion of warfarin administration.) A nomogram is supplied by the manufacturer to assist in this transition. No properly designed head-to-head trials have been performed to determine whether argatroban or lepirudin is superior in the treatment of HIT. However, in practice, the choice of which DTI to use in a patient with HIT is usually dictated by the condition of the clearing organ. If the patient has severe renal insufficiency, then argatroban would be preferred. If there is severe hepatic insufficiency, then lepirudin would be a better choice.

ORAL DIRECT THROMBIN INHIBITORS

Advantages of oral direct thrombin inhibitors include predictable pharmacokinetics and bioavailability, which allow for fixed dosing and predictable anticoagulant response, and make routine coagulation monitoring unnecessary. In addition, these agents do not interact with P450-interacting drugs, and their rapid onset and offset of action allow for immediate anticoagulation, thus avoiding the need for overlap with additional anticoagulant drugs.

Dabigatran etexilate mesylate is the first oral direct thrombin inhibitor approved by the FDA. Dabigatran was approved in 2010 to reduce risk of stroke and systemic embolism with nonvalvular atrial fibrillation. In the EU, dabigatran is approved for prevention of venous thromboembolism in patients who have undergone hip or knee replacement surgery. The pivotal trial leading to FDA approval was a study of > 18,000 patients with nonvalvular atrial fibrillation and at least one other defined risk factor. Dabigatran at a dose of 150 mg bid was shown to be superior to warfarin with an INR target of 2–3 in preventing stroke and systemic embolization.

Pharmacology

Dabigatran and its metabolites are direct thrombin inhibitors. Following oral administration, dabigatran etexilate mesylate is converted to dabigatran. The oral bioavailability is 3–7% in normal volunteers. The drug is a substrate for the P-glycoprotein efflux pump; however, P-glycoprotein inhibitors or inducers do not have a significant effect on drug clearance. Concomitant use of ketoconazole, amiodarone, quinidine, and clopidogrel increases the effect of dabigatran. The half-life of the drug in normal volunteers is 12–17 hours. Renal impairment results in prolonged drug clearance and may require dose adjustment; the drug should be avoided in patients with severe renal impairment.

Administration & Dosage

For prevention of stroke and systemic embolism in nonvalvular atrial fibrillation, 150 mg should be given bid to patients with creatinine clearance > 30 mL/min. For decreased creatinine clearance of 15–30 mL/min, the dose is 75 mg bid. No monitoring is required. Dabigatran will prolong the PTT and thrombin time, which can be used to estimate drug effect if necessary.

Toxicity

As with any anticoagulant drug, the primary toxicity of dabigatran is bleeding. In the RE-LY study, there was an increase in gastrointestinal adverse reactions and gastrointestinal bleeding compared to warfarin. There was also a trend toward increased bleeding with dabigatran in patients older than 75 years. There is no antidote for dabigatran. In a drug overdose situation, it is important to maintain renal function or dialyze if necessary. Use of recombinant factor VIIa or prothrombin complex concentrates may be considered as an unproven, off-label use in cases of life-threatening bleeding associated with dabigatran use.

Oral direct thrombin inhibitors and oral direct Xa inhibitors offer significant advantages over warfarin (discussed next), which has a narrow therapeutic window, is affected by diet and many drugs, and requires monitoring for dosage adjustment. It appears that the oral anti-Xa drugs and oral direct thrombin inhibitors are poised to challenge warfarin's dominance in the prevention and therapy of thrombotic disease.

WARFARIN & OTHER COUMARIN ANTICOAGULANTS

Chemistry & Pharmacokinetics

The clinical use of the coumarin anticoagulants began with the discovery of an anticoagulant substance formed in spoiled sweet clover silage which caused hemorrhagic disease in cattle. At the behest of local farmers, a chemist at the University of Wisconsin identified the toxic agent as bishydroxycoumarin. A synthesized derivative, dicumarol and its congeners, most notably warfarin (**W**isconsin **A**lumni **R**esearch **F**oundation, with "arin" from coumarin added; Figure 34–5), were initially used as rodenticides. In the 1950s warfarin (under the brand name Coumadin) was introduced as an antithrombotic agent in humans. Warfarin is one of the most commonly prescribed drugs, used by approximately 1.5 million individuals, and several studies have indicated that the drug is significantly underused in clinical situations where it has proven benefit.

Warfarin is generally administered as the sodium salt and has 100% bioavailability. Over 99% of racemic warfarin is bound to plasma albumin, which may contribute to its small volume of distribution (the albumin space), its long half-life in plasma (36 hours), and the lack of urinary excretion of unchanged drug. Warfarin used

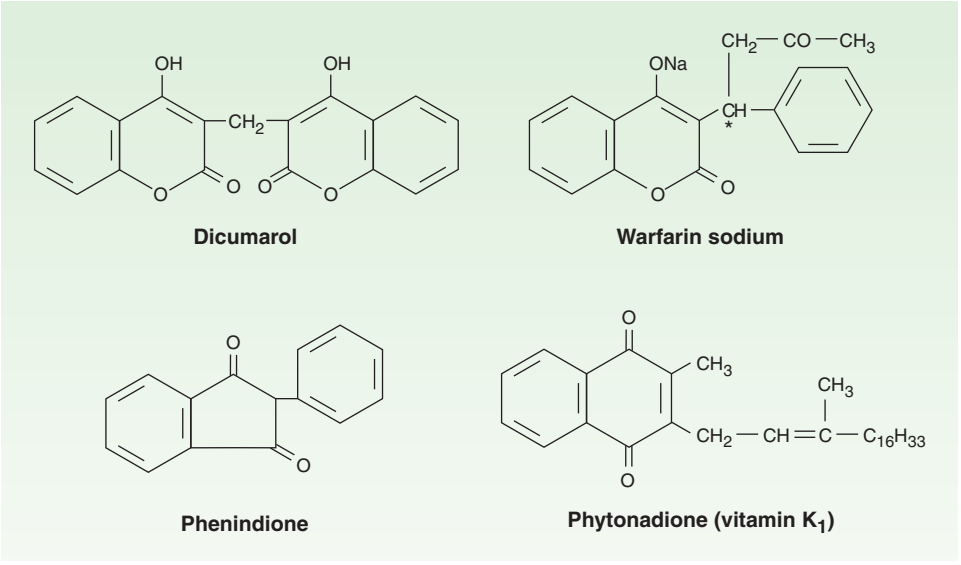

FIGURE 34–5 Structural formulas of several oral anticoagulant drugs and of vitamin K. The carbon atom of warfarin shown at the asterisk is an asymmetric center.

clinically is a racemic mixture composed of equal amounts of two enantiomorphs. The levorotatory *S*-warfarin is four times more potent than the dextrorotatory *R*-warfarin. This observation is useful in understanding the stereoselective nature of several drug interactions involving warfarin.

Mechanism of Action

Coumarin anticoagulants block the γ-carboxylation of several glutamate residues in prothrombin and factors VII, IX, and X as well as the endogenous anticoagulant proteins C and S (Figure 34–2, Table 34–1). The blockade results in incomplete coagulation factor molecules that are biologically inactive. The protein carboxylation reaction is coupled to the oxidation of vitamin K. The vitamin must then be reduced to reactivate it. Warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form (Figure 34–6). Mutational change of the responsible enzyme, vitamin K epoxide reductase, can give rise to genetic resistance to warfarin in humans and especially in rats.

There is an 8- to 12-hour delay in the action of warfarin. Its anticoagulant effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K-dependent clotting factors. The resulting inhibition of coagulation is dependent on their degradation half-lives in the circulation. These half-lives are 6, 24, 40, and 60 hours for factors VII, IX, X, and II, respectively. Larger initial doses of warfarin—up to about 0.75 mg/kg—hasten the onset of the anticoagulant effect. Beyond this dosage, the speed of onset is independent of the dose size. The only effect of a larger loading dose is to prolong the time that the plasma concentration of drug remains above that required for suppression of clotting factor synthesis. The only difference among oral anticoagulants in producing and maintaining hypoprothrombinemia is the half-life of each drug.

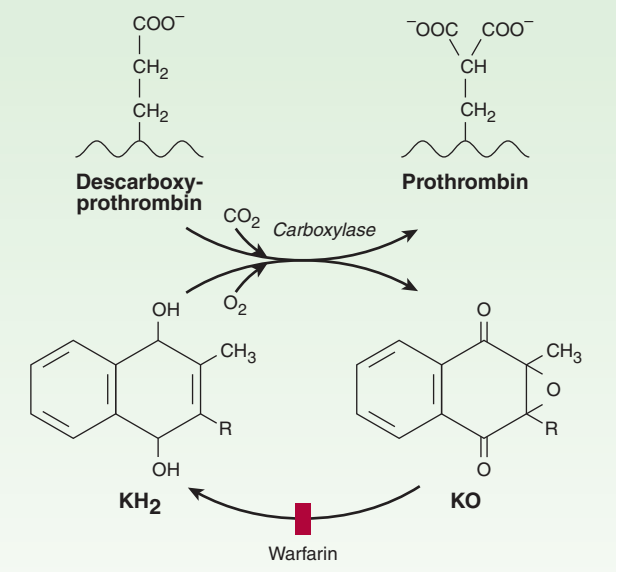

FIGURE 34–6 Vitamin K cycle—metabolic interconversions of vitamin K associated with the synthesis of vitamin K–dependent clotting factors. Vitamin K_1 or K_2 is activated by reduction to the hydroquinone form (KH_2). Stepwise oxidation to vitamin K epoxide (KO) is coupled to prothrombin carboxylation by the enzyme carboxylase. The reactivation of vitamin K epoxide is the warfarin-sensitive step (warfarin). The R on the vitamin K molecule represents a 20-carbon phytyl side chain in vitamin K_1 and a 30- to 65-carbon polyprenyl side chain in vitamin K_2.

Toxicity

Warfarin crosses the placenta readily and can cause a hemorrhagic disorder in the fetus. Furthermore, fetal proteins with γ-carboxyglutamate residues found in bone and blood may be affected by warfarin; the drug can cause a serious birth defect

characterized by abnormal bone formation. Thus, warfarin should never be administered during pregnancy. Cutaneous necrosis with reduced activity of protein C sometimes occurs during the first weeks of therapy. Rarely, the same process causes frank infarction of the breast, fatty tissues, intestine, and extremities. The pathologic lesion associated with the hemorrhagic infarction is venous thrombosis, suggesting that it is caused by warfarin-induced depression of protein C synthesis.

Administration & Dosage

Treatment with warfarin should be initiated with standard doses of 5–10 mg rather than the large loading doses formerly used. The initial adjustment of the prothrombin time takes about 1 week, which usually results in a maintenance dose of 5–7 mg/d. The **prothrombin time (PT)** should be increased to a level representing a reduction of prothrombin activity to 25% of normal and maintained there for long-term therapy. When the activity is less than 20%, the warfarin dosage should be reduced or omitted until the activity rises above 20%.

The therapeutic range for oral anticoagulant therapy is defined in terms of an international normalized ratio (INR). The INR is the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for lab)^{ISI}, where the ISI exponent refers to the International Sensitivity Index, and is dependent on the specific reagents and instruments used for the determination. The ISI serves to relate measured prothrombin times to a World Health Organization reference standard thromboplastin; thus the prothrombin times performed on different properly calibrated instruments with a variety of thromboplastin reagents should give the same INR results for a given sample. For most reagent and instrument combinations in current use, the ISI is close to 1, making the INR roughly the ratio of the patient prothrombin time to the mean normal prothrombin time. The recommended INR for prophylaxis and treatment of thrombotic disease is 2–3. Patients with some types of artificial heart valves (eg, tilting disk) or other medical conditions increasing thrombotic risk have a recommended range of 2.5–3.5.

Occasionally patients exhibit warfarin resistance, defined as progression or recurrence of a thrombotic event while in the therapeutic range. These individuals may have their INR target raised (which is accompanied by an increase in bleeding risk) or be changed to an alternative form of anticoagulation (eg, daily injections of LMWH). Warfarin resistance is most commonly seen in patients with advanced cancers, typically of gastrointestinal origin (Trousseau's syndrome). A recent study has demonstrated the superiority of LMWH over warfarin in preventing recurrent venous thromboembolism in patients with cancer.

Drug Interactions

The oral anticoagulants often interact with other drugs and with disease states. These interactions can be broadly divided into pharmacokinetic and pharmacodynamic effects (Table 34–2). Pharmacokinetic mechanisms for drug interaction with oral anticoagulants are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. Pharmacodynamic mechanisms for interactions with warfarin are synergism (impaired hemostasis, reduced clotting factor synthesis, as in hepatic disease), competitive antagonism (vitamin K), and an altered physiologic control loop for vitamin K (hereditary resistance to oral anticoagulants).

The most serious interactions with warfarin are those that increase the anticoagulant effect and the risk of bleeding. The most dangerous of these interactions are the pharmacokinetic interactions with the mostly obsolete pyrazolones phenylbutazone and sulfinpyrazone. These drugs not only augment the hypoprothrombinemia but also inhibit platelet function and may induce peptic ulcer disease (see Chapter 36). The mechanisms for their hypoprothrombinemic interaction are a stereoselective inhibition of oxidative metabolic transformation of *S*-warfarin (the more potent isomer) and displacement of albumin-bound warfarin, increasing the free fraction. For this and other reasons, neither phenylbutazone nor sulfinpyrazone is in common use in the USA. Metronidazole, fluconazole, and trimethoprim-sulfamethoxazole also stereoselectively inhibit the

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	***Pharmacodynamic***	***Pharmacokinetic***	***Pharmacodynamic***
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

[1]Stereoselectively inhibits the oxidative metabolism of the *S*-warfarin enantiomorph of racemic warfarin.

metabolic transformation of *S*-warfarin, whereas amiodarone, disulfiram, and cimetidine inhibit metabolism of both enantiomorphs of warfarin. Aspirin, hepatic disease, and hyperthyroidism augment warfarin's effects—aspirin by its effect on platelet function and the latter two by increasing the turnover rate of clotting factors. The third-generation cephalosporins eliminate the bacteria in the intestinal tract that produce vitamin K and, like warfarin, also directly inhibit vitamin K epoxide reductase.

Barbiturates and rifampin cause a marked *decrease* of the anticoagulant effect by induction of the hepatic enzymes that transform racemic warfarin. Cholestyramine binds warfarin in the intestine and reduces its absorption and bioavailability.

Pharmacodynamic reductions of anticoagulant effect occur with vitamin K (increased synthesis of clotting factors), the diuretics chlorthalidone and spironolactone (clotting factor concentration), hereditary resistance (mutation of vitamin K reactivation cycle molecules), and hypothyroidism (decreased turnover rate of clotting factors).

Drugs with *no* significant effect on anticoagulant therapy include ethanol, phenothiazines, benzodiazepines, acetaminophen, opioids, indomethacin, and most antibiotics.

Reversal of Warfarin Action

Excessive anticoagulant effect and bleeding from warfarin can be reversed by stopping the drug and administering oral or parenteral vitamin K_1 (phytonadione), fresh-frozen plasma, prothrombin complex concentrates such as Bebulin and Proplex T, and recombinant factor VIIa (rFVIIa). The disappearance of excessive effect is not correlated with plasma warfarin concentrations but rather with re-establishment of normal activity of the clotting factors. A modest excess of anticoagulant effect without bleeding may require no more than cessation of the drug. The warfarin effect can be rapidly reversed in the setting of severe bleeding with the administration of prothrombin complex or rFVIIa coupled with intravenous vitamin K. It is important to note that due to the long half-life of warfarin, a single dose of vitamin K or rFVIIa may not be sufficient.

BASIC PHARMACOLOGY OF THE FIBRINOLYTIC DRUGS

Fibrinolytic drugs rapidly lyse thrombi by catalyzing the formation of the serine protease **plasmin** from its precursor zymogen, plasminogen (Figure 34–3). These drugs create a generalized lytic state when administered intravenously. Thus, both protective hemostatic thrombi and target thromboemboli are broken down. The Box: Thrombolytic Drugs for Acute Myocardial Infarction describes the use of these drugs in one major application.

Pharmacology

Streptokinase is a protein (but not an enzyme in itself) synthesized by streptococci that combines with the proactivator plasminogen. This enzymatic complex catalyzes the conversion of inactive plasminogen to active plasmin. **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin. Plasmin itself cannot be used because naturally occurring inhibitors in plasma prevent its effects. However, the absence of inhibitors for urokinase and the streptokinase-proactivator complex permits their use clinically. Plasmin formed inside a thrombus by these activators is protected from plasma antiplasmins, which allows it to lyse the thrombus from within.

Thrombolytic Drugs for Acute Myocardial Infarction

The paradigm shift in 1980 on the causation of acute myocardial infarction to acute coronary occlusion by a thrombus created the rationale for thrombolytic therapy of this common lethal disease. At that time—and for the first time—intravenous thrombolytic therapy for acute myocardial infarction in the European Cooperative Study Group trial was found to reduce mortality significantly. Later studies, with thousands of patients in each trial, provided enough statistical power for the 20% reduction in mortality to be considered statistically significant. Although the standard of care in areas with adequate facilities and experience in percutaneous coronary intervention (PCI) now favors catheterization and placement of a stent, thrombolytic therapy is still very important where PCI is not readily available.

The proper selection of patients for thrombolytic therapy is critical. The diagnosis of acute myocardial infarction is made clinically and is confirmed by electrocardiography. Patients with ST-segment elevation and bundle branch block on electrocardiography have the best outcomes. All trials to date show the greatest benefit for thrombolytic therapy when it is given early, within 6 hours after symptomatic onset of acute myocardial infarction.

Thrombolytic drugs reduce the mortality of acute myocardial infarction. The early and appropriate use of any thrombolytic drug probably transcends possible advantages of a particular drug. Adjunctive drugs such as aspirin, heparin, β blockers, and angiotensin-converting enzyme (ACE) inhibitors reduce mortality even further. The principles of management are outlined in Antman, et al, 2008 (see References).

Anistreplase (anisoylated plasminogen streptokinase activator complex; APSAC) consists of a complex of purified human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme's active site. When administered, the acyl group spontaneously hydrolyzes, freeing the activated streptokinase-proactivator complex. This product (now discontinued in the USA) allows for rapid intravenous injection, greater clot selectivity (ie, more activity on plasminogen associated with clots than on free plasminogen in the blood), and more thrombolytic activity.

Plasminogen can also be activated endogenously by **tissue plasminogen activators (t-PAs).** These activators preferentially activate plasminogen that is bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus and avoids systemic activation. Human t-PA is manufactured as **alteplase** by means of recombinant DNA technology. **Reteplase** is another recombinant human t-PA from which several amino acid sequences have been deleted. Reteplase is less expensive to produce than t-PA. Because it lacks the major fibrin-binding domain, reteplase is less fibrin-specific than t-PA. **Tenecteplase** is a mutant form of t-PA that has a longer half-life, and it can be given as an intravenous bolus. Tenecteplase is slightly more fibrin-specific than t-PA.

Indications & Dosage

Administration of fibrinolytic drugs by the intravenous route is indicated in cases of **pulmonary embolism with hemodynamic instability,** severe **deep venous thrombosis** such as the superior vena caval syndrome, and **ascending thrombophlebitis** of the iliofemoral vein with severe lower extremity edema. These drugs are also given intra-arterially, especially for peripheral vascular disease.

Thrombolytic therapy in the management of **acute myocardial infarction** requires careful patient selection, the use of a specific thrombolytic agent, and the benefit of adjuvant therapy. Streptokinase is administered by intravenous infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24–72 hours. Patients with antistreptococcal antibodies can develop fever, allergic reactions, and therapeutic resistance. Urokinase requires a loading dose of 300,000 units given over 10 minutes and a maintenance dose of 300,000 units/h for 12 hours. Alteplase (t-PA) is given by intravenous infusion of 60 mg over the first hour and then 40 mg at a rate of 20 mg/h. Reteplase is given as two intravenous bolus injections of 10 units each, separated by 30 minutes. Tenecteplase is given as a single intravenous bolus of 0.5 mg/kg. Anistreplase (where available) is given as a single intravenous injection of 30 units over 3–5 minutes. A single course of fibrinolytic drugs is expensive: hundreds of dollars for streptokinase and thousands for urokinase and t-PA.

Recombinant t-PA has also been approved for use in acute ischemic stroke within 3 hours of symptom onset. In patients without hemorrhagic infarct or other contraindications, this therapy has been demonstrated to provide better outcomes in several randomized clinical trials. The recommended dose is 0.9 mg/kg, not to exceed 90 mg, with 10% given as a bolus and the remainder during a 1 hour infusion. Streptokinase has been associated with increased bleeding risk in acute ischemic stroke when given at a dose of 1.5 million units, and its use is not recommended in this setting.

BASIC PHARMACOLOGY OF ANTIPLATELET AGENTS

Platelet function is regulated by three categories of substances. The first group consists of agents generated outside the platelet that interact with platelet membrane receptors, eg, catecholamines, collagen, thrombin, and prostacyclin. The second category contains agents generated within the platelet that interact with membrane receptors, eg, ADP, prostaglandin D_2, prostaglandin E_2, and serotonin. The third group comprises agents generated within the platelet that act within the platelet, eg, prostaglandin endoperoxides and thromboxane A_2, the cyclic nucleotides cAMP and cGMP, and calcium ion. From this list of agents, several targets for platelet inhibitory drugs have been identified (Figure 34–1): inhibition of prostaglandin synthesis (aspirin), inhibition of ADP-induced platelet aggregation (clopidogrel, prasugrel, ticlopidine), and blockade of glycoprotein IIb/IIIa receptors on platelets (abciximab, tirofiban, and eptifibatide). Dipyridamole and cilostazol are additional antiplatelet drugs.

ASPIRIN

The prostaglandin **thromboxane A_2** is an arachidonate product that causes platelets to change shape, release their granules, and aggregate (see Chapter 18). Drugs that antagonize this pathway interfere with platelet aggregation in vitro and prolong the bleeding time in vivo. Aspirin is the prototype of this class of drugs.

As described in Chapter 18, aspirin inhibits the synthesis of thromboxane A_2 by irreversible acetylation of the enzyme cyclooxygenase. Other salicylates and nonsteroidal anti-inflammatory drugs also inhibit cyclooxygenase but have a shorter duration of inhibitory action because they cannot acetylate cyclooxygenase; that is, their action is reversible.

The FDA has approved the use of 325 mg/d aspirin for *primary* prophylaxis of myocardial infarction but urges caution in this use of aspirin by the general population except when prescribed as an adjunct to risk factor management by smoking cessation and lowering of blood cholesterol and blood pressure. Meta-analysis of many published trials of aspirin and other antiplatelet agents confirms the value of this intervention in the *secondary* prevention of vascular events among patients with a history of vascular events.

TICLOPIDINE, CLOPIDOGREL, & PRASUGREL

Ticlopidine, clopidogrel, and prasugrel reduce platelet aggregation by inhibiting the ADP pathway of platelets. These drugs irreversibly block the ADP receptor on platelets. Unlike aspirin, these drugs have no effect on prostaglandin metabolism. Use of ticlopidine, clopidogrel, or prasugrel to prevent thrombosis is now considered standard practice in patients undergoing placement of a coronary stent. As the indications and adverse effects of these drugs are different, they will be considered individually.

Ticlopidine is approved for prevention of stroke in patients with a history of a transient ischemic attack (TIA) or thrombotic stroke, and in combination with aspirin for prevention of coronary stent thrombosis. Adverse effects of ticlopidine include nausea, dyspepsia, and diarrhea in up to 20% of patients, hemorrhage in 5%, and, most seriously, leukopenia in 1%. The leukopenia is detected by regular monitoring of the white blood cell count during the first 3 months of treatment. Development of thrombotic thrombocytopenic purpura has also been associated with the ingestion of ticlopidine. The dosage of ticlopidine is 250 mg twice daily. Because of the significant side effect profile, the use of ticlopidine for stroke prevention should be restricted to those who are intolerant of or have failed aspirin therapy. Doses of ticlopidine less than 500 mg/d may be efficacious with fewer adverse effects.

Clopidogrel is approved for patients with unstable angina or non-ST-elevation acute myocardial infarction (NSTEMI) in combination with aspirin; for patients with ST-elevation myocardial infarction (STEMI); or recent myocardial infarction, stroke, or established peripheral arterial disease. For NSTEMI, the dosage is a 300 mg loading dose followed by 75 mg daily of clopidogrel, with a daily aspirin dose of 75–325 mg. For patients with STEMI, the dose is 75 mg daily of clopidogrel, in association with aspirin as above; and for recent myocardial infarction, stroke, or peripheral vascular disease, the dose is 75 mg/d.

Clopidogrel has fewer adverse effects than ticlopidine and is rarely associated with neutropenia. Thrombotic thrombocytopenic purpura has been reported. Because of its superior side effect profile and dosing requirements, clopidogrel is frequently preferred over ticlopidine. The antithrombotic effects of clopidogrel are dose-dependent; within 5 hours after an oral loading dose of 300 mg, 80% of platelet activity will be inhibited. The maintenance dose of clopidogrel is 75 mg/d, which achieves maximum platelet inhibition. The duration of the antiplatelet effect is 7–10 days. Clopidogrel is a prodrug that requires activation via the cytochrome P450 enzyme isoform CYP2C19. Depending on the single nucleotide polymorphism inheritance pattern in CYP2C19, individuals may be poor metabolizers of clopidogrel, and these patients may be at increased risk of cardiovascular events due to inadequate drug effect. The FDA has recommended CYP2C19 genotyping to identify such patients and advises prescribers to consider alternative therapies in poor metabolizers. However, more recent studies have questioned the impact of CYP2C19 metabolizer status on outcomes. Drugs that impair CYP2C19 function, such as omeprazole, should be used with caution pending clarification of the importance of CYP2C19 status.

Prasugrel, similar to clopidogrel, is approved for patients with acute coronary syndromes. The drug is given as a 60-mg loading dose and then 10 mg/d in combination with aspirin as outlined for clopidogrel. The Trial to assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI38) compared prasugrel with clopidogrel in a randomized, double-blind trial with aspirin and other standard therapies managed with percutaneous coronary interventions. This trial showed a reduction in the primary composite cardiovascular endpoint (cardiovascular death, nonfatal stroke or nonfatal myocardial infarction) for prasugrel in comparison with clopidogrel. However, the major and minor bleeding risk was increased with prasugrel. Prasugrel is contraindicated in patients with history of TIA or stroke because of increased bleeding risk. Although cytochrome P450 genotype status is an issue with clopidogrel, it does not have an impact on the use of prasugrel.

Aspirin & Clopidogrel Resistance

The reported incidence of resistance to these drugs varies greatly, from less than 5% to 75%. In part this tremendous variation in incidence reflects the definition of resistance (recurrent thrombosis while on antiplatelet therapy vs in vitro testing), methods by which drug response is measured, and patient compliance. Several methods for testing aspirin and clopidogrel resistance in vitro are now FDA-approved. However, the incidence of drug resistance varies considerably by testing method. These tests may be useful in selected patients to assess compliance or the cause of a recurrent thrombotic event, but their utility in routine clinical decision making outside of clinical trials remains controversial.

BLOCKADE OF PLATELET GLYCOPROTEIN IIB/IIIA RECEPTORS

The glycoprotein IIb/IIIa inhibitors are used in patients with acute coronary syndromes. These drugs target the platelet IIb/IIIa receptor complex (Figure 34–1). The IIb/IIIa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common pathway" for platelet aggregation. There are approximately 50,000 copies of this complex on the surface of each platelet. Persons lacking this receptor have a bleeding disorder called Glanzmann's thrombasthenia.

Abciximab, a chimeric monoclonal antibody directed against the IIb/IIIa complex including the vitronectin receptor, was the first agent approved in this class of drugs. It has been approved for use in percutaneous coronary intervention and in acute coronary syndromes. **Eptifibatide** is an analog of the sequence at the extreme carboxyl terminal of the delta chain of fibrinogen, which mediates the binding of fibrinogen to the receptor. **Tirofiban** is a smaller molecule with similar properties. Eptifibatide and tirofiban inhibit ligand binding to the IIb/IIIa receptor by their occupancy of the receptor but do not block the vitronectin receptor.

The three agents described above are administered parenterally. Oral formulations of IIb/IIIa antagonists are in various stages of development.

ADDITIONAL ANTIPLATELET-DIRECTED DRUGS

Dipyridamole is a vasodilator that also inhibits platelet function by inhibiting adenosine uptake and cGMP phosphodiesterase activity. Dipyridamole by itself has little or no beneficial effect. Therefore, therapeutic use of this agent is primarily in combination with aspirin to prevent cerebrovascular ischemia. It may also be used in combination with warfarin for primary prophylaxis of

thromboemboli in patients with prosthetic heart valves. A combination of dipyridamole complexed with 25 mg of aspirin is now available for secondary prophylaxis of cerebrovascular disease.

Cilostazol is a newer phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation. Cilostazol is used primarily to treat intermittent claudication.

■ CLINICAL PHARMACOLOGY OF DRUGS USED TO PREVENT CLOTTING

VENOUS THROMBOSIS

Risk Factors

A. Inherited Disorders

The inherited disorders characterized by a tendency to form thrombi (thrombophilia) derive from either quantitative or qualitative abnormalities of the natural anticoagulant system. Deficiencies (loss of function mutations) in the natural anticoagulants antithrombin, protein C, and protein S account for approximately 15% of selected patients with juvenile or recurrent thrombosis and 5–10% of unselected cases of acute venous thrombosis. Additional causes of thrombophilia include gain of function mutations such as the factor V Leiden mutation and the prothrombin 20210 mutation, elevated clotting factor and cofactor levels, and hyperhomocysteinemia that together account for the greater number of hypercoagulable patients. Although the loss of function mutations is less common, they are associated with the greatest thrombosis risk. Some patients have multiple inherited risk factors or combinations of inherited and acquired risk factors as discussed below. These individuals are at higher risk for recurrent thrombotic events and are often considered candidates for lifelong therapy.

B. Acquired Disease

The increased risk of thromboembolism associated with atrial fibrillation and with the placement of mechanical heart valves has long been recognized. Similarly, prolonged bed rest, high-risk surgical procedures, and the presence of cancer are clearly associated with an increased incidence of deep venous thrombosis and embolism. Antiphospholipid antibody syndrome is another important acquired risk factor. Drugs may function as synergistic risk factors in concert with inherited risk factors. For example, women who have the factor V Leiden mutation and take oral contraceptives have a synergistic increase in risk.

Antithrombotic Management

A. Prevention

Primary prevention of venous thrombosis reduces the incidence of and mortality rate from pulmonary emboli. Heparin and warfarin may be used to prevent venous thrombosis. Subcutaneous administration of low-dose unfractionated heparin, LMWH, or fondaparinux provides effective prophylaxis. Warfarin is also effective but requires laboratory monitoring of the prothrombin time.

B. Treatment of Established Disease

Treatment for established venous thrombosis is initiated with unfractionated or LMWH for the first 5–7 days, with an overlap with warfarin. Once therapeutic effects of warfarin have been established, therapy with warfarin is continued for a minimum of 3–6 months. Patients with recurrent disease or identifiable, nonreversible risk factors may be treated indefinitely. Small thrombi confined to the calf veins may be managed without anticoagulants if there is documentation over time that the thrombus is not extending.

Warfarin readily crosses the placenta. It can cause hemorrhage at any time during pregnancy as well as developmental defects when administered during the first trimester. Therefore, venous thromboembolic disease in pregnant women is generally treated with heparin, best administered by subcutaneous injection.

ARTERIAL THROMBOSIS

Activation of platelets is considered an essential process for arterial thrombosis. Thus, treatment with platelet-inhibiting drugs such as aspirin and clopidogrel or ticlopidine is indicated in patients with TIAs and strokes or unstable angina and acute myocardial infarction. Prasugrel is an alternative to clopidogrel for patients with acute coronary syndromes managed with percutaneous coronary interventions. In angina and infarction, these drugs are often used in conjunction with β blockers, calcium channel blockers, and fibrinolytic drugs.

■ DRUGS USED IN BLEEDING DISORDERS

VITAMIN K

Vitamin K confers biologic activity upon prothrombin and factors VII, IX, and X by participating in their postribosomal modification. Vitamin K is a fat-soluble substance found primarily in leafy green vegetables. The dietary requirement is low, because the vitamin is additionally synthesized by bacteria that colonize the human intestine. Two natural forms exist: vitamins K_1 and K_2. Vitamin K_1 (phytonadione; Figure 34–5) is found in food. Vitamin K_2 (menaquinone) is found in human tissues and is synthesized by intestinal bacteria.

Vitamins K_1 and K_2 require bile salts for absorption from the intestinal tract. Vitamin K_1 is available clinically in oral and parenteral forms. Onset of effect is delayed for 6 hours but the effect is complete by 24 hours when treating depression of prothrombin activity by excess warfarin or vitamin K deficiency. Intravenous administration of vitamin K_1 should be slow, because rapid infusion can produce dyspnea, chest and back pain, and even death. Vitamin K repletion is best achieved with intravenous or oral administration, because its bioavailability after subcutaneous administration is erratic. Vitamin K_1 is currently administered to all newborns to prevent the hemorrhagic disease of vitamin K deficiency, which is especially common in premature infants.

The water-soluble salt of vitamin K_3 (menadione) should never be used in therapeutics. It is particularly ineffective in the treatment of warfarin overdosage. Vitamin K deficiency frequently occurs in hospitalized patients in intensive care units because of poor diet, parenteral nutrition, recent surgery, multiple antibiotic therapy, and uremia. Severe hepatic failure results in diminished protein synthesis and a hemorrhagic diathesis that is unresponsive to vitamin K.

PLASMA FRACTIONS

Sources & Preparations

Deficiencies in plasma coagulation factors can cause bleeding (Table 34–3). Spontaneous bleeding occurs when factor activity is less than 5–10% of normal. Factor VIII deficiency **(classic hemophilia,** or **hemophilia A)** and factor IX deficiency **(Christmas disease,** or **hemophilia B)** account for most of the heritable coagulation defects. Concentrated plasma fractions are available for the treatment of these deficiencies. Administration of plasma-derived, heat- or detergent-treated factor concentrates and recombinant factor concentrates are the standard treatments for bleeding associated with hemophilia. Lyophilized factor VIII concentrates are prepared from large pools of plasma. Transmission of viral diseases such as hepatitis B and C and HIV is reduced or eliminated by pasteurization and by extraction of plasma with solvents and detergents. However, this treatment does not remove other potential causes of transmissible diseases such as prions. For this reason, recombinant clotting factor preparations are recommended whenever possible for factor replacement. The best use of these therapeutic materials requires diagnostic specificity of the deficient factor and quantitation of its activity in plasma. Intermediate purity factor VIII concentrates (as opposed to recombinant or high purity concentrates) contain significant amounts of von Willebrand factor. Humate-P is a factor VIII concentrate that is approved by the FDA for the treatment of bleeding associated with von Willebrand disease.

Clinical Uses

An uncomplicated hemorrhage into a joint should be treated with sufficient factor VIII or factor IX replacement to maintain a level of at least 30–50% of the normal concentration for 24 hours. Soft tissue hematomas require a minimum of 100% activity for 7 days. Hematuria requires at least 10% activity for 3 days. Surgery and

TABLE 34–3 Therapeutic products for the treatment of coagulation disorders.

Factor	Deficiency State	Hemostatic Levels	Half-Life of Infused Factor	Replacement Source
I	Hypofibrinogenemia	1 g/dL	4 days	Cryoprecipitate FFP
II	Prothrombin deficiency	30–40%	3 days	Prothrombin complex concentrates (intermediate purity factor IX concentrates)
V	Factor V deficiency	20%	1 day	FFP
VII	Factor VII deficiency	30%	4–6 hours	FFP Prothrombin complex concentrates (intermediate purity factor IX concentrates) Recombinant factor VIIa
VIII	Hemophilia A	30–50% 100% for major bleeding or trauma	12 hours	Recombinant factor VIII products Plasma-derived high purity concentrates Cryoprecipitate[1] Some patients with mild deficiency will respond to DDAVP
IX	Hemophilia B Christmas disease	30–50% 100% for major bleeding or trauma	24 hours	Recombinant factor IX products Plasma-derived high purity concentrates
X	Stuart-Prower defect	25%	36 hours	FFP Prothrombin complex concentrates
XI	Hemophilia C	30–50%	3 days	FFP
XII	Hageman defect	Not required		Treatment not necessary
von Willebrand	von Willebrand disease	30%	Approximately 10 hours	Intermediate purity factor VIII concentrates that contain von Willebrand factor Some patients respond to DDAVP Cryoprecipitate[1]
XIII	Factor XIII deficiency	5%	6 days	FFP Cryoprecipitate

FFP, fresh frozen plasma; DDAVP, 1-deamino-8-D-arginine vasopressin.

Antithrombin and activated protein C concentrates are available for the appropriate indications that include thrombosis in the setting of antithrombin deficiency and sepsis respectively.

[1]Cryoprecipitate should be used to treat bleeding in the setting of factor VIII deficiency and von Willebrand disease only in an emergency in which pathogen-inactivated products are not available.

major trauma require a minimum of 100% activity for 10 days. The initial loading dose for factor VIII is 50 units/kg of body weight to achieve 100% activity of factor VIII from a baseline of 1% or less, assuming a normal hemoglobin. Each unit of factor VIII per kilogram of body weight raises its activity in plasma 2%. Replacement should be administered every 12 hours. Factor IX therapy requires twice the dose of factor VIII, but with an administration of about every 24 hours because of its longer half-life. Recombinant factor IX has only 80% recovery compared with plasma-derived factor IX products. Therefore, dosing with recombinant factor IX requires 120% of the dose used with the plasma-derived product.

Desmopressin acetate increases the factor VIII activity of patients with mild hemophilia A or von Willebrand disease. It can be used in preparation for minor surgery such as tooth extraction without any requirement for infusion of clotting factors if the patient has a documented adequate response. High-dose intranasal desmopressin (see Chapter 17) is available and has been shown to be efficacious and well tolerated by patients.

Freeze-dried concentrates of plasma containing prothrombin, factors IX and X, and varied amounts of factor VII (Proplex, etc) are commercially available for treating deficiencies of these factors (Table 34–3). Each unit of factor IX per kilogram of body weight raises its activity in plasma 1.5%. Heparin is often added to inhibit coagulation factors activated by the manufacturing process. However, addition of heparin does not eliminate all thromboembolic risk.

Some preparations of factor IX concentrate contain *activated* clotting factors, which has led to their use in treating patients with inhibitors or antibodies to factor VIII or factor IX. Two products are available expressly for this purpose: **Autoplex** (with factor VIII correctional activity) and **FEIBA** (**F**actor **E**ight **I**nhibitor **B**ypassing **A**ctivity). These products are not uniformly successful in arresting hemorrhage, and the factor IX inhibitor titers often rise after treatment with them. Acquired inhibitors of coagulation factors may also be treated with porcine factor VIII (for factor VIII inhibitors) and recombinant activated factor VII. Recombinant activated factor VII **(NovoSeven)** is being increasingly used to treat coagulopathy associated with liver disease and major blood loss in trauma and surgery. These recombinant and plasma-derived factor concentrates are very expensive, and the indications for them are very precise. Therefore, close consultation with a hematologist knowledgeable in this area is essential.

Cryoprecipitate is a plasma protein fraction obtainable from whole blood. It is used to treat deficiencies or qualitative abnormalities of fibrinogen, such as that which occurs with disseminated intravascular coagulation and liver disease. A single unit of cryoprecipitate contains 300 mg of fibrinogen.

Cryoprecipitate may also be used for patients with factor VIII deficiency and von Willebrand disease if desmopressin is not indicated and a pathogen-inactivated, recombinant, or plasma-derived product is not available. The concentration of factor VIII and von Willebrand factor in cryoprecipitate is not as great as that found in the concentrated plasma fractions. Moreover, cryoprecipitate is not treated in any manner to decrease the risk of viral exposure. For infusion, the frozen cryoprecipitate unit is thawed and dissolved in a small volume of sterile citrate-saline solution and pooled with other units. Rh-negative women with potential for childbearing should receive only Rh-negative cryoprecipitate because of possible contamination of the product with Rh-positive blood cells.

RECOMBINANT FACTOR VIIA

Recombinant factor VIIa is approved for treatment of inherited or acquired hemophilia A or B with inhibitors, treatment of bleeding associated with invasive procedures in congenital or acquired hemophilia, or factor VII deficiency. In the EU, the drug is also approved for treatment of Glanzmann's thrombasthenia.

Factor VIIa initiates activation of the clotting pathway by activating factor IX and factor X in association with tissue factor (see Figure 34–2). The drug is given by bolus injection. For hemophilia A or B with inhibitors and bleeding, the dose is 90 mg/kg every 2 hours until hemostasis is achieved, and then continued at 3–6 hour intervals until stable. For congenital factor VII deficiency, the recommended dosage is 15–30 mg/kg every 4–6 hours until hemostasis is achieved.

Factor VIIa has been widely used for off-label indications, including bleeding with trauma, surgery, intracerebral hemorrhage, and warfarin toxicity. A major concern of off-label use has been the possibility that thrombotic events may be increased. A recent study examined rates of thromboembolic events in 35 placebo-controlled trials where factor VIIa was administered for nonapproved indications. This study found an increase in arterial, but not venous, thrombotic events, particularly among elderly individuals.

FIBRINOLYTIC INHIBITORS: AMINOCAPROIC ACID

Aminocaproic acid (EACA), which is chemically similar to the amino acid lysine, is a synthetic inhibitor of fibrinolysis. It competitively inhibits plasminogen activation (Figure 34–3). It is rapidly absorbed orally and is cleared from the body by the kidney. The usual oral dosage of EACA is 6 g four times a day. When the drug is administered intravenously, a 5 g loading dose should be infused over 30 minutes to avoid hypotension. **Tranexamic acid** is an analog of aminocaproic acid and has the same properties. It is administered orally with a 15 mg/kg loading dose followed by 30 mg/kg every 6 hours.

Clinical uses of EACA are as adjunctive therapy in hemophilia, as therapy for bleeding from fibrinolytic therapy, and as prophylaxis for rebleeding from intracranial aneurysms. Treatment success has also been reported in patients with postsurgical gastrointestinal bleeding and postprostatectomy bleeding and bladder hemorrhage secondary to radiation- and drug-induced cystitis. Adverse effects of the drug include intravascular thrombosis from inhibition of plasminogen activator, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness. The drug should not be used in patients with disseminated intravascular coagulation or genitourinary bleeding of the upper tract, eg, kidney and ureters, because of the potential for excessive clotting.

SERINE PROTEASE INHIBITORS: APROTININ

Aprotinin is a serine protease inhibitor (serpin) that inhibits fibrinolysis by free plasmin and may have other antihemorrhagic effects as well. It also inhibits the plasmin-streptokinase complex in patients who have received that thrombolytic agent. Aprotinin was shown to reduce bleeding—by as much as 50%—from many types of surgery, especially that involving extracorporeal circulation for open heart procedures and liver transplantation. However, clinical trials and internal data from the manufacturer suggested that use of the drug was associated with an increased risk of renal failure, heart attack, and stroke. A prospective trial was initiated in Canada but halted early because of concerns that use of the drug was associated with increased mortality. The drug was removed from the market in 2007.

PREPARATIONS AVAILABLE

Abciximab (ReoPro)
Parenteral: 2 mg/mL for IV injection

Alteplase recombinant [t-PA] (Activase*)
Parenteral: 50, 100 mg lyophilized powder to reconstitute for IV injection; 2 mg for catheter clots

Aminocaproic acid (generic, Amicar)
Oral: 500 mg tablets; 250 mg/mL syrup
Parenteral: 250 mg/mL for IV injection

Anisindione (Miradon)
Oral: 50 mg tablets

Antihemophilic factor [factor VIII, AHF] (Alphanate, Bioclate,* Helixate,* Hemofil M, Koate-HP, Kogenate,* Monoclate, Recombinate,* others)
Parenteral: in vials

Anti-inhibitor coagulant complex (Autoplex T, Feiba VH Immuno)
Parenteral: in vials

Antithrombin III (Thrombate III)
Parenteral: 500, 1000 IU powder to reconstitute for IV injection

Argatroban
Parenteral: 100 mg/mL in 2.5 mL vials

Bivalirudin (Angiomax)
Parenteral: 250 mg per vial

Cilostazol (generic, Pletal)
Oral: 50, 100 mg tablets

Clopidogrel (generic, Plavix)
Oral: 75, 300 mg tablets

Coagulation factor VIIa recombinant (Novo-Seven*)
Parenteral: 1.2, 4.8 mg powder/vial for IV injection

Dabigatran (Pradaxa)
Oral: 75, 150 mg capsules

Dalteparin (Fragmin)
Parenteral: 2500, 5000, 10,000, 15,000, 18,000 anti-factor Xa units/0.2 mL for SC injection only

Danaparoid (Orgaran)
Parenteral: 750 anti-Xa units/vial

Desirudin (Iprivask)
Parenteral: 15 mg for injection

Dipyridamole (generic, Persantine)
Oral: 25, 50, 75 mg tablets
Oral combination product (Aggrenox): 200 mg extended-release dipyridamole plus 25 mg extended-release dipyridamole plus 25 mg aspirin

Enoxaparin (low-molecular-weight heparin, Lovenox)
Parenteral: pre-filled, multiple-dose syringes for SC injection only

Eptifibatide (Integrilin)
Parenteral: 0.75, 2 mg/mL for IV infusion

Factor VIIa: see Coagulation factor VIIa recombinant

Factor VIII: see Antihemophilic factor

Factor IX complex, human (AlphaNine SD, Bebulin VH, BeneFix*, Konyne 80, Mononine, Profilnine SD, Proplex T, Proplex SX-T)
Parenteral: in vials

Fondaparinux (Arixtra)
Parenteral: 2.5, 5, 7.5, 10 mg in single-dose pre-filled syringes

Heparin sodium (generic, Liquaemin)
Parenteral: 1000, 2000, 2500, 5000, 10,000, 20,000, 40,000 units/mL for injection

Lepirudin (Refludan*)
Parenteral: 50 mg powder for IV injection

Prasugrel (Effient)
Oral: 5, 10 mg tablets

Protamine (generic)
Parenteral: 10 mg/mL for injection

Reteplase (Retavase*)
Parenteral: 10.4 IU powder for injection

Rivaroxaban (Xarelto)
Oral: 10 mg tablets

Streptokinase (Streptase)
Parenteral: 250,000, 750,000, 1,500,000 IU per vial powders to reconstitute for injection

Tenecteplase (TNKase*)
Parenteral: 50 mg powder for injection

Ticlopidine (Ticlid)
Oral: 250 mg tablets

Tinzaparin (Innohep)
Parenteral: 20,000 anti-Xa units/mL for subcutaneous injection only

Tirofiban (Aggrastat)
Parenteral: 50, 250 mcg/mL for IV infusion

Tranexamic acid (Cyklokapron, Lysteda)
Oral: 500 mg tablets
Parenteral: 100 mg/mL for IV infusion

Urokinase (Abbokinase)
Parenteral: 250,000 IU per vial for systemic use

Vitamin K (generic, various)
Oral: 5 mg tablets
Parenteral: 2, 10 mg/mL solution for injection

Warfarin (generic, Coumadin)
Oral: 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg tablets

*Recombinant product.

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Drugs Used in Thrombotic Disorders

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CASE STUDY ANSWER

This patient has pulmonary embolism secondary to a deep venous thrombosis (DVT). Immediate therapy with intravenous heparin is indicated. If hemodynamic instability or pulmonary function deteriorates, suggesting further embolization to the lung, percutaneous placement of an inferior vena cava filter may be considered. Long-term therapy with warfarin is traditional standard of care, using a target of 2–3 international normalized ratio. This patient should be advised to use other methods of contraception.

CHAPTER

35

Agents Used in Dyslipidemia

Mary J. Malloy, MD, & John P. Kane, MD, PhD

CASE STUDY

RL, a 42-year-old man with moderately severe coronary artery disease, has a body mass index (BMI) of 29, increased abdominal girth, and hypertension that is well controlled. In addition to medicine for hypertension, he is taking 40 mg atorvastatin. Current lipid panel (mg/dL): cholesterol 184, triglycerides 200, low-density lipoprotein cholesterol (LDL-C) 110, HDL-C 34, non–HDL-C 150. Lipoprotein(a) (Lp[a]) is twice normal. Fasting glucose is 102 mg/dL, and fasting insulin is 38 μU/mL. Liver enzymes are normal. Creatine kinase level is mildly elevated. The patient is referred for help with management of his dyslipidemia. You advise dietary measures, exercise, and weight loss. Which additional drugs would help him achieve his lipoprotein treatment goals: LDL-C 60–70 mg/dL; triglycerides < 120 mg/dL; HDL-C > 45 mg/dL; and reduced level of Lp(a)? Would this patient also benefit from a drug to manage insulin resistance? If so, which drug?

Plasma lipids are transported in complexes called **lipoproteins.** Metabolic disorders that involve elevations in any lipoprotein species are termed **hyperlipoproteinemias** or **hyperlipidemias. Hyperlipemia** denotes increased levels of triglycerides.

The two major clinical sequelae of hyperlipidemias are acute pancreatitis and atherosclerosis. The former occurs in patients with marked hyperlipemia. Control of triglycerides can prevent recurrent attacks of this life-threatening disease.

Atherosclerosis is the leading cause of death for both genders in the USA and other Western countries. Lipoproteins that contain **apolipoprotein (apo) B-100** convey lipids into the artery wall. These are **low-density (LDL), intermediate-density (IDL), very-low-density (VLDL),** and **lipoprotein(a) (Lp[a]).** Remnant lipoproteins formed during the catabolism of chylomicrons that contain the B-48 protein (apo B-48) can also enter the artery wall, contributing to atherosclerosis.

Cellular components in atherosclerotic plaques include foam cells, which are transformed macrophages, and smooth muscle cells filled with **cholesteryl esters.** These cellular alterations result from endocytosis of modified lipoproteins via at least four species of **scavenger receptors.** Chemical modification of lipoproteins by free radicals creates ligands for these receptors. The atheroma grows with the accumulation of foam cells, collagen, fibrin, and frequently calcium. Whereas such lesions can slowly occlude coronary vessels, clinical symptoms are more frequently precipitated by rupture of unstable atheromatous plaques, leading to activation of platelets and formation of occlusive thrombi.

Although treatment of hyperlipidemia can cause slow physical regression of plaques, the well-documented reduction in acute coronary events that follows vigorous lipid-lowering treatment is attributable chiefly to mitigation of the inflammatory activity of macrophages and is evident within 2–3 months after starting therapy.

High-density lipoproteins (HDL) exert several *anti*atherogenic effects. They participate in retrieval of cholesterol from the artery wall and inhibit the oxidation of atherogenic lipoproteins. Low levels of HDL (hypoalphalipoproteinemia) are an independent risk factor for atherosclerotic disease and thus are a target for intervention.

Cigarette smoking is a major risk factor for coronary disease. It is associated with reduced levels of HDL, impairment of cholesterol retrieval, cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis. Diabetes, also a major risk factor, is another source of oxidative stress.

Normal coronary arteries can dilate in response to ischemia, increasing delivery of oxygen to the myocardium. This process is

mediated by nitric oxide, acting on smooth muscle cells of the arterial media. This function is impaired by atherogenic lipoproteins, thus aggravating ischemia. Reducing levels of atherogenic lipoproteins and inhibiting their oxidation restores endothelial function.

Because atherogenesis is multifactorial, therapy should be directed toward all modifiable risk factors. Atherogenesis is a dynamic process. Quantitative angiographic trials have demonstrated net regression of plaques during aggressive lipid-lowering therapy. Primary and secondary prevention trials have shown significant reduction in mortality from new coronary events and in all-cause mortality.

■ PATHOPHYSIOLOGY OF HYPERLIPOPROTEINEMIA

NORMAL LIPOPROTEIN METABOLISM

Structure

Lipoproteins have hydrophobic core regions containing cholesteryl esters and triglycerides surrounded by unesterified cholesterol, phospholipids, and apoproteins. Certain lipoproteins contain very high-molecular-weight B proteins that exist in two forms: **B-48,** formed in the intestine and found in chylomicrons and their remnants; and **B-100,** synthesized in liver and found in **VLDL, VLDL remnants (IDL), LDL** (formed from VLDL), and **Lp(a) lipoproteins.** HDL consist of at least 20 discrete molecular species. All species contain apolipoprotein A-I (apo A-I). Fifty-three other proteins are known to be distributed variously among the HDL species.

Synthesis & Catabolism

A. Chylomicrons

Chylomicrons are formed in the intestine and carry **triglycerides** of dietary origin, **unesterified cholesterol,** and **cholesteryl esters.** They transit the thoracic duct to the bloodstream.

ACRONYMS

Apo	Apolipoprotein
CETP	Cholesteryl ester transfer protein
CK	Creatine kinase
HDL	High-density lipoproteins
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
IDL	Intermediate-density lipoproteins
LCAT	Lecithin:cholesterol acyltransferase
LDL	Low-density lipoproteins
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
PPAR	Peroxisome proliferator-activated receptor
VLDL	Very-low-density lipoproteins

Triglycerides are removed in extrahepatic tissues through a pathway shared with VLDL that involves hydrolysis by the **lipoprotein lipase (LPL)** system. Decrease in particle diameter occurs as triglycerides are depleted. Surface lipids and small apoproteins are transferred to HDL. The resultant chylomicron remnants are taken up by receptor-mediated endocytosis into hepatocytes.

B. Very-Low-Density Lipoproteins

VLDL are secreted by liver and export triglycerides to peripheral tissues (Figure 35–1). VLDL triglycerides are hydrolyzed by LPL, yielding free fatty acids for storage in adipose tissue and for oxidation in tissues such as cardiac and skeletal muscle. Depletion of triglycerides produces remnants (IDL), some of which undergo endocytosis directly by liver. The remainder is converted to LDL by further removal of triglycerides mediated by hepatic lipase. This process explains the "beta shift" phenomenon, the increase of LDL (beta-lipoprotein) in serum as hypertriglyceridemia subsides. Increased levels of LDL can also result from increased secretion of VLDL and from decreased LDL catabolism.

C. Low-Density Lipoproteins

LDL is catabolized chiefly in hepatocytes and other cells by receptor-mediated endocytosis. Cholesteryl esters from LDL are hydrolyzed, yielding free cholesterol for the synthesis of cell membranes. Cells also obtain cholesterol by synthesis via a pathway involving the formation of mevalonic acid by HMG-CoA reductase. Production of this enzyme and of LDL receptors is transcriptionally regulated by the content of cholesterol in the cell. Normally, about 70% of LDL is removed from plasma by hepatocytes. Even more cholesterol is delivered to the liver via IDL and chylomicrons. Unlike other cells, hepatocytes can eliminate cholesterol by secretion in bile and by conversion to bile acids.

D. Lp(a) Lipoprotein

Lp(a) lipoprotein is formed from LDL and the (a) protein, linked by a disulfide bridge. The (a) protein is highly homologous with plasminogen but is not activated by tissue plasminogen activator. It occurs in a number of isoforms of different molecular weights. Levels of Lp(a) vary from nil to over 500 mg/dL and are determined chiefly by genetic factors. Lp(a) can be found in atherosclerotic plaques and may also contribute to coronary disease by inhibiting thrombolysis. Levels are elevated in certain inflammatory states. The risk of coronary disease is strongly related to the level of Lp(a). A common variant (I4399M) in the coding region is associated with elevated levels.

E. High-Density Lipoproteins

The apoproteins of HDL are secreted by the liver and intestine. Much of the lipid comes from the surface monolayers of chylomicrons and VLDL during lipolysis. HDL also acquires cholesterol from peripheral tissues, protecting the cholesterol homeostasis of cells. Free cholesterol is transported from the cell membrane by a

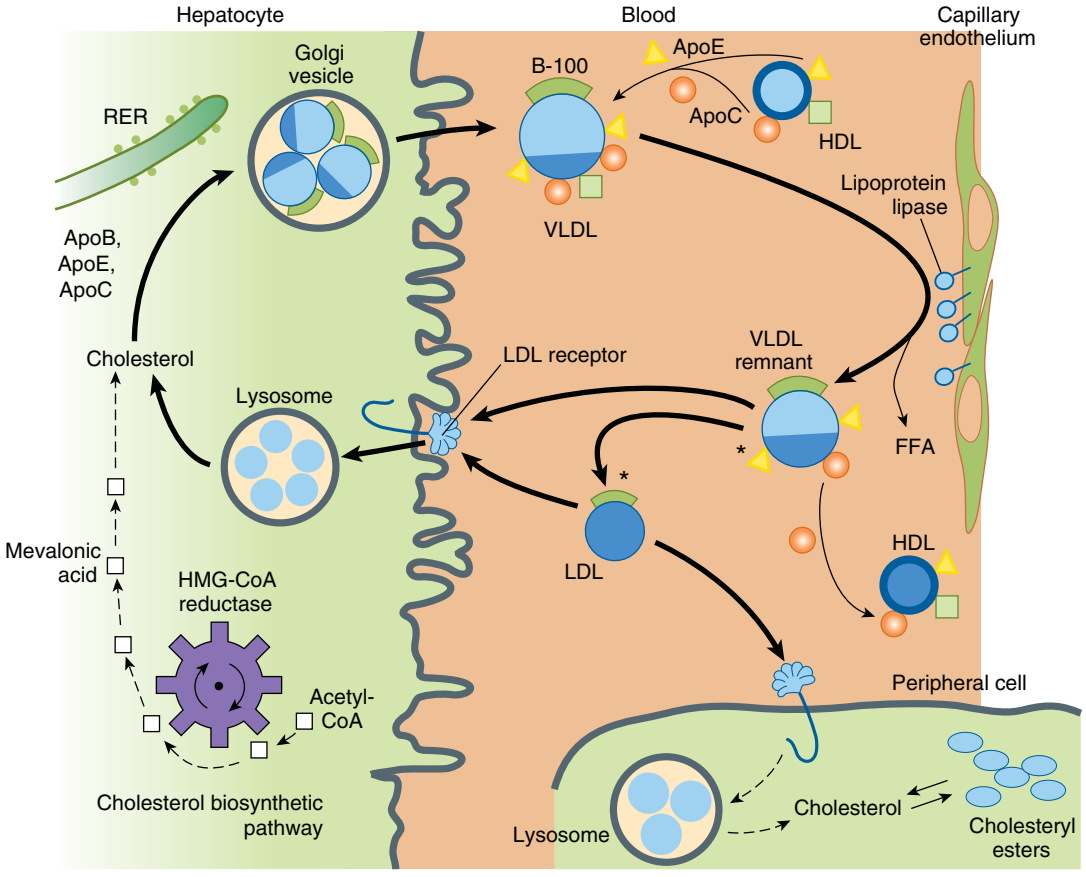


FIGURE 35–1 Metabolism of lipoproteins of hepatic origin. The heavy arrows show the primary pathways. Nascent VLDL are secreted via the Golgi apparatus. They acquire additional apo C lipoproteins and apo E from HDL. Very-low-density lipoproteins (VLDL) are converted to VLDL remnants (IDL) by lipolysis via lipoprotein lipase in the vessels of peripheral tissues. In the process, C apolipoproteins and a portion of the apo E are given back to high-density lipoproteins (HDL). Some of the VLDL remnants are converted to LDL by further loss of triglycerides and loss of apo E. A major pathway for LDL degradation involves the endocytosis of LDL by LDL receptors in the liver and the peripheral tissues, for which apo B-100 is the ligand. Dark color denotes cholesteryl esters; light color denotes triglycerides; the asterisk denotes a functional ligand for LDL receptors; triangles indicate apo E; circles and squares represent C apolipoproteins. FFA, free fatty acid; RER, rough endoplasmic reticulum. (Modified and redrawn, with permission, from Kane J, Malloy M: Disorders of lipoproteins. In: Rosenberg RN et al [editors]: *The Molecular and Genetic Basis of Neurological Disease.* Butterworth-Heinemann, 1993.)

transporter, ABCA1, acquired by a small particle termed prebeta-1 HDL, and then esterified by lecithin:cholesterol acyltransferase (LCAT), leading to the formation of larger HDL species. Cholesterol is also exported from macrophages by the ABCG1 transporter to large HDL particles. The cholesteryl esters are transferred to VLDL, IDL, LDL, and chylomicron remnants with the aid of cholesteryl ester transfer protein (CETP). Much of the cholesteryl ester thus transferred is ultimately delivered to the liver by endocytosis of the acceptor lipoproteins. HDL can also deliver cholesteryl esters directly to the liver via a docking receptor (scavenger receptor, SR-BI) that does not cause endocytosis of the lipoproteins. HDL-C levels relate inversely to risk at the population level. Among individuals, the capacity to accept exported cholesterol can vary widely at identical levels of HDL-C. The ability of peripheral tissues to export cholesterol via the transporter mechanism and the acceptor capacity of HDL are emerging as major determinants of coronary atherosclerosis.

LIPOPROTEIN DISORDERS

Lipoprotein disorders are detected by measuring lipids in serum after a 10-hour fast. Risk of heart disease increases with concentrations of the atherogenic lipoproteins, is inversely related to levels of HDL, and is modified by other risk factors (Table 35–1). Evidence from clinical trials suggests that LDL cholesterol levels of 60 mg/dL may be optimal for patients with coronary disease. Ideally, triglycerides should be below 120 mg/dL. Although LDL-C is still the primary target of treatment, reducing the levels of VLDL and IDL is also important. Calculation of non-HDL cholesterol provides a means of assessing levels of all the

TABLE 35–1 National Cholesterol Education Program: Adult Treatment Guidelines (2001).

	Desirable	Borderline to High[1]	High
Total cholesterol	< 200 (5.2)[2]	200–239 (5.2–6.2)[2]	> 240 (6.2)[2]
LDL cholesterol	< 130 (3.4)[3]	130–159 (3.4–4.1)	> 160 (4.1)
HDL cholesterol			> 60 (1.55)
Men	> 40 (1.04)		
Women	> 50 (1.30)		
Triglycerides	< 120 (1.4)	120–199 (1.4–2.3)	> 200 (2.3)

[1]Consider as high if coronary disease or more than two risk factors are present.

[2]mg/dL (mmol/L).

[3]Optimal level is < 100 (2.6); if known atherosclerotic disease, goal is 60–70 mg/dL.

lipoproteins in the VLDL to LDL cascade. Differentiation of the disorders requires identification of the lipoproteins involved (Table 35–2). Diagnosis of a primary disorder usually requires further clinical and genetic data as well as ruling out secondary hyperlipidemias (Table 35–3).

Phenotypes of abnormal lipoprotein distribution are described in this section. Drugs mentioned for use in these conditions are described in the following section on basic and clinical pharmacology.

THE PRIMARY HYPERTRIGLYCERIDEMIAS

Hypertriglyceridemia is associated with increased risk of coronary disease. VLDL and IDL have been found in atherosclerotic plaques. These patients tend to have cholesterol-rich VLDL of small-particle diameter and small, dense LDL. Hypertriglyceridemic patients with coronary disease or risk equivalents should be treated

TABLE 35–2 The primary hyperlipoproteinemias and their treatment.

Disorder	Manifestations	Diet + Single Drug[1]	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase or cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management (omega-3 fatty acids, niacin, or fibrate)	Niacin plus fibrate
Familial hypertriglyceridemia- Severe	VLDL, chylomicrons increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
Moderate	VLDL increased; chylomicrons may be increased	Omega-3 fatty acids, niacin, or fibrate	Niacin plus fibrate
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Omega-3 fatty acids, niacin, fibrate, or reductase inhibitor	Two or three of the individual drugs
	LDL predominantly increased	Niacin, reductase inhibitor, or ezetimibe	Two or three of the individual drugs
	VLDL, LDL increased	Omega-3 fatty acids, niacin, or reductase inhibitor	Niacin or fibrate plus reductase inhibitor[2]
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Omega-3 fatty acids, fibrate, or niacin	Fibrate plus niacin, or either plus reductase inhibitor
Familial hypercholesterolemia			
Heterozygous	LDL increased	Reductase inhibitor, resin, niacin, or ezetimibe	Two or three of the individual drugs
Homozygous	LDL increased	Niacin, atorvastatin, rosuvastatin, or ezetimibe	Niacin plus reductase inhibitor plus ezetimibe
Familial ligand-defective apo B	LDL increased	Niacin, reductase inhibitor, or ezetimibe	Niacin plus reductase inhibitor or ezetimibe
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin	

[1]Single-drug therapy with marine omega-3 dietary supplement should be evaluated before drug combinations are used.

[2]Select pharmacologically compatible reductase inhibitor (see text).

TABLE 35–3 Secondary causes of hyperlipoproteinemia.

Hypertriglyceridemia	Hypercholesterolemia
Diabetes mellitus	Hypothyroidism
Alcohol ingestion	Early nephrosis
Severe nephrosis	Resolving lipemia
Estrogens	Immunoglobulin-lipoprotein complex disorders
Uremia	Anorexia nervosa
Corticosteroid excess	Cholestasis
Myxedema	Hypopituitarism
Glycogen storage disease	Corticosteroid excess
Hypopituitarism	
Acromegaly	
Immunoglobulin-lipoprotein complex disorders	
Lipodystrophy	
Protease inhibitors	

aggressively. Patients with triglycerides above 700 mg/dL should be treated to prevent acute pancreatitis because the LPL clearance mechanism is saturated at about this level.

Hypertriglyceridemia is an essential component of the metabolic syndrome, which also includes low levels of HDL-C, insulin resistance, hypertension, and abdominal obesity. Hyperuricemia is also frequently present. Insulin resistance appears to be central to this process. Management of these patients frequently requires, in addition to a fibrate or niacin, the use of metformin or a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist or both (see Chapter 41). In the latter case, pioglitazone is the drug of choice because it reduces triglycerides and does not increase levels of LDL. The severity of hypertriglyceridemia of any cause is increased in the presence of the metabolic syndrome or type 2 diabetes.

Primary Chylomicronemia

Chylomicrons are not present in the serum of normal individuals who have fasted 10 hours. The recessive traits of deficiency of LPL or its cofactor, apo C-II, are usually associated with severe lipemia (2000–3000 mg/dL of triglycerides when the patient is consuming a typical American diet). These disorders might not be diagnosed until an attack of acute pancreatitis occurs. Patients may have eruptive xanthomas, hepatosplenomegaly, hypersplenism, and lipid-laden foam cells in bone marrow, liver, and spleen. The lipemia is aggravated by estrogens because they stimulate VLDL production, and pregnancy may cause marked increases in triglycerides despite strict dietary control. Although these patients have a predominant chylomicronemia, they may also have moderately elevated VLDL, presenting with a pattern called mixed lipemia (fasting chylomicronemia and elevated VLDL). LPL deficiency is diagnosed by assay of lipolytic activity after intravenous injection of heparin. A presumptive diagnosis is made by demonstrating a pronounced decrease in triglycerides a few days after reduction of daily fat intake below 15 g. Marked restriction of total dietary fat is the basis of effective long-term treatment. Niacin, a fibrate, or marine omega-3 fatty acids may be of some benefit if VLDL levels are increased. Genetic variants at other loci that participate in intravascular lipolysis, including LMF1, apo A-V, GPI-HDL BP1, and apo C-III, can have profound effects on triglyceride levels.

Familial Hypertriglyceridemia

A. Severe (Usually Mixed Lipemia)

Mixed lipemia usually results from impaired removal of triglyceride-rich lipoproteins. Factors that increase VLDL production aggravate the lipemia because VLDL and chylomicrons are competing substrates for LPL. The primary mixed lipemias probably reflect a variety of genetic determinants. Most patients have centripetal obesity with insulin resistance. Other factors that increase secretion of VLDL also worsen the lipemia. Eruptive xanthomas, lipemia retinalis, epigastric pain, and pancreatitis are variably present depending on the severity of the lipemia. Treatment is primarily dietary, with restriction of total fat, avoidance of alcohol and exogenous estrogens, weight reduction, exercise, and supplementation with marine omega-3 fatty acids. Most patients also require treatment with a fibrate or niacin.

B. Moderate

Primary increases of VLDL also reflect a genetic predisposition and are worsened by factors that increase the rate of VLDL secretion from liver, ie, obesity, alcohol, diabetes, and estrogens. Treatment includes addressing these issues and the use of fibrates or niacin as needed. Marine omega-3 fatty acids are a valuable adjuvant.

Familial Combined Hyperlipoproteinemia

In this common disorder associated with an increased incidence of coronary disease, individuals may have elevated levels of VLDL, LDL, or both, and the pattern may change with time. Familial combined hyperlipoproteinemia involves an approximate doubling in VLDL secretion and appears to be transmitted as a semidominant trait. Triglycerides can be increased by the factors noted above. Elevations of cholesterol and triglycerides are generally moderate, and xanthomas are usually absent. Diet alone does not normalize lipid levels. A reductase inhibitor alone, or in combination with niacin or fenofibrate, is usually required to treat these patients. When fenofibrate is combined with a reductase inhibitor, either pravastatin or rosuvastatin is recommended because neither is metabolized via CYP3A4.

Familial Dysbetalipoproteinemia

In this disorder, remnants of chylomicrons and VLDL accumulate and levels of LDL are decreased. Because remnants are rich in cholesteryl esters, the level of cholesterol may be as high as that of

triglycerides. Diagnosis is confirmed by the absence of the ε3 and ε4 alleles of apo E, the ε2/ε2 genotype. Patients often develop tuberous or tuberoeruptive xanthomas, or characteristic planar xanthomas of the palmar creases. They tend to be obese, and some have impaired glucose tolerance. These factors, as well as hypothyroidism, can aggravate the lipemia. Coronary and peripheral atherosclerosis occurs with increased frequency. Weight loss, together with decreased fat, cholesterol, and alcohol consumption, may be sufficient, but a fibrate or niacin is usually needed to control the condition. These agents can be given together in more resistant cases, or a reductase inhibitor may be added.

Apo E is also secreted by glia in the central nervous system and plays a role in sterol transport. The ε4 allele is associated in a dose-dependent manner with early-onset Alzheimer's disease (see Chapter 60).

THE PRIMARY HYPERCHOLESTEROLEMIAS

Familial Hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant trait. Although levels of LDL tend to increase throughout childhood, the diagnosis can often be made on the basis of elevated umbilical cord blood cholesterol. In most heterozygotes, cholesterol levels range from 260 to 500 mg/dL. Triglycerides are usually normal, tendon xanthomas are often present, and arcus corneae and xanthelasma may appear in the third decade. Coronary disease tends to occur prematurely. In homozygous familial hypercholesterolemia, which can lead to coronary disease in childhood, levels of cholesterol often exceed 1000 mg/dL and early tuberous and tendinous xanthomas occur. These patients may also develop elevated plaque-like xanthomas of the aortic valve, digital webs, buttocks, and extremities.

Defects of LDL receptors underlie familial hypercholesterolemia. Some individuals have combined heterozygosity for alleles producing nonfunctional and kinetically impaired receptors. In heterozygous patients, LDL can be normalized with combined drug regimens (Figure 35–2). Homozygotes and those with combined heterozygosity whose receptors retain even minimal function may partially respond to niacin, ezetimibe, or reductase inhibitors.

Familial Ligand-Defective Apolipoprotein B-100

Defects in the domain of apo B-100 that binds to the LDL receptor impair the endocytosis of LDL, leading to hypercholesterolemia of moderate severity. Tendon xanthomas may occur. These disorders are as prevalent as familial hypercholesterolemia. Response to reductase inhibitors is variable. Up-regulation of LDL receptors in liver increases endocytosis of LDL precursors but does not increase uptake of ligand-defective LDL particles. Niacin often has beneficial effects by reducing VLDL production.

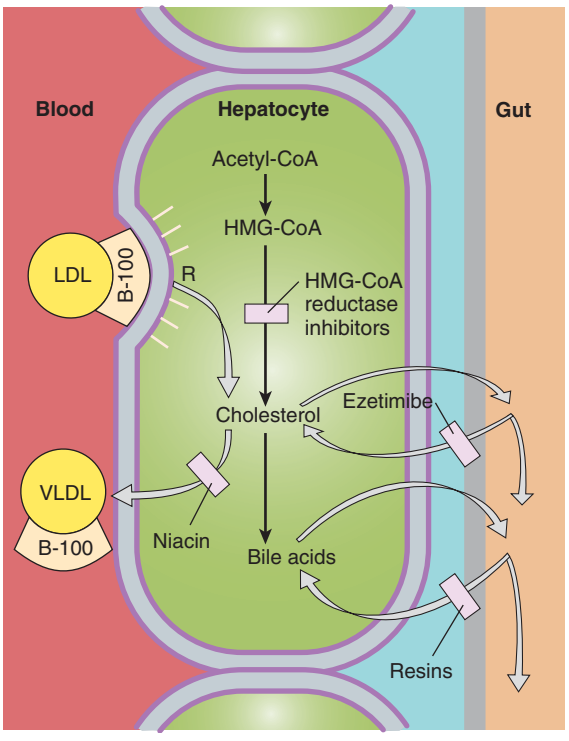


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

Familial Combined Hyperlipoproteinemia

As described, some persons with familial combined hyperlipoproteinemia have only an elevation in LDL. Serum cholesterol is usually less than 350 mg/dL. Dietary and drug treatment, usually with a reductase inhibitor, is indicated. It may be necessary to add niacin or ezetimibe to normalize LDL.

Lp(a) Hyperlipoproteinemia

This familial disorder, which is associated with increased atherogenesis, is determined chiefly by alleles that dictate increased production of the (a) protein moiety. Lp(a) can be secondarily elevated in patients with severe nephrosis and certain other inflammatory states. Niacin reduces levels of Lp(a) in many patients.

Other Disorders

Deficiency of cholesterol 7α-hydroxylase can increase LDL in the heterozygous state. Homozygotes can also have elevated triglycerides, resistance to reductase inhibitors, and increased risk of gallstones and coronary disease. Autosomal recessive hypercholesterolemia is due to mutations in a protein that normally assists in endocytosis of LDL. Some mutations in the *PCSK9* gene also cause isolated elevations of LDL. Niacin, ezetimibe, and reductase inhibitors may be useful, variably, in these disorders.

HDL Deficiency

Rare genetic disorders, including Tangier disease and LCAT (lecithin:cholesterol acyltransferase) deficiency, are associated with extremely low levels of HDL. Familial hypoalphalipoproteinemia is a more common disorder with levels of HDL cholesterol usually below 35 mg/dL in men and 45 mg/dL in women. These patients tend to have premature atherosclerosis, and the low HDL may be the only identified risk factor. Management should include special attention to avoidance or treatment of other risk factors. Niacin increases HDL in many of these patients. Reductase inhibitors and fibric acid derivatives exert lesser effects.

In the presence of hypertriglyceridemia, HDL cholesterol is low because of exchange of cholesteryl esters from HDL into triglyceride-rich lipoproteins. Treatment of the hypertriglyceridemia may increase or normalize the HDL level.

SECONDARY HYPERLIPOPROTEINEMIA

Before primary disorders can be diagnosed, secondary causes of the phenotype must be considered. The more common conditions are summarized in Table 35–3. The lipoprotein abnormality usually resolves if the underlying disorder can be treated successfully.

■ DIETARY MANAGEMENT OF HYPERLIPOPROTEINEMIA

Dietary measures are initiated first—unless the patient has evident coronary or peripheral vascular disease—and may obviate the need for drugs. Patients with familial hypercholesterolemia or familial combined hyperlipidemia always require drug therapy. Cholesterol and saturated and *trans*-fats are the principal factors that increase LDL, whereas total fat, alcohol, and excess calories increase triglycerides.

Sucrose and fructose raise VLDL. Alcohol can cause significant hypertriglyceridemia by increasing hepatic secretion of VLDL. Synthesis and secretion of VLDL are increased by excess calories. During weight loss, LDL and VLDL levels may be much lower than can be maintained during neutral caloric balance. The conclusion that diet suffices for management can be made only after weight has stabilized for at least 1 month.

General recommendations include limiting total calories from fat to 20–25% of daily intake, saturated fats to less than 8%, and cholesterol to less than 200 mg/d. Reductions in serum cholesterol range from 10% to 20% on this regimen. Use of complex carbohydrates and fiber is recommended, and *cis*-monounsaturated fats should predominate. Weight reduction, caloric restriction, and avoidance of alcohol are especially important for patients with elevated VLDL and IDL.

The effect of dietary fats on hypertriglyceridemia is dependent on the disposition of double bonds in the fatty acids. Omega-3 fatty acids found in fish oils, but not those from plant sources, activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and can induce profound reduction of triglycerides in some patients. They also have anti-inflammatory and antiarrhythmic activities. Omega-3 fatty acids are available over the counter as triglycerides from marine sources or as a prescription medication (Lovaza) containing ethyl esters of omega-3 fatty acids. The recommended dose of Lovaza is 4 g/d. It is necessary to determine the content of docosahexaenoic acid and eicosapentaenoic acid in over-the-counter preparations. Appropriate amounts should be taken to provide up to 3–4 g of these fatty acids daily. It is important to select preparations free of mercury and other contaminants. The omega-6 fatty acids present in vegetable oils may cause triglycerides to increase.

Patients with primary chylomicronemia and some with mixed lipemia must consume a diet severely restricted in total fat (10–20 g/d, of which 5 g should be vegetable oils rich in essential fatty acids), and fat-soluble vitamins should be given.

Homocysteine, which initiates proatherogenic changes in endothelium, can be reduced in many patients by restriction of total protein intake to the amount required for amino acid replacement. Supplementation with folic acid plus other B vitamins is indicated in severe homocysteinemia.

■ BASIC & CLINICAL PHARMACOLOGY OF DRUGS USED IN HYPERLIPIDEMIA

The decision to use drug therapy for hyperlipidemia is based on the specific metabolic defect and its potential for causing atherosclerosis or pancreatitis. Suggested regimens for the principal lipoprotein disorders are presented in Table 35–2. Diet should be continued to achieve the full potential of the drug regimen. These drugs should be avoided in pregnant and lactating women and those likely to become pregnant. All drugs that alter plasma lipoprotein concentrations may require adjustment of doses of warfarin and indandione anticoagulants. Children with heterozygous familial hypercholesterolemia may be treated with a resin or reductase inhibitor, usually after 7 or 8 years of age, when myelination of the central nervous system is essentially complete. The decision to treat a child should be based on the level of LDL, other risk factors, the family history, and the child's age. Drugs are rarely indicated before age 16 in the absence of multiple risk factors or compound genetic dyslipidemias.

COMPETITIVE INHIBITORS OF HMG-COA REDUCTASE (REDUCTASE INHIBITORS; "STATINS")

These compounds are structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A, Figure 35–3). **Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin,** and **pitavastatin** belong to this class. They are most effective in reducing LDL. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic

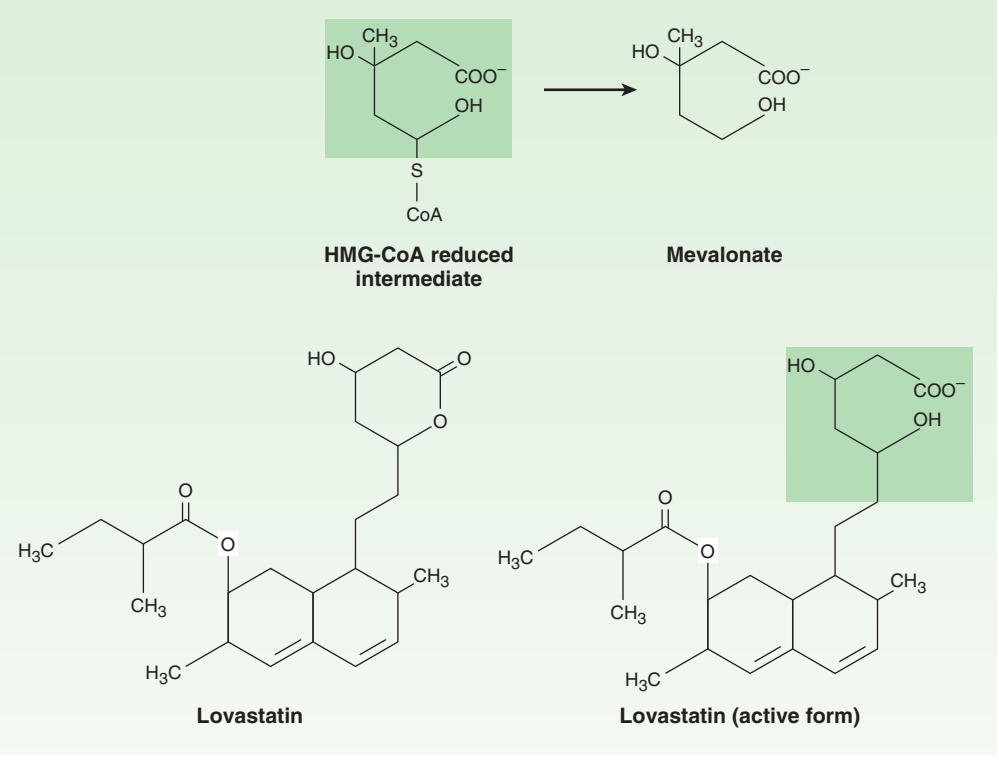


FIGURE 35–3 Inhibition of HMG-CoA reductase. **Top:** The HMG-CoA intermediate that is the immediate precursor of mevalonate, a critical compound in the synthesis of cholesterol. **Bottom:** The structure of lovastatin and its active form, showing the similarity to the normal HMG-CoA intermediate (shaded areas).

lesions. It has become standard practice to initiate reductase inhibitor therapy immediately after acute coronary syndromes, regardless of lipid levels.

Chemistry & Pharmacokinetics

Lovastatin and simvastatin are inactive lactone prodrugs that are hydrolyzed in the gastrointestinal tract to the active β-hydroxyl derivatives, whereas pravastatin has an open, active lactone ring. Atorvastatin, fluvastatin, and rosuvastatin are fluorine-containing congeners that are active as given. Absorption of the ingested doses of the reductase inhibitors varies from 40% to 75% with the exception of fluvastatin, which is almost completely absorbed. All have high first-pass extraction by the liver. Most of the absorbed dose is excreted in the bile; 5–20% is excreted in the urine. Plasma half-lives of these drugs range from 1 to 3 hours except for atorvastatin (14 hours), pitavastatin (12 hours), and rosuvastatin (19 hours).

Mechanism of Action

HMG-CoA reductase mediates the first committed step in sterol biosynthesis. The active forms of the reductase inhibitors are structural analogs of the HMG-CoA intermediate (Figure 35–3) that is formed by HMG-CoA reductase in the synthesis of mevalonate. These analogs cause partial inhibition of the enzyme and thus may impair the synthesis of isoprenoids such as ubiquinone and dolichol and the prenylation of proteins. It is not known whether this has biologic significance. However, the reductase inhibitors clearly induce an increase in high-affinity LDL receptors. This effect increases both the fractional catabolic rate of LDL and the liver's extraction of LDL precursors (VLDL remnants) from the blood, thus reducing LDL (Figure 35–2). Because of marked first-pass hepatic extraction, the major effect is on the liver. Preferential activity in liver of some congeners appears to be attributable to tissue-specific differences in uptake. Modest decreases in plasma triglycerides and small increases in HDL also occur.

Clinical trials involving many of the statins have demonstrated significant reduction of new coronary events and atherothrombotic stroke. Mechanisms other than reduction of lipoprotein levels appear to be involved. The availability of isoprenyl groups from the HMG-CoA pathway for prenylation of proteins is reduced by statins, resulting in reduced prenylation of Rho and Rab proteins. Prenylated Rho activates Rho kinase, which mediates a number of mechanisms in vascular biology. The observation that reduction in new coronary events occurs more rapidly than changes in morphology of arterial plaques suggests that these pleiotropic effects may be important. Likewise, decreased prenylation of Rab reduces the accumulation of Aβ protein in neurons, possibly mitigating the manifestations of Alzheimer's disease.

Therapeutic Uses & Dosage

Reductase inhibitors are useful alone or with resins, niacin, or ezetimibe in reducing levels of LDL. Women with hyperlipidemia

who are pregnant, lactating, or likely to become pregnant should not be given these agents. Use in children is restricted to selected patients with familial hypercholesterolemia or familial combined hyperlipidemia.

Because cholesterol synthesis occurs predominantly at night, reductase inhibitors—except atorvastatin and rosuvastatin—should be given in the evening if a single daily dose is used. Absorption generally (with the exception of pravastatin) is enhanced by food. Daily doses of lovastatin vary from 10 to 80 mg. Pravastatin is nearly as potent on a mass basis as lovastatin with a maximum recommended daily dose of 80 mg. Simvastatin is twice as potent and is given in doses of 5–80 mg daily. Because of increased risk of myopathy with the 80 mg/day dose, the FDA issued labelling for scaled dosing of simvastatin and Vytorin in June 2011. Fluvastatin appears to be about half as potent as lovastatin on a mass basis and is given in doses of 10–80 mg daily. Atorvastatin is given in doses of 10–80 mg/d, and rosuvastatin, the most efficacious agent for severe hypercholesterolemia, at 5–40 mg/d. The dose-response curves of pravastatin and especially of fluvastatin tend to level off in the upper part of the dosage range in patients with moderate to severe hypercholesterolemia. Those of other statins are somewhat more linear.

Toxicity

Elevations of serum aminotransferase activity (up to three times normal) occur in some patients. This is often intermittent and usually not associated with other evidence of hepatic toxicity. Therapy may be continued in such patients in the absence of symptoms if aminotransferase levels are monitored and stable. In some patients, who may have underlying liver disease or a history of alcohol abuse, levels may exceed three times normal. This finding portends more severe hepatic toxicity. These patients may present with malaise, anorexia, and precipitous decreases in LDL. Medication should be discontinued immediately in these patients and in asymptomatic patients whose aminotransferase activity is persistently elevated to more than three times the upper limit of normal. These agents should be used with caution and in reduced dosage in patients with hepatic parenchymal disease, Asians, and the elderly. Severe hepatic disease may preclude their use. In general, aminotransferase activity should be measured at baseline, at 1–2 months, and then every 6–12 months (if stable). Monitoring of liver enzymes should be more frequent if the patient is taking other drugs that have potential interactions with the statin. Fasting plasma glucose levels tend to increase 5–7 mg/dL with statin treatment.

Minor increases in creatine kinase (CK) activity in plasma are observed in some patients receiving reductase inhibitors, frequently associated with heavy physical activity. Rarely, patients may have marked elevations in CK activity, often accompanied by generalized discomfort or weakness in skeletal muscles. If the drug is not discontinued, myoglobinuria can occur, leading to renal injury. Myopathy may occur with monotherapy, but there is an increased incidence in patients also receiving certain other drugs. Genetic variation in an anion transporter (OATP1B1) is associated with severe myopathy and rhabdomyolysis induced by statins.

The catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through CYP3A4, whereas that of fluvastatin and rosuvastatin, and to a lesser extent pitavastatin, is mediated by CYP2C9. Pravastatin is catabolized through other pathways, including sulfation. The 3A4-dependent reductase inhibitors tend to accumulate in plasma in the presence of drugs that inhibit or compete for the 3A4 cytochrome. These include the macrolide antibiotics, cyclosporine, ketoconazole and its congeners, some HIV protease inhibitors, tacrolimus, nefazodone, fibrates, paroxetine, venlafaxine, and others (see Chapter 4). Concomitant use of reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.

Conversely, drugs such as phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase expression of CYP3A4 and can reduce the plasma concentrations of the 3A4-dependent reductase inhibitors. Inhibitors of CYP2C9 such as ketoconazole and its congeners, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin. Pravastatin and rosuvastatin appear to be the statins of choice for use with verapamil, the ketoconazole group of antifungal agents, macrolides, and cyclosporine. Doses should be kept low and the patient monitored frequently. Plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated in patients ingesting more than 1 liter of grapefruit juice daily. All statins undergo glycosylation, thus creating an interaction with gemfibrozil.

Creatine kinase activity should be measured in patients receiving potentially interacting drug combinations. In all patients, CK should be measured at baseline. If muscle pain, tenderness, or weakness appears, CK should be measured immediately and the drug discontinued if activity is elevated significantly over baseline. The myopathy usually reverses promptly upon cessation of therapy. If the association is unclear, the patient can be rechallenged under close surveillance. Myopathy in the absence of elevated CK can occur. Rarely, hypersensitivity syndromes have been reported that include a lupus-like disorder and peripheral neuropathy.

Reductase inhibitors should be temporarily discontinued in the event of serious illness, trauma, or major surgery.

NIACIN (NICOTINIC ACID)

Niacin (but not niacinamide) decreases VLDL and LDL levels, and Lp(a) in most patients. It often increases HDL levels significantly.

Chemistry & Pharmacokinetics

Niacin (vitamin B_3) is converted in the body to the amide, which is incorporated into niacinamide adenine dinucleotide (NAD). It is excreted in the urine unmodified and as several metabolites.

Mechanism of Action

Niacin inhibits VLDL secretion, in turn decreasing production of LDL (Figure 35–2). Increased clearance of VLDL via the LPL pathway contributes to reduction of triglycerides. Niacin has no effect on bile acid production. Excretion of neutral sterols in the

stool is increased acutely as cholesterol is mobilized from tissue pools and a new steady state is reached. The catabolic rate for HDL is decreased. Fibrinogen levels are reduced, and levels of tissue plasminogen activator appear to increase. Niacin inhibits the intracellular lipase of adipose tissue via receptor-mediated signaling, possibly reducing VLDL production by decreasing the flux of free fatty acids to the liver. Sustained inhibition of lipolysis has not been established, however.

Therapeutic Uses & Dosage

In combination with a resin or reductase inhibitor, niacin normalizes LDL in most patients with heterozygous familial hypercholesterolemia and other forms of hypercholesterolemia. These combinations are also indicated in some cases of nephrosis. In severe mixed lipemia that is incompletely responsive to diet, niacin often produces marked reduction of triglycerides, an effect enhanced by marine omega-3 fatty acids. It is useful in patients with combined hyperlipidemia and in those with dysbetalipoproteinemia. It is clearly the most effective agent for increasing HDL and the only agent that may reduce Lp(a).

For treatment of heterozygous familial hypercholesterolemia, most patients require 2–6 g of niacin daily; more than this should not be given. For other types of hypercholesterolemia and for hypertriglyceridemia, 1.5–3.5 g daily is often sufficient. Crystalline niacin should be given in divided doses with meals, starting with 100 mg two or three times daily and increasing gradually.

Toxicity

Most persons experience a harmless cutaneous vasodilation and sensation of warmth after each dose when niacin is started or the dose increased. Taking 81–325 mg of aspirin one half hour beforehand blunts this prostaglandin-mediated effect. Ibuprofen, once daily, also mitigates the flush. Tachyphylaxis to flushing usually occurs within a few days at doses above 1.5–3 g daily. Patients should be warned to expect the flush and understand that it is a harmless side effect. Pruritus, rashes, dry skin or mucous membranes, and acanthosis nigricans have been reported. The latter contraindicates use of niacin because of its association with insulin resistance. Some patients experience nausea and abdominal discomfort. Many can continue the drug at reduced dosage, with inhibitors of gastric acid secretion or with antacids not containing aluminum. Niacin should be avoided in most patients with severe peptic disease.

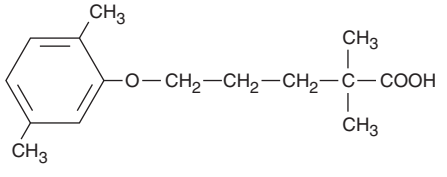
Reversible elevations in aminotransferases up to twice normal may occur, usually not associated with liver toxicity. However, liver function should be monitored at baseline and at appropriate intervals. Rarely, true hepatotoxicity may occur, and in these cases the drug should be discontinued. The association of severe hepatic dysfunction, including acute necrosis, with the use of over-the-counter sustained-release preparations of niacin has been reported. This effect has not been noted to date with an extended-release preparation, Niaspan, given at bedtime in doses of 2 g or less. Carbohydrate tolerance may be moderately impaired, especially in obese patients, but this is usually reversible except in some patients with latent diabetes. Niacin may be given to diabetics who are receiving insulin and to some receiving oral agents. Niacin may increase insulin resistance in some patients. This can often be addressed by increasing the dose of insulin or the oral agents. Hyperuricemia occurs in some patients and occasionally precipitates gout. Allopurinol can be given with niacin if needed. Red cell macrocytosis is frequently observed with higher doses of niacin and is not an indication for discontinuing treatment. Significant platelet deficiency can occur rarely and is reversible on cessation of treatment. Rarely, niacin is associated with arrhythmias, mostly atrial, and with macular edema. Patients should be instructed to report blurring of distance vision. Niacin may potentiate the action of antihypertensive agents, requiring adjustment of their dosages. Birth defects have been reported in animals given very high doses.

FIBRIC ACID DERIVATIVES (FIBRATES)

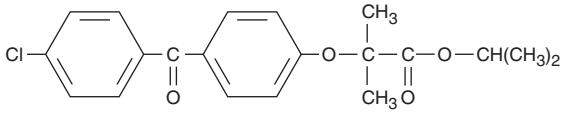
Gemfibrozil and **fenofibrate** decrease levels of VLDL and, in some patients, LDL as well. Another fibrate, **bezafibrate,** is not yet available in the USA.

Chemistry & Pharmacokinetics

Gemfibrozil is absorbed quantitatively from the intestine and is tightly bound to plasma proteins. It undergoes enterohepatic circulation and readily passes the placenta. The plasma half-life is 1.5 hours. Seventy percent is eliminated through the kidneys, mostly unmodified. The liver modifies some of the drug to hydroxymethyl, carboxyl, or quinol derivatives. Fenofibrate is an isopropyl ester that is hydrolyzed completely in the intestine. Its plasma half-life is 20 hours. Sixty percent is excreted in the urine as the glucuronide, and about 25% in feces.



Gemfibrozil



Fenofibrate

Mechanism of Action

Fibrates function primarily as ligands for the nuclear transcription receptor, PPAR-α. They transcriptionally up-regulate LPL, apo A-I and apo A-II, and down-regulate apo C-III, an inhibitor of lipolysis. A major effect is an increase in oxidation of fatty acids in liver and striated muscle (Figure 35–4). They increase lipolysis of lipoprotein triglyceride via LPL. Intracellular lipolysis in adipose

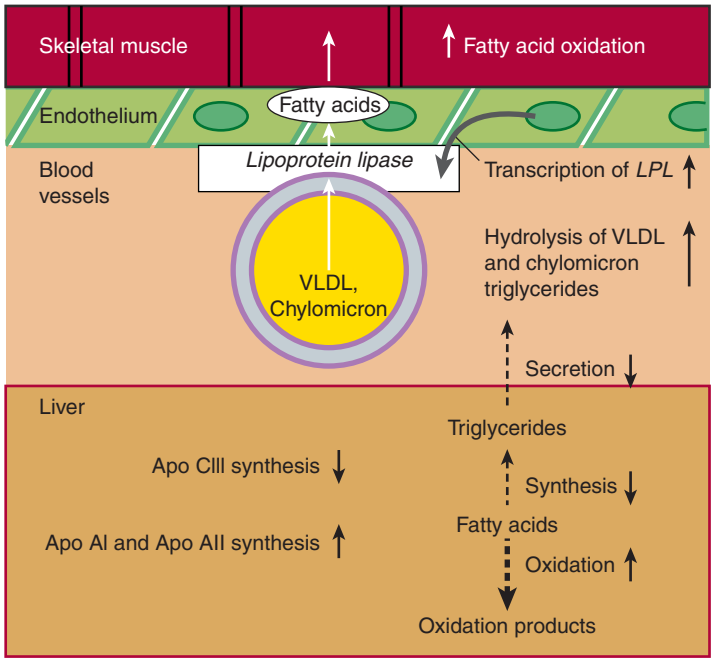


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

tissue is decreased. Levels of VLDL decrease, in part as a result of decreased secretion by the liver. Only modest reductions of LDL occur in most patients. In others, especially those with combined hyperlipidemia, LDL often increases as triglycerides are reduced. HDL cholesterol increases moderately. Part of this apparent increase is a consequence of decreasing triglycerides in plasma, with reduction in exchange of triglycerides into HDL in place of cholesteryl esters.

Therapeutic Uses & Dosage

Fibrates are useful drugs in hypertriglyceridemias in which VLDL predominate and in dysbetalipoproteinemia. They also may be of benefit in treating the hypertriglyceridemia that results from treatment with viral protease inhibitors. The usual dose of gemfibrozil is 600 mg orally once or twice daily. The dosage of fenofibrate (as Tricor) is one to three 48 mg tablets (or a single 145 mg tablet) daily. Absorption of gemfibrozil is improved when the drug is taken with food.

Toxicity

Rare adverse effects of fibrates include rashes, gastrointestinal symptoms, myopathy, arrhythmias, hypokalemia, and high blood levels of aminotransferases or alkaline phosphatase. A few patients show decreases in white blood count or hematocrit. Both agents potentiate the action of coumarin and indanedione anticoagulants, and doses of these agents should be adjusted. Rhabdomyolysis has occurred rarely. Risk of myopathy increases when fibrates are given with reductase inhibitors. Fenofibrate is the fibrate of choice for use in combination with a statin. Fibrates should be avoided in patients with hepatic or renal dysfunction. There appears to be a modest increase in the risk of cholesterol gallstones, reflecting an increase in the cholesterol content of bile. Therefore, fibrates should be used with caution in patients with biliary tract disease or in those at high risk such as women, obese patients, and Native Americans.

BILE ACID-BINDING RESINS

Colestipol, cholestyramine, and **colesevelam** are useful only for isolated increases in LDL. In patients who also have hypertriglyceridemia, VLDL levels may be further increased during treatment with resins.

Chemistry & Pharmacokinetics

The bile acid-binding agents are large polymeric cationic exchange resins that are insoluble in water. They bind bile acids in the intestinal lumen and prevent their reabsorption. The resin itself is not absorbed.

Mechanism of Action

The bile acids, metabolites of cholesterol, are normally efficiently reabsorbed in the jejunum and ileum (Figure 35–2). Excretion is increased up to tenfold when resins are given, resulting in enhanced conversion of cholesterol to bile acids in liver via 7α-hydroxylation, which is normally controlled by negative feedback by bile acids. Decreased activation of the FXR receptor by bile acids may result in a modest increase in plasma triglycerides but can also improve glucose metabolism in patients with diabetes. The latter effect is due to increased secretion of the incretin

glucagon-like peptide-1 from the intestine, thus increasing insulin secretion. Increased uptake of LDL and IDL from plasma results from up-regulation of LDL receptors, particularly in liver. Therefore, the resins are without effect in patients with homozygous familial hypercholesterolemia who have no functioning receptors but may be useful in patients with receptor-defective combined heterozygous states.

Therapeutic Uses & Dosage

The resins are used in treatment of patients with primary hypercholesterolemia, producing approximately 20% reduction in LDL cholesterol in maximal dosage. If resins are used to treat LDL elevations in persons with combined hyperlipidemia, they may cause an increase in VLDL, requiring the addition of a second agent such as niacin. Resins are also used in combination with other drugs to achieve further hypocholesterolemic effect (see below). They may be helpful in relieving pruritus in patients who have cholestasis and bile salt accumulation. Because the resins bind digitalis glycosides, they may be useful in digitalis toxicity.

Colestipol and cholestyramine are available as granular preparations. A gradual increase of dosage of granules from 4 or 5 g/d to 20 g/d is recommended. Total dosages of 30–32 g/d may be needed for maximum effect. The usual dosage for a child is 10–20 g/d. Granular resins are mixed with juice or water and allowed to hydrate for 1 minute. Colestipol is also available in 1 g tablets that must be swallowed whole, with a maximum dose of 16 g daily. Colesevelam is available in 625 mg tablets and as a suspension (1875-mg or 3750-mg packets). The maximum dose is six tablets or 3750 mg as suspension, daily. Resins should be taken in two or three doses with meals. They lack effect when taken between meals.

Toxicity

Common complaints are constipation and bloating, usually relieved by increasing dietary fiber or mixing psyllium seed with the resin. Resins should be avoided in patients with diverticulitis. Heartburn and diarrhea are occasionally reported. In patients who have preexisting bowel disease or cholestasis, steatorrhea may occur. Malabsorption of vitamin K occurs rarely, leading to hypoprothrombinemia. Prothrombin time should be measured frequently in patients who are taking resins and anticoagulants. Malabsorption of folic acid has been reported rarely. Increased formation of gallstones, particularly in obese persons, was an anticipated adverse effect but has rarely occurred in practice.

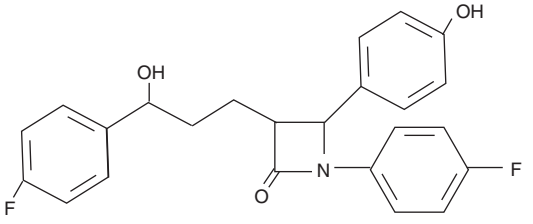
Absorption of certain drugs, including those with neutral or cationic charge as well as anions, may be impaired by the resins. These include digitalis glycosides, thiazides, warfarin, tetracycline, thyroxine, iron salts, pravastatin, fluvastatin, ezetimibe, folic acid, phenylbutazone, aspirin, and ascorbic acid, among others. In general, additional medication (except niacin) should be given 1 hour before or at least 2 hours after the resin to ensure adequate absorption. Colesevelam does not bind digoxin, warfarin, or reductase inhibitors.

INHIBITORS OF INTESTINAL STEROL ABSORPTION

Ezetimibe is the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol. Its primary clinical effect is reduction of LDL levels. In one trial, patients receiving ezetimibe in combination with simvastatin had marginal, but not statistically significant, increases in carotid intimal-medial thickness (IMT) compared with those receiving simvastatin alone. Interpretation of this observation is difficult for several reasons, including the fact that baseline IMT was unexpectedly small, probably due to prior lipid-lowering therapy. Because reducing LDL levels by virtually every modality has been associated with reduced risk of coronary events, it is reasonable to assume that reduction of LDL by ezetimibe will have a similar impact. Further studies are pending.

Chemistry & Pharmacokinetics

Ezetimibe is readily absorbed and conjugated in the intestine to an active glucuronide, reaching peak blood levels in 12–14 hours. It undergoes enterohepatic circulation, and its half-life is 22 hours. Approximately 80% of the drug is excreted in feces. Plasma concentrations are substantially increased when it is administered with fibrates and reduced when it is given with cholestyramine. Other resins may also decrease its absorption. There are no significant interactions with warfarin or digoxin.



Ezetimibe

Mechanism of Action

Ezetimibe is a selective inhibitor of intestinal absorption of cholesterol and phytosterols. A transport protein, NPC1L1, appears to be the target of the drug. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

Therapeutic Uses & Dosage

The effect of ezetimibe on cholesterol absorption is constant over the dosage range of 5–20 mg/d. Therefore, a single daily dose of 10 mg is used. Average reduction in LDL cholesterol with ezetimibe alone in patients with primary hypercholesterolemia is about 18%, with minimal increases in HDL cholesterol. It is also effective in patients with phytosterolemia. Ezetimibe is synergistic with reductase inhibitors, producing decrements as great as 25% in LDL cholesterol beyond that achieved with the reductase inhibitor alone.

Toxicity

Ezetimibe does not appear to be a substrate for cytochrome P450 enzymes. Experience to date reveals a low incidence of reversible impaired hepatic function with a small increase in incidence when given with a reductase inhibitor. Myositis has been reported rarely.

CETP INHIBITORS

Cholesteryl ester transfer protein (CETP) inhibitors are under active investigation. The first drug in this class, **torcetrapib,** aroused great interest because it markedly increased HDL and reduced LDL. However, it was withdrawn from clinical trials because it increased cardiovascular events and deaths in the treatment group. **Anacetrapib** and **dalcetrapib** are analogs currently in clinical trials.

TREATMENT WITH DRUG COMBINATIONS

Combined drug therapy is useful (1) when VLDL levels are significantly increased during treatment of hypercholesterolemia with a resin; (2) when LDL and VLDL levels are both elevated initially; (3) when LDL or VLDL levels are not normalized with a single agent, or (4) when an elevated level of Lp(a) or an HDL deficiency coexists with other hyperlipidemias. The lowest effective doses should be used in combination therapy and the patient should be monitored more closely for evidence of toxicity.

FIBRIC ACID DERIVATIVES & BILE ACID-BINDING RESINS

This combination is sometimes useful in treating patients with familial combined hyperlipidemia who are intolerant of niacin or statins. However, it may increase the risk of cholelithiasis.

HMG-COA REDUCTASE INHIBITORS & BILE ACID-BINDING RESINS

This synergistic combination is useful in the treatment of familial hypercholesterolemia but may not control levels of VLDL in some patients with familial combined hyperlipoproteinemia. Statins should be given 1 hour before or at least 2 hours after the resin to ensure their absorption.

NIACIN & BILE ACID-BINDING RESINS

This combination effectively controls VLDL levels during resin therapy of familial combined hyperlipoproteinemia or other disorders involving both increased VLDL and LDL levels. When VLDL and LDL levels are both initially increased, doses of niacin as low as 1–3 g/d may be sufficient in combination with a resin. The niacin-resin combination is effective for treating heterozygous familial hypercholesterolemia.

The drugs may be taken together, because niacin does not bind to the resins. LDL levels in patients with heterozygous familial hypercholesterolemia require daily doses of up to 6 g of niacin with 24–30 g of resin.

NIACIN & REDUCTASE INHIBITORS

This regimen is more effective than either agent alone in treating hypercholesterolemia. Experience indicates that it is an efficacious and practical combination for treatment of familial combined hyperlipoproteinemia.

REDUCTASE INHIBITORS & EZETIMIBE

This combination is highly synergistic in treating primary hypercholesterolemia and has some use in the treatment of patients with homozygous familial hypercholesterolemia who have some receptor function.

REDUCTASE INHIBITORS & FENOFIBRATE

Fenofibrate appears to be complementary with most statins in the treatment of familial combined hyperlipoproteinemia and other conditions involving elevations of both LDL and VLDL. The combination of fenofibrate with rosuvastatin appears to be well tolerated. Some other statins may interact unfavorably owing to effects on cytochrome P450 metabolism. In any case, particular vigilance for liver and muscle toxicity is indicated.

COMBINATIONS OF RESINS, EZETIMIBE, NIACIN, & REDUCTASE INHIBITORS

These agents act in a complementary fashion to normalize cholesterol in patients with severe disorders involving elevated LDL. The effects are sustained, and little compound toxicity has been observed. Effective doses of the individual drugs may be lower than when each is used alone; for example, as little as 1–2 g of niacin may substantially increase the effects of the other agents.

SUMMARY Drugs Used in Dyslipidemia

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
STATINS				
• Atorvastatin, simvastatin, rosuvastatin, pitavastatin	Inhibit HMG-CoA reductase	Reduce cholesterol synthesis and up-regulate low-density lipoprotein (LDL) receptors on hepatocytes • modest reduction in triglycerides	Atherosclerotic vascular disease (primary and secondary prevention) • acute coronary syndromes	Oral • duration 12–24 h • *Toxicity:* Myopathy, hepatic dysfunction • *Interactions:* CYP-dependent metabolism (3A4, 2C9) interacts with CYP inhibitors
• *Fluvastatin, pravastatin, lovastatin: Similar but somewhat less efficacious*				
FIBRATES				
• Fenofibrate, gemfibrozil	Peroxisome proliferator-activated receptor-alpha (PPAR-α) agonists	Decrease secretion of very-low-density lipoproteins (VLDL) • increase lipoprotein lipase activity • increase high-density lipoproteins (HDL)	Hypertriglyceridemia, low HDL	Oral • duration 3–24 h • *Toxicity:* Myopathy, hepatic dysfunction
BILE ACID SEQUESTRANTS				
• Colestipol	Binds bile acids in gut • prevents reabsorption • increases cholesterol catabolism • up-regulates LDL receptors	Decreases LDL	Elevated LDL, digitalis toxicity, pruritus	Oral • taken with meals • not absorbed • *Toxicity:* Constipation, bloating • interferes with absorption of some drugs and vitamins
• *Cholestyramine, colesevelam: Similar to colestipol*				
STEROL ABSORPTION INHIBITOR				
• Ezetimibe	Blocks sterol transporter NPC1L1 in intestine brush border	Inhibits reabsorption of cholesterol excreted in bile • decreases LDL and phytosterols	Elevated LDL, phytosterolemia	Oral • duration 24 h • *Toxicity:* Low incidence of hepatic dysfunction, myositis
NIACIN				
	Decreases catabolism of apo AI • reduces VLDL secretion from liver	Increases HDL • decreases lipoprotein(a) [Lp(a)], LDL, and triglycerides	Low HDL • elevated VLDL, LDL, Lp(a)	Oral • large doses • *Toxicity:* Gastric irritation, flushing, low incidence of hepatic toxicity • may reduce glucose tolerance
• *Extended-release niacin: Similar to regular niacin*				
• *Sustained-release niacin (not the same as extended-release product): Should be avoided*				

PREPARATIONS AVAILABLE

Atorvastatin (Lipitor)
Oral: 10, 20, 40, 80 mg tablets

Cholestyramine (generic, Questran, Questran Light)
Oral: 4 g packets anhydrous granules cholestyramine resin

Colesevelam (WelChol)
Oral: 625 mg tablets; 1.875 g and 3.75 g packets powder

Colestipol (Colestid)
Oral: 5 g packets granules; 1 g tablets

Ezetimibe (Zetia)
Oral: 10 mg tablets

Fenofibrate (generic, Tricor, Antara, Lofibra)
Oral: 48, 50, 54, 107, 145, 160 mg tablets; 45, 50, 67, 100, 130, 134, 135 150, 200 mg capsules

Fluvastatin (Lescol)
Oral: 20, 40 mg capsules; extended-release (Lescol XL): 80 mg capsules

Gemfibrozil (generic, Lopid)
Oral: 600 mg tablets

Lovastatin (generic, Mevacor)
Oral: 10, 20, 40 mg tablets; extended-release (Altoprev): 20, 40, 60 mg

Niacin, nicotinic acid, vitamin B_3 (generic, others)
Oral: 100, 250, 500, 1000 mg tablets; extended-release (Niaspan): 500, 750, 1000 mg

Omega-3 fatty acids-marine (generic, Lovaza)
Oral: 1 g (300 mg PUFA, generic) or 1 g (900 mg PUFA, Lovaza) capsules

Pitavastatin (Livalo)
Oral: 1, 2, 4 mg tablets

Pravastatin (generic, Pravachol)
Oral: 10, 20, 40, 80 mg tablets

Rosuvastatin (Crestor)
Oral: 5, 10, 20, 40 mg tablets

Simvastatin (generic, Zocor)
Oral: 5, 10, 20, 40, 80 mg tablets

COMBINATION TABLETS

Advicor (extended-release niacin/lovastatin)
Oral: 500/20, 750/20, 1000/20, 1000/40 mg tablets

Simcor (extended-release niacin/simvastatin)
Oral: 500/20, 750/20, 1000/20 mg tablets

Vytorin (ezetimibe/simvastatin)
Oral: 10/10, 10/20, 10/40, 10/80 mg tablets

PUFA, polyunsaturated fatty acid.

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CASE STUDY ANSWER

This patient has combined hyperlipidemia. The statin should be continued. A drug that reduces VLDL production would be beneficial (niacin or fenofibrate). Niacin is the preferred agent to increase HDL-C and to reduce triglycerides and Lp(a). However, increased insulin resistance may occur, necessitating frequent monitoring and, if necessary, the addition of metformin. If the LDL-C goal is not reached with the addition of niacin (or fenofibrate), the statin dose should be increased. Creatine kinase should be monitored. Marine omega-3 fatty acids will help to reduce triglycerides.