Drugs acting in the central nervous system (CNS) were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. In addition to their use in therapy, many drugs acting on the CNS are used without prescription to increase one's sense of well-being.

The mechanisms by which various drugs act in the CNS have not always been clearly understood. Since the causes of many of the conditions for which these drugs are used (schizophrenia, anxiety, etc) are themselves poorly understood, it is not surprising that in the past much of CNS pharmacology has been purely descriptive. In the last 3 decades, however, dramatic advances have been made in the methodology of CNS pharmacology. It is now possible to study the action of a drug on individual cells and even single ion channels within synapses. The information obtained from such studies is the basis for several major developments in studies of the CNS.

First, it is clear that nearly all drugs with CNS effects act on specific receptors that modulate synaptic transmission. A very few agents such as general anesthetics and alcohol may have nonspecific actions on membranes (although these exceptions are not fully accepted), but even these non-receptor-mediated actions result in demonstrable alterations in synaptic transmission.

Second, drugs are among the most important tools for studying all aspects of CNS physiology, from the mechanism of convulsions to the laying down of long-term memory. As will be described below, agonists that mimic natural transmitters (and in many cases are more selective than the endogenous substances) and antagonists are extremely useful in such studies. The section on Natural Toxins: Tools for Characterizing Ion Channels describes the uses of some of these substances.

Third, unraveling the actions of drugs with known clinical efficacy has led to some of the most fruitful hypotheses regarding the mechanisms of disease. For example, information on the action of antipsychotic drugs on dopamine receptors has provided the basis for important hypotheses regarding the pathophysiology of schizophrenia. Studies of the effects of a variety of agonists and antagonists on \( \gamma \)-aminobutyric acid (GABA) receptors are resulting in new concepts pertaining to the pathophysiology of several diseases, including anxiety and epilepsy.

This chapter provides an introduction to the functional organization of the CNS and its synaptic transmitters as a basis for understanding the actions of the drugs described in the following
Methods for the Study of CNS Pharmacology

Although scientists (and the public) have always been interested in the action of drugs in the CNS, a detailed description of synaptic transmission was not possible until glass microelectrodes, which permit intracellular recording, were developed. Detailed electrophysiologic studies of the action of drugs on both voltage- and transmitter-operated channels were further facilitated by the introduction of the patch clamp technique, which permits the recording of current through single channels. Histochemical, immunologic, and radioisotopic methods are widely used to map the distribution of specific transmitters, their associated enzyme systems, and their receptors. Molecular cloning has had a major impact on our understanding of CNS receptors. These techniques make it possible to determine the precise molecular structure of the receptors and their associated channels. Finally, mice with mutated genes for specific receptors or enzymes (knockout mice) can provide important information regarding the physiologic and pharmacologic roles of these components.

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Natural Toxins: Tools for Characterizing Ion Channels

Evolution is a tireless chemist when it comes to inventing toxins. A vast number of variations are possible with even a small number of amino acids in peptides, and peptides are only one of a broad array of toxic compounds. For example, the predatory marine snail genus Conus is estimated to include at least 500 different species. Each species kills or paralyzes its prey with a venom that contains 50–200 different peptides or proteins. Furthermore, there is little duplication of peptides among Conus species. Other animals with useful toxins include snakes, frogs, spiders, bees, wasps, and scorpions. Plant species with toxic (or therapeutic) substances are too numerous to mention here; they are referred to in many chapters of this book.

Since many toxins act on ion channels, they provide a wealth of chemical tools for studying the function of these channels. In fact, much of our current understanding of the properties of ion channels comes from studies utilizing only a small fraction of the highly potent and selective toxins that are now available. The toxins typically target voltage-sensitive ion channels, but a number of very useful toxins block ionotropic neurotransmitter receptors. Table 21–1 lists some of the toxins most commonly used in research, their mode of action, and their source.

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Ion Channels & Neurotransmitter Receptors

The membranes of nerve cells contain two types of channels defined on the basis of the mechanisms controlling their gating (opening and closing): voltage-gated and ligand-gated channels (Figures 21–1 A and B). Voltage-gated channels respond to changes in the membrane potential of the cell. The voltage-gated sodium channel described in Chapter 14: Agents Used in Cardiac Arrhythmias for the heart is an example of the first type and is very important in the CNS. In nerve cells, these channels are concentrated on the initial segment and the axon and are responsible for the fast action potential, which transmits the signal from cell body to nerve terminal. There are many types of voltage-sensitive calcium and potassium channels on the cell body, dendrites, and initial segment,
which act on a much slower time scale and modulate the rate at which the neuron discharges. For example, some types of potassium channels opened by depolarization of the cell result in slowing of further depolarization and act as a brake to limit further action potential discharge.

Figure 21–1.

<table>
<thead>
<tr>
<th>A</th>
<th>Voltage-gated</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Voltage-gated channel" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Ligand-gated</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Ligand-gated channel" /></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>G protein coupled receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="G protein coupled receptor" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>G protein coupled receptor, which when bound, activates an enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="G protein coupled receptor, which when bound, activates an enzyme" /></td>
<td></td>
</tr>
</tbody>
</table>

Types of ion channels and neurotransmitter receptors in the CNS. A shows a voltage-gated channel in which a voltage sensor controls the gating (broken arrow) of the channel. B shows a ligand-gated channel in which the binding of the neurotransmitter to the channel controls the gating (broken arrow) of the channel. C shows a G protein coupled receptor, which when bound, activates a G protein which then interacts directly with an ion channel. D shows a G protein coupled receptor, which when bound, activates a G protein which then activates an enzyme. The activated enzyme generates a diffusible second messenger that interacts with an ion channel.
Ligand-gated channels, also called *ionotropic receptors*, are opened by the binding of neurotransmitters to the channel. The receptor is formed of subunits, and the channel is an integral part of the receptor complex. These channels are insensitive or only weakly sensitive to membrane potential. Activation of these channels typically results in a brief (a few milliseconds to tens of milliseconds) opening of the channel. Ligand-gated channels are responsible for fast synaptic transmission typical of hierarchical pathways in the CNS (see below).

It is now well established that the traditional view of completely separate voltage-gated and ligand-gated channels requires substantial modifications. As discussed in Chapter 2: Drug Receptors & Pharmacodynamics, most neurotransmitters, in addition to binding to ionotropic receptors, also bind to G protein-coupled receptors, often referred to as *metabotropic* receptors. Metabotropic receptors, via G proteins, modulate voltage-gated channels. This interaction can occur entirely within the membrane and is referred to as a *membrane delimited* pathway (Figure 21–1 C). In this case the G protein interacts directly with the voltage-gated ion channel. In general, two types of voltage-gated ion channel are involved in this type of signaling: calcium channels and potassium channels. When G proteins interact with calcium channels, they inhibit channel function. This mechanism accounts for the presynaptic inhibition that occurs when presynaptic metabotropic receptors are activated. In contrast, when these receptors are postsynaptic, they activate (cause the opening of) potassium channels, resulting in a slow postsynaptic inhibition. Metabotropic receptors can also modulate voltage-gated channels less directly by the generation of *diffusible second messengers* (Figure 21–1 D). A classic example of this type of action is provided by the β adrenoceptor, which generates cAMP via the activation of adenylyl cyclase (see Chapter 2: Drug Receptors & Pharmacodynamics). Whereas membrane-delimited actions occur within microdomains in the membrane, second messenger-mediated effects can occur over considerable distances. Finally, an important consequence of the involvement of G proteins in receptor signaling is that, in contrast to the brief effect of ionotropic receptors, the effects of metabotropic receptor activation can last tens of seconds to minutes. Metabotropic receptors predominate in the diffuse neuronal systems in the CNS (see below).
membrane. Binding of the transmitter to its receptor causes a brief change in membrane conductance (permeability to ions) of the postsynaptic cell. The time delay from the arrival of the presynaptic action potential to the onset of the postsynaptic response is approximately 0.5 ms. Most of this delay is consumed by the release process, particularly the time required for calcium channels to open.

<table>
<thead>
<tr>
<th>Channel Types</th>
<th>Mode of Toxin Action</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voltage-gated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium channels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrodotoxin (TTX)</td>
<td>Blocks from outside</td>
<td>Puffer fish</td>
</tr>
<tr>
<td>α-Scorpion toxin</td>
<td>Slows inactivation</td>
<td>Scorpion</td>
</tr>
<tr>
<td>Batrachotoxin (BTX)</td>
<td>Slows inactivation, shifts activation</td>
<td>Colombian frog</td>
</tr>
<tr>
<td><strong>Potassium channels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apamin</td>
<td>Blocks &quot;small Ca(^{2+})-activated&quot; K(^{+}) channel</td>
<td>Honeybee</td>
</tr>
<tr>
<td>Charybdotoxin</td>
<td>Blocks &quot;big Ca(^{2+})-activated&quot; K(^{+}) channel</td>
<td>Scorpion</td>
</tr>
<tr>
<td>Dendrotoxin</td>
<td>Blocks delayed rectifier</td>
<td>Snake</td>
</tr>
<tr>
<td><strong>Calcium channels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega conotoxin (α-CTX-GVIA)</td>
<td>Blocks N-type channel</td>
<td>Pacific cone snail</td>
</tr>
<tr>
<td>Agatoxin (α-AGA-IVA)</td>
<td>Blocks P-type channel</td>
<td>Funnel web spider</td>
</tr>
<tr>
<td><strong>Ligand-gated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic ACh receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Bungarotoxin</td>
<td>Irreversible antagonist</td>
<td>Marine snake</td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td>Competitive antagonist</td>
<td>Amazon plant</td>
</tr>
<tr>
<td>GABA(_A) receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picrotoxin</td>
<td>Blocks channel</td>
<td>South Pacific plant</td>
</tr>
<tr>
<td>Bicuculline</td>
<td>Competitive antagonist</td>
<td>Plant</td>
</tr>
<tr>
<td>Glycine receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strychnine</td>
<td>Competitive antagonist</td>
<td>Indian plant</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philanthotoxin</td>
<td>Blocks channel</td>
<td>Wasp</td>
</tr>
</tbody>
</table>
associates, who recorded intracellularly from spinal motoneurons. When a microelectrode enters a cell, there is a sudden change in the potential recorded by the electrode, which is typically about –70 mV (Figure 21–2). This is the resting membrane potential of the neuron. Two types of pathways, excitatory and inhibitory, impinge on the motoneuron. When an excitatory pathway is stimulated, a small depolarization or excitatory postsynaptic potential (EPSP) is recorded. This potential is due to the excitatory transmitter acting on an ionotropic receptor, causing an increase in sodium and potassium permeability. The duration of these potentials is quite brief, usually less than 20 ms. Changing the stimulus intensity to the pathway and therefore the number of presynaptic fibers activated results in a graded change in the size of the depolarization. This indicates that the contribution a single fiber makes to the EPSP is quite small. When a sufficient number of excitatory fibers are activated, the EPSP depolarizes the postsynaptic cell to threshold, and an all-or-none action potential is generated.

![Figure 21–2.](image)

Excitatory synaptic potentials and spike generation. The figure shows a resting membrane potential of –70 mV in a postsynaptic cell. Stimulation of an excitatory pathway (E) generates transient depolarization. Increasing the stimulus strength (second E) increases the size of the depolarization, so that the threshold for spike generation is reached.

When an inhibitory pathway is stimulated, the postsynaptic membrane is hyperpolarized, producing an inhibitory postsynaptic potential (IPSP) (Figure 21–3). A number of inhibitory synapses must be activated simultaneously to appreciably alter the membrane potential. This hyperpolarization is due to a selective increase in membrane permeability to chloride ions that flow into the cell during the IPSP. If an EPSP that under resting conditions would evoke an action potential in the postsynaptic cell (Figure 21–3) is elicited during an IPSP, it no longer evokes an action potential, because the IPSP has moved the membrane potential farther away from the threshold for action potential generation. A second type of inhibition is termed presynaptic inhibition. It was first described for sensory fibers entering the spinal cord, where excitatory synaptic terminals receive synapses called axoaxonic synapses (Figure 21–5 B). When activated, axoaxonic synapses reduce the amount of transmitter released from the synapses of sensory fibers. Interestingly, presynaptic inhibitory receptors are present on virtually all presynaptic terminals in the brain even though axoaxonic synapses appear to be restricted to the spinal cord. In this case, transmitter spills over to neighboring synapses to activate those presynaptic receptors.
Interaction of excitatory and inhibitory synapses. On the left, a suprathreshold stimulus is given to an excitatory pathway (E). On the right, this same stimulus is given shortly after stimulating an inhibitory pathway (I), which prevents the excitatory potential from reaching threshold.

**Sites of Drug Action**

Virtually all of the drugs that act in the CNS produce their effects by modifying some step in chemical synaptic transmission. Figure 21–4 illustrates some of the steps that can be altered. These transmitter-dependent actions can be divided into presynaptic and postsynaptic categories.
Drugs acting on the synthesis, storage, metabolism, and release of neurotransmitters fall into the presynaptic category. Synaptic transmission can be depressed by blockade of transmitter synthesis or storage. For example, \( p \)-chlorophenylalanine blocks the synthesis of serotonin, and reserpine depletes the synapses of monoamines by interfering with intracellular storage. Blockade of transmitter catabolism can increase transmitter concentrations and has been reported to increase the amount of transmitter released per impulse. Drugs can also alter the release of transmitter. The stimulant amphetamine induces the release of catecholamines from adrenergic synapses. Capsaicin causes the release of the peptide substance \( P \) from sensory neurons, and tetanus toxin blocks the release of transmitters. After a transmitter has been released into the synaptic cleft, its action is terminated either by uptake or degradation. For most neurotransmitters, there are uptake mechanisms into the synaptic terminal and also into surrounding neuroglia. Cocaine, for example, blocks the uptake of catecholamines at adrenergic synapses and thus potentiates the action of these amines. However, acetylcholine is inactivated by enzymatic degradation. Anticholinesterases block the degradation of acetylcholine and thereby prolong its action. In contrast, no uptake mechanism has been found for any of the numerous CNS peptides, and it has yet to be demonstrated whether specific enzymatic degradation terminates the action of peptide transmitters.

In the postsynaptic region, the transmitter receptor provides the primary site of drug action. Drugs...
can act either as neurotransmitter agonists, such as the opioids, which mimic the action of enkephalin, or they can block receptor function. Receptor antagonism is a common mechanism of action for CNS drugs. An example is strychnine's blockade of the receptor for the inhibitory transmitter glycine. This block, which underlies strychnine's convulsant action, illustrates how the blockade of inhibitory processes results in excitation. Drugs can also act directly on the ion channel of ionotropic receptors. For example, barbiturates can enter and block the channel of many excitatory ionotropic receptors. In the case of metabotropic receptors, drugs can act at any of the steps downstream of the receptor. Perhaps the best example is provided by the methylxanthines, which can modify neurotransmitter responses mediated through the second-messenger cAMP. At high concentrations, the methylxanthines elevate the level of cAMP by blocking its metabolism and thereby prolong its action in the postsynaptic cell.

The selectivity of CNS drug action is based almost entirely on the fact that different transmitters are used by different groups of neurons. Furthermore, these transmitters are often segregated into neuronal systems that subserve broadly different CNS functions. Without such segregation, it would be impossible to selectively modify CNS function even if one had a drug that operated on a single neurotransmitter system. It is not entirely clear why the CNS has relied on so many neurotransmitters and segregated them into different neuronal systems, since the primary function of a transmitter is either excitation or inhibition; this could be accomplished with two transmitter substances or perhaps even one. That such segregation does occur has provided neuroscientists with a powerful pharmacologic approach for analyzing CNS function and treating pathologic conditions.

Identification of Central Neurotransmitters

Since drug selectivity is based on the fact that different pathways utilize different transmitters, it is a primary goal of neuropharmacologists to identify the transmitters in CNS pathways. Establishing that a chemical substance is a transmitter has been far more difficult for central synapses than for peripheral synapses. In theory, to identify a transmitter it is sufficient to show that stimulation of a pathway releases enough of the substance to produce the postsynaptic response. In practice, this experiment cannot be done satisfactorily for at least two reasons. First, the anatomic complexity of the CNS prevents the selective activation of a single set of synaptic terminals. Second, available techniques for measuring the released transmitter and applying the transmitter are not sufficiently precise to satisfy the quantitative requirements. Therefore, the following criteria have been established for transmitter identification.

Localization

A number of approaches have been used to prove that a suspected transmitter resides in the presynaptic terminal of the pathway under study. These include biochemical analysis of regional concentrations of suspected transmitters, often combined with interruption of specific pathways, and microcytochemical techniques. Immunocytochemical techniques have proved very useful in localizing peptides and enzymes that synthesize or degrade nonpeptide transmitters.

Release

To determine whether the substance can be released from a particular region, local collection (in vivo) of the extracellular fluid can sometimes be accomplished. In addition, slices of brain tissue can be electrically or chemically stimulated in vitro and the released substances measured. To determine if the release is relevant to synaptic transmission, it is important to establish that the
release is calcium-dependent. As mentioned above, anatomic complexity often prevents identification of the synaptic terminals responsible for the release, and the amount collected in the perfusate is a small fraction of the amount actually released.

Synaptic Mimicry

Finally, application of the suspected substance should produce a response that mimics the action of the transmitter released by nerve stimulation. Microiontophoresis, which permits highly localized drug administration, has been a valuable technique in assessing the action of suspected transmitters. In practice, this criterion has two parts: physiologic and pharmacologic identity. To establish physiologic identity of action, the substance must be shown to initiate the same change in ionic conductance in the postsynaptic cell as synaptically released transmitter. This requires intracellular recording and determination of the reversal potential and ionic dependencies of the responses. However, since different transmitters can elicit identical ionic conductance changes, this finding is not sufficient. Thus, selective pharmacologic antagonism is used to further establish that the suspected transmitter is acting in a manner identical to synaptically released transmitter. Because of the complexity of the CNS, specific pharmacologic antagonism of a synaptic response provides a particularly powerful technique for transmitter identification.

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Cellular Organization of the Brain

Most of the neuronal systems in the CNS can be divided into two broad categories: hierarchical systems and nonspecific or diffuse neuronal systems.

Hierarchical Systems

These systems include all of the pathways directly involved in sensory perception and motor control. The pathways are generally clearly delineated, being composed of large myelinated fibers that can often conduct action potentials at a rate in excess of 50 m/s. The information is typically phasic, and in sensory systems the information is processed sequentially by successive integrations at each relay nucleus on its way to the cortex. A lesion at any link will incapacitate the system. Within each nucleus and in the cortex, there are two types of cells: relay or projection neurons and local circuit neurons (Figure 21–5 A). The projection neurons that form the interconnecting pathways transmit signals over long distances. The cell bodies are relatively large, and their axons emit collaterals that arborize extensively in the vicinity of the neuron. These neurons are excitatory, and their synaptic influences, which involve ionotropic receptors, are very short-lived. The excitatory transmitter released from these cells is, in most instances, glutamate. Local circuit neurons are typically smaller than projection neurons, and their axons arborize in the immediate vicinity of the cell body. The vast majority of these neurons are inhibitory, and they release either GABA or glycine. They synapse primarily on the cell body of the projection neurons but can also synapse on the dendrites of projection neurons as well as with each other. A special class of local circuit neurons in the spinal cord forms axoaxonic synapses on the terminals of sensory axons (Figure 21–5 B). Two common types of pathways for these neurons (Figure 21–5 A) include recurrent feedback pathways and feed-forward pathways. In some sensory pathways such as the retina and olfactory bulb, local circuit neurons may actually lack an axon and release neurotransmitter from dendritic synapses in a graded fashion in the absence of action potentials.
Some pathways involving presynaptic dendrites of local circuit neurons are shown in Figure 21–5 C.

**Figure 21–5.**

Pathways in the central nervous system. **A** shows two relay neurons and two types of inhibitory pathways, recurrent and feed-forward. The inhibitory neurons are shown in black. **B** shows the pathway responsible for presynaptic inhibition in which the axon of an inhibitory neuron synapses on the axon terminal of an excitatory fiber. **C:** Diagram illustrating that dendrites may be both presynaptic and postsynaptic to each other, forming reciprocal synapses, two of which are shown between the same dendrite pair. In triads, an axon synapses on two dendrites, and one of these dendrites synapses on the second. In serial synapses, a dendrite may be postsynaptic to one dendrite and presynaptic to another, thus connecting a series of dendrites. Dendrites also interact through low-resistance electrotonic ("gap") junctions (two of which are shown). Except for one axon, all
Although there is a great variety of synaptic connections in these hierarchical systems, the fact that a limited number of transmitters are utilized by these neurons indicates that any major pharmacologic manipulation of this system will have a profound effect on the overall excitability of the CNS. For instance, selectively blocking GABA receptors with a drug such as picrotoxin results in generalized convulsions. Thus, while the mechanism of action of picrotoxin is quite specific in blocking the effects of GABA, the overall functional effect appears to be quite nonspecific, since GABA-mediated synaptic inhibition is so widely utilized in the brain.

Nonspecific or Diffuse Neuronal Systems

Neuronal systems that contain one of the monoamines—norepinephrine, dopamine, or 5-hydroxytryptamine (serotonin)—provide examples in this category. Certain other pathways emanating from the reticular formation and possibly some peptide-containing pathways also fall into this category. These systems differ in fundamental ways from the hierarchical systems, and the noradrenergic systems will serve to illustrate the differences.

Noradrenergic cell bodies are found primarily in a compact cell group called the locus ceruleus located in the caudal pontine central gray matter. The number of neurons in this cell group is quite small, approximately 1500 on each side of the brain in the rat. The axons of these neurons are very fine and unmyelinated. Indeed, they were entirely missed with classic anatomic techniques. It was not until the mid 1960s, when the formaldehyde fluorescence histochemical technique was applied to the study of CNS tissues, that the anatomy of the monoamine-containing systems was described. Because these axons are fine and unmyelinated, they conduct very slowly, at about 0.5 m/s. The axons branch repeatedly and are extraordinarily divergent. Branches from the same neuron can innervate several functionally different parts of the CNS. In the neocortex, these fibers have a tangential organization and therefore can monosynaptically influence large areas of cortex. The pattern of innervation in the cortex and nuclei of the hierarchical systems is diffuse, and the noradrenergic fibers form a very small percentage of the total number in the area. In addition, the axons are studded with periodic enlargements called varicosities that contain large numbers of vesicles. In some instances, these varicosities do not form synaptic contacts, suggesting that norepinephrine may be released in a rather diffuse manner, as occurs with the noradrenergic innervation of smooth muscle. This indicates that the cellular targets of these systems will be determined largely by the location of the receptors rather than the location of the release sites. Finally, most neurotransmitters utilized by diffuse neuronal systems, including norepinephrine, act—perhaps exclusively—on metabotropic receptors and therefore initiate long-lasting synaptic effects. Based on all of these observations, it is clear that the monoamine systems cannot be conveying specific topographic types of information—rather, vast areas of the CNS must be affected simultaneously and in a rather uniform way. It is not surprising, then, that these systems have been implicated in such global functions as sleeping and waking, attention, appetite, and emotional states.
the evidence for some of these compounds follows.

Table 21–2. Summary of Neurotransmitter Pharmacology in the Central Nervous System.

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Anatomy</th>
<th>Receptor Subtypes and Preferred Agonists</th>
<th>Receptor Antagonists</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Muscarinic (M₁): muscarine, McN-A-343</td>
<td>Pirenzepine, atropine</td>
<td>Excitatory: ↑ in K⁺ conductance; ↓ IP₃, DAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscarinic (M₂): muscarine, bethanechol</td>
<td>Atropine, methoctramine</td>
<td>Inhibitory: ↓K⁺ conductance; ↑ cAMP</td>
</tr>
<tr>
<td></td>
<td>Motoneuron-Renshaw cell synapse</td>
<td>Nicotinic: nicotine</td>
<td>Dihydro-β-erythroidine, α-bungarotoxin</td>
<td>Excitatory: ↑ cation conductance</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Cell bodies at all levels; short, medium, and long connections</td>
<td>D₁: SKF 38393</td>
<td>Phenothiazines, SCH 23390</td>
<td>Inhibitory (?): ↓ cAMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D₂: quinpirole, bromocriptine</td>
<td>Phenothiazines, butyrophenones</td>
<td>Inhibitory (presynaptic): ↓ Ca²⁺; Inhibitory (postsynaptic): ↑ in K⁺ conductance, ↓ cAMP</td>
</tr>
<tr>
<td>GABA</td>
<td>Supraspinal interneurons involved in pre- and postsynaptic inhibition</td>
<td>GABAₐ: muscimol</td>
<td>Bicuculline, picrotoxin</td>
<td>Inhibitory: ↑Cl⁻ conductance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABAₐ: baclofen</td>
<td>2-OH saclofen, CGP 35348, CGP55845</td>
<td>Inhibitory (presynaptic): ↓ Ca²⁺ conductance; Inhibitory (postsynaptic): ↑ K⁺ conductance</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Relay neurons at all levels and some interneurons</td>
<td>N-Methyl-D-aspartate (NMDA): NMDA</td>
<td>2-Amino-5-phosphonovalerate, CPP, MK-801</td>
<td>Excitatory: ↑ cation conductance, particularly Ca²⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMPA: AMPA</td>
<td>CNQX,</td>
<td>Excitatory: ↑</td>
</tr>
<tr>
<td></td>
<td>Glycine</td>
<td>Spinal interneurons and some brain stem interneurons</td>
<td>Taurine, β-alanine</td>
<td>Strychnine</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------------------------</td>
<td>-------------------</td>
<td>------------</td>
</tr>
<tr>
<td>5-Hydroxytryptamine</td>
<td>Cell bodies in midbrain and pons project to all levels</td>
<td>5-HT₁A: LSD, 8-OH-DPAT</td>
<td>Metergoline, spiperone</td>
<td>Ketanserin</td>
</tr>
<tr>
<td>(serotonin)</td>
<td></td>
<td>5-HT₂A: LSD, DOB</td>
<td>Ketanserin</td>
<td>ICS 205930, ondansetron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-HT₃: 2-methyl-5-HT, phenylbiguanide</td>
<td>ICS 205930, ondansetron</td>
<td>GR 1138089</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-HT₄: BIMU8</td>
<td>GR 1138089</td>
<td>GR 1138089</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>α₁: phenylephrine</td>
<td>Prazosin</td>
<td>GR 1138089</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₂: clonidine</td>
<td>Yohimbine</td>
<td>Atenolol, practolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β₁: isoproterenol, dobutamine</td>
<td>Atenolol, practolol</td>
<td>Atenolol, practolol</td>
</tr>
<tr>
<td>Receptor Type</td>
<td>Description</td>
<td>Example Molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
<td>Cells in ventral posterior hypothalamus</td>
<td>$H_1$: 2-(m-fluorophenyl)-histamine phenylhistamine, Mepyramine</td>
<td>Excitatory: $\beta^+$K conductance, IP$_3$, DAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$H_2$: dimaprit, Ranitidine</td>
<td>Inhibitory: αK conductance, cAMP</td>
<td></td>
</tr>
<tr>
<td><strong>Opioid peptides</strong></td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Mu: bendorphin, DAMGO, Naloxone, CTOP</td>
<td>Inhibitory (presynaptic): $\beta$Ca conductance, cAMP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delta: enkephalin, DPDPE, Naloxone</td>
<td>Inhibitory (postsynaptic): $\tau$K conductance, cAMP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kappa: dynorphin, U-69593, Naloxone, nor-BNI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tachykinins</strong></td>
<td>Primary sensory neurons, cell bodies at all levels; long and short connections</td>
<td>NK1: Substance P methylester, CP99994</td>
<td>Excitatory: $\beta^+$K conductance, IP$_3$, DAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NK2: $\beta$-[Ala$^8$]NKA$_{4–10}$, SR48968</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NK3: GR138676, [Pro$^+$]NKB</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocannabinoids</strong></td>
<td>Widely distributed</td>
<td>CB1: WIN55212-2 methylester, SR141716</td>
<td>Inhibitory (presynaptic): $\beta$Ca conductance, cAMP</td>
<td></td>
</tr>
</tbody>
</table>

8-OH DPAT, 8-hydroxy-2-(di-n-propylamino)tetrinal; ACPD, trans-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL-$\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionate; BIMU8, [endo-N-8-methyl-8-azabicyclo(3.2.1)oct-3-yl]-2,3-dihydro-3-isopropyl-2-oxo-1H-benzimidazol-1-carboxamide hydrochloride; CGP 35348, 3-aminopropyl(diethoxymethyl)phosphinic acid; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CP 99994, (+)-(2S,3S)-3-(2-methoxybenzylamino)-2-
Amino Acids

The amino acids of primary interest to the pharmacologist fall into two categories: the neutral amino acids glycine and GABA and the acidic amino acid glutamate. All of these compounds are present in high concentrations in the CNS and are extremely potent modifiers of neuronal excitability.

Neutral Amino Acids

The neutral amino acids are inhibitory and increase membrane permeability to chloride ions, thus mimicking the IPSP. Glycine concentrations are particularly high in the gray matter of the spinal cord, and strychnine, which is a potent spinal cord convulsant and has been used in some rat poisons, selectively antagonizes both the action of glycine and the IPSPs recorded in spinal cord neurons. Thus, it is generally agreed that glycine is released from spinal cord inhibitory local circuit neurons involved in postsynaptic inhibition.

GABA receptors are divided into two types: GABA_A and GABA_B. GABA_A receptors open chloride channels and are antagonized by picrotoxin and bicuculline, which both cause generalized convulsions. GABA_B receptors, which can be selectively activated by the antispastic drug baclofen, are coupled to G proteins that either inhibit calcium channels or activate potassium channels. In most regions of the brain, IPSPs have a fast and slow component mediated by GABA_A and GABA_B receptors, respectively. Immunohistochemical studies indicate that a large majority of the local circuit neurons synthesize GABA. A special class of local circuit neuron localized in the dorsal horn of the spinal cord also synthesizes GABA. These neurons form axoaxonic synapses with primary sensory nerve terminals and are responsible for presynaptic inhibition (Figure 21–5 B).

Acidic Amino Acids

Glutamate is present in very high concentrations in the CNS. Virtually all neurons that have been tested are strongly excited by this amino acid. This excitation is caused by the activation of both ionotropic and metabotropic receptors, which have been extensively characterized by molecular cloning. The ionotropic receptors can be further divided into three subtypes based on the action of the selective agonists: kainate (KA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and N-methyl-D-aspartate (NMDA). The AMPA- and KA-activated channels are permeable to sodium and potassium ions and, for certain subtypes, calcium as well. They are often grouped together and referred to as non-NMDA channels. The NMDA-activated channel is highly permeable to sodium, potassium, and calcium ions.
The metabotropic glutamate receptors act indirectly on ion channels via G proteins. They are selectively activated by trans-1-amino-cyclopentyl-1,3-dicarboxylate (ACPD). These G protein-coupled receptors are either positively coupled to (i.e., stimulate) phospholipase C or negatively coupled to adenyl cyclase. Depending on the type of synapse, metabotropic glutamate receptors can initiate a slow postsynaptic excitation or a presynaptic inhibition. Although the presence of metabotropic receptors at excitatory synapses varies, most excitatory synapses contain both NMDA receptors and non-NMDA receptors in the postsynaptic membrane.

The role of NMDA receptors has received considerable attention. These receptors play a critical role in synaptic plasticity, which is thought to underlie certain forms of learning and memory. They are selectively blocked by the dissociative anesthetic ketamine and the hallucinogenic drug phencyclidine. These drugs exert their effects by entering and blocking the open channel. Some drugs that block this receptor channel have potent antiepileptic activity in animal models, though these drugs have yet to be tested clinically. Considerable evidence exists that the release of glutamate during neuronal injury can, by activating the NMDA receptor, cause further cell injury and death. Thus, a particularly exciting finding is that blocking the NMDA receptor can attenuate the neuronal damage caused by anoxia in experimental animals. The potential therapeutic benefits of this action are considerable, although clinical trials to date have been disappointing.

**Acetylcholine**

Acetylcholine was the first compound to be identified pharmacologically as a transmitter in the CNS. Eccles showed in the early 1950s that excitation of Renshaw cells by motor axon collaterals was blocked by nicotinic antagonists. Furthermore, Renshaw cells were extremely sensitive to nicotinic agonists. These experiments were remarkable for two reasons. First, this early success at identifying a transmitter for a central synapse was followed by disappointment, because it remained the sole central synapse for which the transmitter was known until the late 1960s, when comparable data became available for the neutral amino acids. Second, the motor axon collateral synapse remains one of the best-documented examples of a cholinergic nicotinic synapse in the mammalian CNS, despite the rather widespread distribution of nicotinic receptors as defined by in situ hybridization studies. Most CNS responses to acetylcholine are mediated by a large family of G protein-coupled muscarinic receptors. At a few sites, acetylcholine causes slow inhibition of the neuron by activating the M₂ subtype of receptor, which opens potassium channels. A far more widespread muscarinic action in response to acetylcholine is a slow excitation that in some cases is mediated by M₁ receptors. These muscarinic effects are much slower than either nicotinic effects on Renshaw cells or the effect of amino acids. Furthermore, this muscarinic excitation is unusual in that acetylcholine produces it by decreasing the membrane permeability to potassium, i.e., the opposite of conventional transmitter action.

A number of pathways contain acetylcholine, including neurons in the neostriatum, the medial septal nucleus, and the reticular formation. Cholinergic pathways appear to play an important role in cognitive functions, especially memory. Presenile dementia of the Alzheimer type is reportedly associated with a profound loss of cholinergic neurons. However, the specificity of this loss has been questioned since the levels of other putative transmitters, e.g., somatostatin, are also decreased.

**Monoamines**

Monoamines include the catecholamines (dopamine and norepinephrine) and 5-hydroxytryptamine. Although these compounds are present in very small amounts in the CNS, they can be localized using extremely sensitive histochemical methods. These pathways are the site of action of many drugs; for example, the CNS stimulants cocaine and amphetamine are believed to act primarily at
catecholamine synapses. Cocaine blocks the reuptake of dopamine and norepinephrine, while amphetamines cause presynaptic terminals to release these transmitters.

Dopamine

The major pathways containing dopamine are the projection linking the substantia nigra to the neostriatum and the projection linking the ventral tegmental region to limbic structures, particularly the limbic cortex. The therapeutic action of the antiparkinsonism drug levodopa is associated with the former area, whereas the therapeutic action of the antipsychotic drugs is thought to be associated with the latter area. Dopamine-containing neurons in the tuberobasal ventral hypothalamus play an important role in regulating hypothalamohypophysial function. A number of dopamine receptors have been identified, and they fall into two categories: D<sub>1</sub>-like and D<sub>2</sub>-like. All dopamine receptors are metabotropic. Dopamine generally exerts a slow inhibitory action on CNS neurons. This action has been best characterized on dopamine-containing substantia nigra neurons, where D<sub>2</sub> receptor activation opens potassium channels.

Norepinephrine

This system has already been discussed. Most noradrenergic neurons are located in the locus ceruleus or the lateral tegmental area of the reticular formation. Although the density of fibers innervating various sites differs considerably, most regions of the central nervous system receive diffuse noradrenergic input. All noradrenergic receptor subtypes are metabotropic. When applied to neurons, norepinephrine can hyperpolarize them by increasing potassium conductance. This effect is mediated by α<sub>2</sub> receptors and has been characterized most thoroughly on locus ceruleus neurons. In many regions of the CNS, norepinephrine actually enhances excitatory inputs by both indirect and direct mechanisms. The indirect mechanism involves disinhibition, i.e., inhibitory local circuit neurons are inhibited. The direct mechanism is blockade of potassium conductances that slow neuronal discharge. Depending on the type of neuron, this effect is mediated by either α<sub>1</sub> or β receptors. Facilitation of excitatory synaptic transmission is in accordance with many of the behavioral processes thought to involve noradrenergic pathways, e.g., attention and arousal.

5-Hydroxytryptamine

Most 5-hydroxytryptamine (5-HT, serotonin) pathways originate from neurons in the raphe or midline regions of the pons and upper brainstem. 5-HT is contained in unmyelinated fibers that diffusely innervate most regions of the CNS, but the density of the innervation varies. 5-HT acts on more than a dozen receptor subtypes. Except for the 5-HT<sub>3</sub> receptor, all of these receptors are metabotropic. The ionotropic 5-HT<sub>3</sub> receptor exerts a rapid excitatory action at a very limited number of sites in the CNS. In most areas of the central nervous system, 5-HT has a strong inhibitory action. This action is mediated by 5-HT<sub>1A</sub> receptors and is associated with membrane hyperpolarization caused by an increase in potassium conductance. It has been found that 5-HT<sub>1A</sub> receptors and GABA<sub>B</sub> receptors share the same potassium channels. Some cell types are slowly excited by 5-HT owing to its blockade of potassium channels via 5-HT<sub>2</sub> or 5-HT<sub>4</sub> receptors. Both excitatory and inhibitory actions can occur on the same neurons. It has often been speculated that 5-HT pathways may be involved in the hallucinations induced by LSD, since this compound can antagonize the peripheral actions of 5-HT. However, LSD does not appear to be a 5-HT antagonist in the central nervous system, and typical LSD-induced behavior is still seen in animals after raphe nuclei are destroyed. Other proposed regulatory functions of 5-HT-containing neurons include sleep, temperature, appetite, and neuroendocrine control.

Peptides
A great many CNS peptides have been discovered that produce dramatic effects both on animal behavior and on the activity of individual neurons. Many of the peptides have been mapped with immunohistochemical techniques and include opioid peptides (enkephalins, endorphins, etc), neurotensin, substance P, somatostatin, cholecystokinin, vasoactive intestinal polypeptide, neuropeptide Y, and thyrotropin-releasing hormone. As in the peripheral autonomic nervous system, peptides often coexist with a conventional nonpeptide transmitter in the same neuron. A good example of the approaches used to define the role of these peptides in the central nervous system comes from studies on substance P and its association with sensory fibers. Substance P is contained in and released from small unmyelinated primary sensory neurons of the spinal cord and brain stem and causes a slow EPSP in target neurons. These sensory fibers are known to transmit noxious stimuli, and it is therefore surprising that—while substance P receptor antagonists can modify responses to certain types of pain—they do not block the response. Glutamate, which is released with substance P from these synapses, presumably plays an important role in transmitting pain stimuli. Substance P is certainly involved in many other functions, since it is found in many areas of the central nervous system that are unrelated to pain pathways.

Many of these peptides are also found in peripheral structures, including peripheral synapses. They are described in Chapter 6: Introduction to Autonomic Pharmacology and Chapter 17: Vasoactive Peptides.

Nitric Oxide

The CNS contains a substantial amount of nitric oxide synthase (NOS), which is found within certain classes of neurons. This neuronal NOS is an enzyme activated by calcium-calmodulin, and activation of NMDA receptors, which increases intracellular calcium, results in the generation of nitric oxide. While a physiologic role for nitric oxide has been clearly established for vascular smooth muscle, its role in synaptic transmission and synaptic plasticity remains controversial.

Endocannabinoids

The primary psychoactive ingredient in cannabis, δ9-tetrahydrocannabinol (δ9-THC), affects the brain mainly by activating a specific cannabinoid receptor, CB1. CB1 is expressed at high levels in many brain regions, and several endogenous brain lipids, including anandamide and 2-arachidonylglycerol, have been identified as CB1 ligands. These ligands are not stored, as are classic neurotransmitters, but instead are rapidly synthesized by neurons in response to depolarization and consequent calcium influx. In further contradistinction to classic neurotransmitters, endogenous cannabinoids can function as retrograde synaptic messengers: they are released from postsynaptic neurons and travel backward across synapses, activating CB1 receptors on presynaptic neurons and suppressing transmitter release. Cannabinoids may affect memory, cognition, and pain perception by this mechanism.

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Chapter 22. Sedative-Hypnotic Drugs

Sedative-Hypnotic Drugs: Introduction

Assignment of a drug to the sedative-hypnotic class indicates that its major therapeutic use is to cause sedation (with concomitant relief of anxiety) or to encourage sleep. Because there is considerable chemical variation within this group, this drug classification is based on clinical uses
rather than on similarities in chemical structure. Anxiety states and sleep disorders are common problems, and sedative-hypnotics are among the most widely prescribed drugs worldwide. 

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Basic Pharmacology of Sedative-Hypnotics

An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect. The degree of central nervous system depression caused by a sedative should be the minimum consistent with therapeutic efficacy. A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep. Hypnotic effects involve more pronounced depression of the central nervous system than sedation, and this can be achieved with most drugs in this class simply by increasing the dose. Graded dose-dependent depression of central nervous system function is a characteristic of sedative-hypnotics. However, individual drugs differ in the relationship between the dose and the degree of central nervous system depression. Two examples of such dose-response relationships are shown in Figure 22–1. The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols. With such drugs, an increase in dose above that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, will require proportionately greater dosage increments in order to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and certain newer hypnotics; the greater margin of safety this offers is an important reason for their widespread use to treat anxiety states and sleep disorders.

Figure 22–1. 

Dose-response curves for two hypothetical sedative-hypnotics. 

Chemical Classification

The benzodiazepines (Figure 22–2) are the most widely used sedative-hypnotics. All of the structures shown are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-
membered heterocyclic ring structure. A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative-hypnotic activity. The structures of triazolam and alprazolam include the addition of a triazole ring at the 1,2-position, and such drugs are sometimes referred to as triazolobenzodiazepines.

Figure 22–2.

Chemical structures of benzodiazepines.
The chemical structures of some older and less commonly used sedative-hypnotics, including several barbiturates, are shown in Figure 22–3. Glutethimide (a piperidinedione) and meprobamate (a carbamate) are of distinctive chemical structure but are practically equivalent to barbiturates in their pharmacologic effects, and their clinical use is rapidly declining. The sedative-hypnotic class also includes compounds of simple chemical structure, including ethanol (see Chapter 23: The Alcohols), chloral hydrate, trichloroethanol, and paraldehyde (not shown).

Several drugs with novel chemical structures have been introduced recently. Buspirone is an anxiolytic agent that has actions different from those of conventional sedative-hypnotic drugs. Zolpidem and zaleplon, while structurally unrelated to benzodiazepines, share a similar mechanism of action.
Other classes of drugs not included in Figure 22–3 that may exert sedative effects include most antipsychotic and many antidepressant drugs and certain antihistaminic agents (eg, hydroxyzine, promethazine). As discussed in other chapters, these agents differ from conventional sedative-hypnotics in both their effects and their major therapeutic uses. Since they commonly exert marked effects on the peripheral autonomic nervous system, they are sometimes referred to as "sedative-autonomic" drugs. Certain antihistaminics with sedative effects are available in over-the-counter sleep aids. Their autonomic properties and their long durations of action can result in adverse effects.

The Benzodiazepines & Barbiturates

Pharmacokinetics

Absorption and Distribution

The rates of oral absorption of benzodiazepines differ depending on a number of factors, including lipophilicity. Oral absorption of triazolam is extremely rapid, and that of diazepam and the active metabolite of clorazepate is more rapid than other commonly used benzodiazepines. Clorazepate is converted to its active form, desmethyldiazepam (nordiazepam), by acid hydrolysis in the stomach. Oxazepam, lorazepam, and temazepam are absorbed from the gut at slower rates than other benzodiazepines. The bioavailability of several benzodiazepines, including chlordiazepoxide and diazepam, may be unreliable after intramuscular injection. Most of the barbiturates and other older sedative-hypnotics are absorbed rapidly into the blood following their oral administration.

Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the central nervous system. For example, diazepam and triazolam are more lipid-soluble than chlordiazepoxide and lorazepam; thus, the central nervous system actions of the former drugs are
more rapid in onset. The thiobarbiturates (eg, thiopental), in which the oxygen on C\textsubscript{2} is replaced by sulfur, are very lipid-soluble, and a high rate of entry into the central nervous system contributes to the rapid onset of their central effects (see Chapter 25: General Anesthetics). In contrast, phenobarbital and meprobamate have quite low lipid solubility and penetrate the brain slowly.

All sedative-hypnotics cross the placental barrier during pregnancy. If sedative-hypnotics are given in the predelivery period, they may contribute to the depression of neonatal vital functions. Sedative-hypnotics are detectable in breast milk and may exert depressant effects in the nursing infant.

Although sedative-hypnotic drugs, including benzodiazepines, bind to plasma proteins, few clinically significant interactions involving these drugs appear to be based on such protein binding. One exception is chloral hydrate, which transiently increases the anticoagulant effects of warfarin by displacement of the anticoagulant drug from such binding sites.

Biotransformation

Metabolic transformation to more water-soluble metabolites is necessary for clearance of sedative-hypnotics from the body. The microsomal drug-metabolizing enzyme systems of the liver are most important in this regard. Few sedative-hypnotics are excreted from the body in unchanged form, so elimination half-life depends mainly on the rate of metabolic transformation.

Benzodiazepines

Hepatic metabolism accounts for the clearance of all benzodiazepines. The patterns and rates of metabolism depend on the individual drugs. Most benzodiazepines undergo microsomal oxidation (phase I reactions), including  \textit{N}-dealkylation and aliphatic hydroxylation. The metabolites are subsequently conjugated (phase II reactions) to form glucuronides that are excreted in the urine. However, many phase I metabolites of benzodiazepines are pharmacologically active, with long half-lives.

As shown in Figure 22–4, desmethyldiazepam, which has an elimination half-life of more than 40 hours, is an active metabolite of chlordiazepoxide, diazepam, prazepam, and clorazepate. Desmethyldiazepam in turn is biotransformed to the active compound, oxazepam. Other active metabolites of chlordiazepoxide include desmethylchlordiazepoxide and demoxepam. While diazepam is metabolized mainly to desmethyldiazepam, it is also converted to temazepam (not shown in Figure 22–4), which is further metabolized in part to oxazepam. Flurazepam, which is used mainly for hypnosis, is oxidized by hepatic enzymes to three active metabolites, desalkylflurazepam, hydroxyethylflurazepam, and flurazepam aldehyde (not shown), which have elimination half-lives ranging from 30 to 100 hours. Alprazolam and triazolam undergo \textit{\alpha}-hydroxylation, and the resulting metabolites appear to exert short-lived pharmacologic effects since they are rapidly conjugated to form inactive glucuronides.
Biotransformation of benzodiazepines. (Boldface, drugs available for clinical use; *, active metabolite.)

The formation of active metabolites has complicated studies on the pharmacokinetics of the benzodiazepines in humans because the elimination half-life of the parent drug may have little relationship to the time course of pharmacologic effects. Those benzodiazepines for which the parent drug or active metabolites have long half-lives are more likely to cause cumulative effects with multiple doses. Cumulative and residual effects such as excessive drowsiness appear to be less of a problem with such drugs as estazolam, oxazepam, and lorazepam, which have shorter half-lives and are metabolized directly to inactive glucuronides. Some pharmacokinetic properties of selected benzodiazepines are listed in Table 22–1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Blood Level (hours)</th>
<th>Elimination Half-Life (hours)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1–2</td>
<td>12–15</td>
<td>Rapid oral absorption</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>2–4</td>
<td>15–40</td>
<td>Active metabolites; erratic bioavailability from IM injection</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>1–2 (nordiazepam)</td>
<td>50–100</td>
<td>Prodrug; hydrolyzed to active form in stomach</td>
</tr>
</tbody>
</table>
### Diazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>1–2</td>
<td>20–80</td>
<td>Active metabolites; erratic bioavailability from IM injection</td>
</tr>
</tbody>
</table>

### Estazolam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam</td>
<td>2</td>
<td>10–24</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>

### Flurazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>1–2</td>
<td>40–100</td>
<td>Active metabolites with long half-lives</td>
</tr>
</tbody>
</table>

### Lorazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1–6</td>
<td>10–20</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>

### Oxazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>2–4</td>
<td>10–20</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>

### Prazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazepam</td>
<td>1–2</td>
<td>50–100</td>
<td>Active metabolites with long half-lives</td>
</tr>
</tbody>
</table>

### Quazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quazepam</td>
<td>2</td>
<td>30–100</td>
<td>Active metabolites with long half-lives</td>
</tr>
</tbody>
</table>

### Temazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>2–3</td>
<td>10–40</td>
<td>Slow oral absorption</td>
</tr>
</tbody>
</table>

### Triazolam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>1</td>
<td>2–3</td>
<td>Rapid onset; short duration of action</td>
</tr>
</tbody>
</table>

\(^1\) Includes half-lives of major metabolites.

---

**Barbiturates**

With the exception of phenobarbital, only insignificant quantities of the barbiturates are excreted unchanged. The major metabolic pathways involve oxidation by hepatic enzymes of chemical groups attached to C₅, which are different for the individual barbiturates. The alcohols, acids, and ketones formed appear in the urine as glucuronide conjugates. With very few exceptions, the metabolites of the barbiturates lack pharmacologic activity. The overall rate of hepatic metabolism in humans depends on the individual drug but (with the exception of the thiobarbiturates) is usually slow. The elimination half-lives of secobarbital and pentobarbital range from 18 to 48 hours in different individuals. The elimination half-life of phenobarbital in humans is 4–5 days. Multiple dosing with these agents can lead to cumulative effects.

---

**Excretion**

The water-soluble metabolites of benzodiazepines and other sedative-hypnotics are excreted mainly via the kidney. In most cases, changes in renal function do not have a marked effect on the elimination of parent drugs. Phenobarbital is excreted unchanged in the urine to a certain extent (20–30% in humans), and its elimination rate can be increased significantly by alkalinization of the urine. This is partly due to increased ionization at alkaline pH, since phenobarbital is a weak acid with a pKₐ of 7.4. Only trace amounts of the benzodiazepines appear in the urine unchanged.

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**Factors Affecting Biodisposition**

The biodisposition of sedative-hypnotics can be influenced by several factors, particularly alterations in hepatic function resulting from disease or drug-induced increases or decreases in microsomal enzyme activities (see Chapter 4: Drug Biotransformation).

In very old patients and in patients with severe liver disease, the elimination half-lives of these drugs are often increased significantly. In such cases, multiple normal doses of these sedative-hypnotics often result in excessive central nervous system effects.
The activity of hepatic microsomal drug-metabolizing enzymes may be increased in patients exposed to certain older sedative-hypnotics on a chronic basis (enzyme induction; see Chapter 4: Drug Biotransformation). Barbiturates (especially phenobarbital) and meprobamate are most likely to cause this effect, which may result in an increase in their hepatic metabolism as well as that of other drugs. Increased biotransformation of other pharmacologic agents as a result of enzyme induction by barbiturates is a potential mechanism underlying drug interactions (Appendix II). In contrast, the benzodiazepines do not change hepatic drug-metabolizing enzyme activity with continuous use.

Pharmacodynamics of Benzodiazepines & Barbiturates

Molecular Pharmacology of the GABA<sub>A</sub> Receptor

The benzodiazepines, the barbiturates, zolpidem, and many other drugs bind to molecular components of the GABA<sub>A</sub> receptor present in neuronal membranes in the central nervous system. This receptor, which functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA (see Chapter 21: Introduction to the Pharmacology of CNS Drugs).

The GABA<sub>A</sub> receptor has a pentameric structure assembled from five subunits (each with four transmembrane-spanning domains) selected from multiple polypeptide classes (α, β, γ, δ, ε, θ, etc). Different subunits of several of these classes have been characterized, e.g., six different α, four β, and three γ. A major isoform of the GABA<sub>A</sub> receptor found in many regions of the brain consists of two α<sub>1</sub> and two β<sub>2</sub> subunits and one γ<sub>2</sub> subunit. In this receptor isoform, the binding site for GABA is located between an α<sub>1</sub> and a β<sub>2</sub> subunit and the binding pocket for benzodiazepines (a benzodiazepine receptor subtype, BZ<sub>1</sub> or α<sub>1</sub>) is between an α<sub>1</sub> and the γ<sub>2</sub> subunit. However, GABA<sub>A</sub> receptors in different areas of the central nervous system consist of various combinations of the essential subunits, and the benzodiazepines bind to many of these, including receptor isoforms containing α<sub>2</sub>, α<sub>3</sub>, and α<sub>5</sub> subunits. Barbiturates also bind to multiple isoforms of the GABA<sub>A</sub> receptor but at different sites from those with which benzodiazepines interact. In contrast to benzodiazepines, zolpidem and zaleplon bind more selectively since these drugs only interact with GABA<sub>A</sub> receptor isoforms that contain α<sub>1</sub> subunits (BZ<sub>1</sub> subtype). The heterogeneity of GABA<sub>A</sub> receptors may constitute the molecular basis for the varied pharmacologic actions of benzodiazepines and related drugs (see GABA Receptor Heterogeneity & Pharmacologic Selectivity).

A model of the hypothetical GABA-BZ receptor-chloride ion channel macromolecular complex is shown in Figure 22–5.
A model of the GABA<sub>A</sub> receptor-chloride ion channel macromolecular complex (many others could be proposed). A heteroligomeric glycoprotein, the complex consists of five or more membrane-spanning subunits. Multiple forms of α, β, and γ subunits are arranged in different pentameric combinations so that GABA<sub>A</sub> receptors exhibit molecular heterogeneity. GABA appears to interact with α or β subunits triggering chloride channel opening with resultant membrane hyperpolarization. Binding of benzodiazepines to γ subunits or to an area of the α unit influenced by the β unit facilitates the process of channel opening but does not directly initiate chloride current. (Modified and reproduced, with permission, from Zorumsky CF, Isenberg KE: Insights into the structure and function of GABA-benzodiazepine receptors: Ion channels and psychiatry. Am J Psychiatry 1991;148:162.)

Neuropharmacology

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Electrophysiological studies have shown that benzodiazepines potentiate GABAergic inhibition at all levels of the neuraxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex, and cerebral cortex. Benzodiazepines appear to increase the efficiency of GABAergic synaptic inhibition. The benzodiazepines do not substitute for GABA but appear to enhance GABA’s effects without directly activating GABA receptors or opening the associated chloride channels. The enhancement in chloride ion conductance induced by the interaction of benzodiazepines with GABA takes the form of an increase in the frequency of channel-opening events.

Barbiturates also facilitate the actions of GABA at multiple sites in the central nervous system, but—in contrast to benzodiazepines—they appear to increase the duration of the GABA-gated chloride channel openings. At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels. These effects involve a binding site or sites distinct from the benzodiazepine binding sites. Barbiturates are less selective in their actions than benzodiazepines, since they also depress the actions of excitatory neurotransmitters (eg, glutamic acid) and exert nonsynaptic membrane effects in parallel with their effects on GABA neurotransmission. This
multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia (see Chapter 25: General Anesthetics) and for their more pronounced central depressant effects (which result in their low margin of safety) compared to benzodiazepines.

Benzodiazepine Receptor Ligands

The components of the GABA_A receptor-chloride ion channel macromolecule that function as benzodiazepine receptors exhibit heterogeneity and include BZ_1 (α_1) and BZ_2 (α_2) subtypes (see The Versatility of the Chloride Channel GABA Receptor Complex). Three types of ligand-benzodiazepine receptor interactions have been reported: (1) Agonists facilitate GABA actions, and this occurs at multiple BZ receptor sites in the case of the benzodiazepines. The nonbenzodiazepines zolpidem and zaleplon are selective agonists at the BZ_1 (α_1) receptor subtype. Endogenous agonist ligands for the BZ receptors have been proposed, since benzodiazepine-like chemicals have been isolated from brain tissue of animals never exposed to these drugs. Nonbenzodiazepine molecules that have affinity for benzodiazepine receptors have also been detected in human brain. Such "endozepines" facilitate GABA-mediated chloride channel gating in cultured neurons. (2) Antagonists are typified by the synthetic benzodiazepine derivative flumazenil, which blocks the actions of benzodiazepines and zolpidem but does not antagonize the actions of barbiturates, meprobamate, or ethanol. Certain endogenous compounds, eg, diazepam-binding inhibitor (DBI), are also capable of blocking the interaction of benzodiazepines with benzodiazepine receptors. (3) Inverse agonists act as negative allosteric modulators of GABA receptor function. Their interaction with benzodiazepine receptors can produce anxiety and seizures, an action that has been demonstrated for several compounds, especially the β-carbolines, eg, n-butyl-β-carboline-3-carboxylate (β-CCB). In addition to their direct actions, these molecules can block the effects of benzodiazepines.

The physiologic significance of endogenous modulators of the functions of GABA in the central nervous system remains unclear. To date it has not been established that the putative endogenous ligands of BZ receptors play a role in the control of states of anxiety, sleep patterns, or any other characteristic behavioral expression of central nervous system function.

Organ Level Effects

Sedation

Benzodiazepines, barbiturates, and most older sedative-hypnotic drugs exert calming effects with concomitant reduction of anxiety at relatively low doses. In most cases, however, the anxiolytic actions of sedative-hypnotics are accompanied by some decremental effects on psychomotor and cognitive functions. In experimental animal models, sedative-hypnotic drugs are able to disinhibit punishment-suppressed behavior. This disinhibition has been equated with antianxiety effects of sedative-hypnotics, and it is not a characteristic of all drugs that have sedative effects, eg, the tricyclic antidepressants and antihistamines. However, the disinhibition of previously suppressed behavior may be more related to behavioral disinhibitory effects of sedative-hypnotics, including euphoria, impaired judgment, and loss of self-control, which can occur at dosages in the range of those used for management of anxiety. The benzodiazepines also exert dose-dependent anterograde amnesic effects (inability to remember events occurring during the drug's duration of action).

Hypnosis

By definition, all of the sedative-hypnotics will induce sleep if high enough doses are given. The effects of sedative-hypnotics on the stages of sleep depend on several factors, including the specific
drug, the dose, and the frequency of its administration. The effects of benzodiazepines and older sedative-hypnotics on patterns of normal sleep are as follows: (1) the latency of sleep onset is decreased (time to fall asleep); (2) the duration of stage 2 NREM sleep is increased; (3) the duration of REM sleep is decreased; and (4) the duration of stage 4 NREM slow-wave sleep is decreased. Zolpidem also decreases REM sleep but has minimal effect on slow-wave sleep. Zaleplon decreases the latency of sleep onset with little effect on total sleep time, NREM, or REM sleep.

More rapid onset of sleep and prolongation of stage 2 are presumably clinically useful effects. However, the significance of sedative-hypnotic drug effects on REM and slow-wave sleep is not clear. Deliberate interruption of REM sleep causes anxiety and irritability followed by a rebound increase in REM sleep at the end of the experiment. A similar pattern of "REM rebound" can be detected following abrupt cessation of drug treatment with sedative-hypnotics, especially when drugs with short durations of action are used at high doses. Despite possible reductions in slow-wave sleep, there are no reports of disturbances in the secretion of pituitary or adrenal hormones when either barbiturates or benzodiazepines are used as hypnotics. The use of sedative-hypnotics for more than 1–2 weeks leads to some tolerance to their effects on sleep patterns.

Anesthesia

As shown in Figure 22–1, certain sedative-hypnotics in high doses will depress the central nervous system to the point known as stage III of general anesthesia (see Chapter 25: General Anesthetics). However, the suitability of a particular agent as an adjunct in anesthesia depends mainly on the physicochemical properties that determine its rapidity of onset and duration of effect. Among the barbiturates, thiopental and methohexital are very lipid-soluble, penetrating brain tissue rapidly following intravenous administration, a characteristic favoring their use for induction of the anesthetic state. Rapid tissue redistribution accounts for the short duration of action of these drugs, a feature useful in recovery from anesthesia.

Benzodiazepines—including diazepam, lorazepam, and midazolam—are used intravenously in anesthesia (see Chapter 25: General Anesthetics), often in combination with other agents. Not surprisingly, benzodiazepines given in large doses as adjuncts to general anesthetics may contribute to a persistent postanesthetic respiratory depression. This is probably related to their relatively long half-lives and the formation of active metabolites.

Anticonvulsant Effects

Most of the sedative-hypnotics are capable of inhibiting the development and spread of epileptiform activity in the central nervous system. Some selectivity exists in that some members of the group can exert anticonvulsant effects without marked central nervous system depression (although psychomotor function may be impaired). Several benzodiazepines—including clonazepam, nitrazepam, lorazepam, and diazepam—are sufficiently selective to be clinically useful in the management of seizure states (see Chapter 24: Antiseizure Drugs). Of the barbiturates, phenobarbital and metharbital (converted to phenobarbital in the body) are effective in the treatment of generalized tonic-clonic seizures.

Muscle Relaxation

Some sedative-hypnotics, particularly members of the carbamate and benzodiazepine groups, exert inhibitory effects on polysynaptic reflexes and intermuncial transmission and at high doses may also depress transmission at the skeletal neuromuscular junction. Somewhat selective actions of this type that lead to muscle relaxation can be readily demonstrated in animals and have led to claims of
usefulness for relaxing contracted voluntary muscle in joint disease or muscle spasm (see Clinical Pharmacology).

Effects on Respiration and Cardiovascular Function

At hypnotic doses in healthy patients, the effects of sedative-hypnotics on respiration are comparable to changes during natural sleep. However, even at therapeutic doses, sedative-hypnotics can produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of sedative-hypnotics.

At doses up to those causing hypnosis, no significant effects on the cardiovascular system are observed in healthy patients. However, in hypovolemic states, heart failure, and other diseases that impair cardiovascular function, normal doses of sedative-hypnotics may cause cardiovascular depression, probably as a result of actions on the medullary vasomotor centers. At toxic doses, myocardial contractility and vascular tone may both be depressed by central and peripheral effects, leading to circulatory collapse. Respiratory and cardiovascular effects are more marked when sedative-hypnotics are given intravenously.

Tolerance; Psychologic & Physiologic Dependence

Tolerance—decreased responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use. It may result in an increase in the dose needed to maintain symptomatic improvement or to promote sleep. It is important to recognize that partial cross-tolerance occurs between the sedative-hypnotics described here and also with ethanol (Chapter 23: The Alcohols)—a feature of some clinical importance, as explained below. The mechanisms responsible for tolerance to sedative-hypnotics are not well understood. An increase in the rate of drug metabolism (metabolic tolerance) may be partly responsible in the case of chronic administration of barbiturates, but changes in responsiveness of the central nervous system (pharmacodynamic tolerance) are of greater importance for most sedative-hypnotics. In the case of benzodiazepines, the development of tolerance in animals is associated with down-regulation of brain benzodiazepine receptors.

The perceived desirable properties of relief of anxiety, euphoria, disinhibition, and promotion of sleep have led to the compulsive misuse of virtually all sedative-hypnotics. For this reason, most sedative-hypnotic drugs are classified as Schedule III or Schedule IV drugs for prescribing purposes. (See Chapter 32: Drugs of Abuse for a detailed discussion.) The consequences of abuse of these agents can be defined in both psychologic and physiologic terms. The psychologic component may initially parallel simple neurotic behavior patterns difficult to differentiate from those of the inveterate coffee drinker or cigarette smoker. When the pattern of sedative-hypnotic use becomes compulsive, more serious complications develop, including physiologic dependence and tolerance.

Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent the appearance of an abstinence or withdrawal syndrome. In the case of sedative-hypnotics, this syndrome is characterized by states of increased anxiety, insomnia, and central nervous system excitability that may progress to convulsions. Most sedative-hypnotics—including benzodiazepines—are capable of causing physiologic dependence when used on a chronic basis. However, the severity of withdrawal symptoms differs between individual drugs and depends also on the magnitude of the dose used immediately prior to cessation of use. When higher doses of sedative-hypnotics are used, abrupt withdrawal leads to more serious withdrawal signs. Differences in the severity of withdrawal symptoms between individual sedative-hypnotics relate in part to half-
life, since drugs with long half-lives are eliminated slowly enough to accomplish gradual withdrawal with few physical symptoms. The use of drugs with very short half-lives for hypnotic effects may lead to signs of withdrawal even between doses. For example, triazolam, a benzodiazepine with a half-life of about 4 hours, has been reported to cause daytime anxiety when used to treat sleep disorders.

Benzodiazepine Antagonists: Flumazenil

Flumazenil is one of several 1,4-benzodiazepine derivatives with high affinity for the benzodiazepine receptor that act as competitive antagonists. It is the only benzodiazepine receptor antagonist available for clinical use at present. It blocks many of the actions of benzodiazepines (and imidazopyridines) but does not antagonize the central nervous system effects of other sedative-hypnotics, ethanol, opioids, or general anesthetics. Flumazenil is approved for use in reversing the central nervous system depressant effects of benzodiazepine overdose and to hasten recovery following use of these drugs in anesthetic and diagnostic procedures. While the drug reverses the sedative effects of benzodiazepines, antagonism of benzodiazepine-induced respiratory depression is less predictable. When given intravenously, flumazenil acts rapidly but has a short half-life (0.7–1.3 hours) due to rapid hepatic clearance. Since all benzodiazepines have a longer duration of action than flumazenil, sedation commonly recurs, requiring repeated administration of the antagonist.

Adverse effects of flumazenil include agitation, confusion, dizziness, and nausea. Flumazenil may cause a severe precipitated abstinence syndrome in patients who have developed physiologic benzodiazepine dependence. In patients who have ingested benzodiazepines with tricyclic antidepressants, seizures and cardiac arrhythmias may occur following flumazenil administration. Transient improvement in mental status has been reported with flumazenil when used in patients with hepatic encephalopathy.

Newer Drugs for Anxiety & Sleep Disorders

Although the benzodiazepines continue to be widely used in the treatment of anxiety states and for insomnia, their adverse effects include daytime sedation and drowsiness, synergistic depression of the central nervous system with other drugs (especially alcohol), and the possibility of psychologic and physiologic dependence with repeated use. Anxiolytic drugs that act through non-GABAergic systems might have a reduced propensity for such actions. Several nonbenzodiazepines, including buspirone, have such characteristics. In addition, the newer hypnotics zolpidem and zaleplon are more selective in their central actions even though they appear to act through benzodiazepine receptors.

Buspirone

Buspirone has selective anxiolytic effects, and its pharmacologic characteristics are quite different from those of other drugs described in this chapter. Buspirone relieves anxiety without causing marked sedative or euphoric effects. Unlike benzodiazepines, the drug has no hypnotic, anticonvulsant, or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems. It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT1A receptors, but it also has affinity for brain dopamine D2 receptors. Buspirone-treated patients show no rebound anxiety or withdrawal signs on abrupt discontinuance. The drug is not effective in blocking the acute withdrawal syndrome resulting from abrupt cessation of use of benzodiazepines or other sedative-hypnotics. Buspirone has minimal abuse liability. In marked contrast to the benzodiazepines, the anxiolytic effects of buspirone may take more than a week to become established, making the drug unsuitable for management of acute anxiety states. The drug is used in
generalized anxiety states but is not very effective in panic disorders.

Buspirone is rapidly absorbed orally but undergoes extensive first-pass metabolism via hydroxylation and dealkylation reactions to form several active metabolites. The major metabolite is 1-(2-pyrimidyl)-piperazine (1-PP), which has $\alpha_2$-adrenoceptor-blocking actions and which enters the central nervous system to reach higher levels than the parent drug. It is not known what role (if any) 1-PP plays in the central actions of buspirone. The elimination half-life of buspirone is 2–4 hours, and liver dysfunction may decrease its clearance. Rifampin, an inducer of cytochrome P450, decreases the half-life of buspirone; inhibitors of CYP3A4 (e.g., erythromycin, ketoconazole) increase plasma levels of buspirone.

Buspirone causes less psychomotor impairment than diazepam and does not affect driving skills. The drug does not potentiate the central nervous system depressant effects of conventional sedative-hypnotic drugs, ethanol, or tricyclic antidepressants, and elderly patients do not appear to be more sensitive to its actions. Tachycardia, palpitations, nervousness, gastrointestinal distress, and paresthesias may occur more frequently than with benzodiazepines. Buspirone also causes a dose-dependent pupillary constriction. Blood pressure may be elevated in patients receiving MAO inhibitors. A number of buspirone analogs have been developed (e.g., ipsapirone, gepirone, tandospirone) and are under study.

Zolpidem

Zolpidem, an imidazopyridine derivative structurally unrelated to benzodiazepines, has hypnotic actions. The drug binds selectively to the BZ₁ (M₁) subtype of benzodiazepine receptors that contain $\alpha_1$ subunits and facilitates GABA-mediated neuronal inhibition. Like the benzodiazepines, the actions of zolpidem are antagonized by flumazenil. Unlike benzodiazepines, zolpidem has minimal muscle relaxing and anticonvulsant effects. However, amnestic effects have been reported with use of doses greater than recommended. The drug has a rapid onset of action, and its duration of hypnotic action is close to that of triazolam. Zolpidem causes minor effects on sleep patterns at the recommended hypnotic dose but can suppress REM sleep at higher doses. Rebound insomnia may occur on abrupt discontinuance of higher doses. Respiratory depression occurs if large doses of zolpidem are ingested with other CNS depressants, including ethanol.

The risk of development of tolerance and dependence with extended use of zolpidem appears to be less than with the use of hypnotic benzodiazepines. Zolpidem is rapidly metabolized to inactive metabolites by the liver via oxidation and hydroxylation. The elimination half-life of the drug is 1.5–3.5 hours, with clearance decreased in elderly patients. Dosage reductions are recommended in patients with hepatic dysfunction, in elderly patients, and in patients taking cimetidine. Rifampin, an inducer of hepatic cytochrome P450, decreases the half-life of zolpidem.

Zaleplon

Zaleplon binds selectively to the BZ₁ receptor subtype, facilitating the inhibitory actions of GABA. Zaleplon is rapidly absorbed from the gastrointestinal tract and has an elimination half-life of about 1 hour. The drug is metabolized to inactive metabolites mainly by hepatic aldehyde oxidase and partly by the cytochrome P450 isoform CYP3A4. Dosage should be reduced in patients with hepatic impairment and in the elderly. Metabolism of zaleplon is inhibited by cimetidine; drugs that induce hepatic CYP3A4 increase the clearance of zaleplon.

Zaleplon decreases sleep latency but has little effect on total sleep time or on sleep architecture. Rapid onset and short duration of action are favorable properties for those patients who have
difficulty falling asleep. Amnestic effects and next-day impairment of psychomotor performance may occur, but less commonly than in the case of hypnotic benzodiazepines or zolpidem. The risk of development of tolerance and of withdrawal symptoms indicative of physiologic dependence appears to be low, but the use of high doses (twice the recommended dose) has caused rebound insomnia. Zaleplon potentiates the CNS depressant effects of ethanol and other sedative-hypnotics.

Older Sedative-Hypnotics

These drugs include alcohols (ethchlorvynol, chloral hydrate), piperidinediones (glutethimide, methyprylon), and carbamates (meprobamate). They are rarely used in therapy, though the low cost of chloral hydrate makes it attractive for institutional use. Little is known about their molecular mechanisms of action. Most of these drugs are biotransformed to more water-soluble compounds by hepatic enzymes. Trichloroethanol is the pharmacologically active metabolite of chloral hydrate and has a half-life of 6–10 hours. However, its toxic metabolite, trichloroacetic acid, is cleared very slowly and can accumulate with the nightly administration of chloral hydrate.

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GABA Receptor Heterogeneity & Pharmacologic Selectivity

Studies involving genetically engineered mice have demonstrated that the specific pharmacologic actions elicited by benzodiazepines and other drugs that modulate GABA actions are influenced by the composition of the subunits assembled to form the GABA<sub>A</sub> receptor. Benzodiazepines only interact with brain GABA<sub>A</sub> receptors in which the α subunits (1, 2, 3, and 5) have a conserved histidine residue in the N-terminal domain. Strains of mice in which a point mutation has been inserted (“knock-in” strategy), converting histidine to arginine in the α<sub>1</sub> subunit, show resistance to both the sedative and amnestic effects of benzodiazepines, but anxiolytic and muscle relaxing effects are largely unchanged. These animals are also unresponsive to the hypnotic actions of zolpidem and zaleplon, drugs that bind selectively to GABA<sub>A</sub> receptors containing α<sub>1</sub> subunits. In contrast, mice with selective histidine-arginine mutations in the α<sub>2</sub> subunit of GABA<sub>A</sub> receptors show selective resistance to the antianxiety effects of benzodiazepines. Based on studies of this type it has been suggested that α<sub>1</sub> subunits in GABA<sub>A</sub> receptors mediate sedation, amnesia and possibly antiseizure effects of benzodiazepines, while α<sub>2</sub> subunits are involved in their anxiolytic and muscle-relaxing actions. Other transgenic studies have led to suggestions that an α<sub>5</sub> subtype is involved in at least some of the memory impairment caused by benzodiazepines. It should be noted that these studies involving genetic manipulations of the GABA<sub>A</sub> receptor utilize rodent models of the anxiolytic and amnestic actions of drugs.

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The Versatility of the Chloride Channel GABA Receptor Complex

The GABA<sub>A</sub>-chloride channel macromolecular complex is one of the most versatile drug-responsive machines in the body. In addition to the benzodiazepines, barbiturates and zolpidem, many other drugs with central nervous system effects can modify the function of this important ionotropic receptor. These include alcohol, alphaxolone (a steroid anesthetic), etomidate and propofol (intravenous anesthetics), volatile anesthetics (eg, halothane), several anticonvulsants (eg, gabapentin, vigabatrin), and ivermectin (an anthelmintic agent). Most of these agents facilitate or mimic the action of GABA. (It must be noted that it has not been shown that these drugs act exclusively or even primarily by this mechanism.) Central nervous system excitatory agents that act on the chloride channel include picrotoxin and bicuculline. These convulsant drugs block the
Clinical Pharmacology of Sedative-Hypnotics

Treatment of Anxiety States

The psychologic, behavioral, and physiologic responses that characterize anxiety can take many forms. Typically, the psychic awareness of anxiety is accompanied by enhanced vigilance, motor tension, and autonomic hyperactivity. Before prescribing sedative-hypnotics, one should analyze the patient's symptoms carefully. Anxiety is in many cases secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc—which themselves require specific therapy. Another class of secondary anxiety states (situational anxiety) results from circumstances that may have to be dealt with only once or a few times, including anticipation of frightening medical or dental procedures and family illness or other tragedy. Even though situational anxiety tends to be self-limiting, the short-term use of sedative-hypnotics may be appropriate for the treatment of this and certain disease-associated anxiety states. Similarly, the use of a sedative-hypnotic as premedication prior to surgery or some unpleasant medical procedure is rational and proper (Table 22–2). If the patient presents with chronic anxiety as the primary complaint, it may be appropriate to review the diagnostic criteria set forth in the Diagnostic & Statistical Manual of Mental Disorders (DSM IV) to determine whether the diagnosis is correct and if treatment should include drug therapy. For example, excessive or unreasonable anxiety about life circumstances (generalized anxiety disorder), panic disorders, and agoraphobia are amenable to drug therapy, usually in conjunction with psychotherapy. In many cases, anxiety is a symptom of psychiatric problems that may warrant the use of antidepressant or antipsychotic drugs.

Table 22–2. Clinical Uses of Sedative-Hypnotics.

| For relief of anxiety                      |
| For insomnia                              |
| For sedation and amnesia before medical and surgical procedures |
| For treatment of epilepsy and seizure states |
| As a component of balanced anesthesia (intravenous administration) |
| For control of ethanol or other sedative-hypnotic withdrawal states |
| For muscle relaxation in specific neuromuscular disorders |
| As diagnostic aids or for treatment in psychiatry |

The benzodiazepines continue to be widely used for the management of anxiety states. Since anxiety symptoms may be relieved by many benzodiazepines, it is not always easy to demonstrate the superiority of one drug over another. However, alprazolam is particularly effective in the treatment of panic disorders and agoraphobia and is more selective in this regard than other benzodiazepines. The choice of benzodiazepines for anxiety is based on several sound pharmacologic principles: (1) a relatively high therapeutic index (see drug B in Figure 22–1), plus availability of flumazenil for treatment of overdose; (2) a low risk of drug interactions based on liver enzyme induction; (3) slow elimination rates, which may favor persistence of useful CNS
Disadvantages of the benzodiazepines include the risk of psychologic dependence, the formation of active metabolites, amnestic effects, and their cost. In addition, the benzodiazepines exert additive central nervous system depression when administered with other drugs, including ethanol. The patient should be warned of this possibility to avoid impairment of performance of any task requiring mental alertness and motor coordination. Many of the disadvantages of benzodiazepines are not shared by buspirone, which appears to be a more selective drug. However, limitations of buspirone include the slow onset of its anxiolytic actions—confining its use to generalized anxiety—and its limited efficacy in anxiety states that feature panic attacks and phobic characteristics. In the treatment of generalized anxiety disorders and certain phobias, newer antidepressants such as paroxetine and venlafaxine are now considered by many authorities to be drugs of first choice (see Chapter 30: Antidepressant Agents). However, these agents have minimal effectiveness in acute anxiety states.

Sedative-hypnotics should be used with appropriate caution so as to minimize adverse effects. A dose should be prescribed that does not impair mentation or motor functions during waking hours. Some patients may tolerate the drug better if most of the daily dose is given at bedtime, with smaller doses during the day. Prescriptions should be written for short periods, since there is little justification for long-term therapy. The physician should make an effort to assess the efficacy of therapy from the patient's subjective responses. Combinations of anxiolytic agents should be avoided, and people taking sedatives should be cautioned about the consumption of alcohol and the concurrent use of over-the-counter medications containing antihistaminic or anticholinergic drugs (see Chapter 64: Therapeutic & Toxic Potential of Over-the-Counter Agents).

Phenobarbital, meprobamate, and sedative-autonomic drugs are used occasionally as antianxiety agents. The antihistaminics (diphenhydramine, hydroxyzine, promethazine) continue to be used presurgically for their sedative and muscarinic receptor blocking actions.

Beta-blocking drugs (eg, propranolol) may be used as antianxiety agents in situations such as performance anxiety. The sympathetic nervous system overactivity associated with anxiety appears to be satisfactorily relieved by the β-blockers, and a slight improvement in the nonsomatic components of anxiety may also occur. Adverse central nervous system effects of propranolol include lethargy, vivid dreams, and hallucinations.

Treatment of Sleep Problems

Nonpharmacologic therapies that are sometimes useful for sleep problems include proper diet and exercise, avoiding stimulants before retiring, ensuring a comfortable sleeping environment, and retiring at a regular time each night. In some cases, however, the patient will need and should be given a sedative-hypnotic for a limited period. It should be noted that the abrupt discontinuance of most drugs in this class can lead to rebound insomnia.

Benzodiazepines can cause a dose-dependent decrease in both REM and slow wave sleep, though to a lesser extent than the barbiturates. Zolpidem and zaleplon are less likely than the benzodiazepines to change sleep patterns. However, so little is known about the clinical impact of these effects that statements about the desirability of a particular drug based on its effects on sleep architecture have more theoretical than practical significance. Clinical criteria of efficacy in alleviating a particular sleeping problem are more useful. The drug selected should be one that provides sleep of fairly rapid onset (decreased sleep latency) and sufficient duration, with minimal "hangover" effects such as drowsiness, dysphoria, and mental or motor depression the following day. Older drugs such as
chloral hydrate, secobarbital, and pentobarbital continue to be used, but benzodiazepines, zolpidem, or zaleplon are generally preferred. Daytime sedation is more common with benzodiazepines that have slow elimination rates (eg, lorazepam) and those that are biotransformed to active metabolites (eg, flurazepam, quazepam). If hypnotics are used nightly, tolerance can occur, which may lead to dose increases by the patient to produce the desired effect.

Anterograde amnesia occurs to some degree with all hypnotic benzodiazepines. Zaleplon and zolpidem have efficacies similar to those of the hypnotic benzodiazepines in the management of sleep disorders. Favorable clinical features of zolpidem include modest day-after psychomotor depression with few amnestic effects. Zolpidem is currently the most frequently prescribed hypnotic drug in the United States. Zaleplon acts rapidly, and because of its short half-life the drug appears to have value in the management of patients who awaken early in the sleep cycle. At recommended doses, zaleplon appears to cause less amnesia or day-after somnolence than zolpidem or benzodiazepines. The drugs commonly used for sedation and hypnosis are listed in Table 22–3 together with recommended doses. **Note:** Long-term use of hypnotics is irrational and dangerous medical practice.

| Table 22–3. Dosages of Drugs Used Commonly for Sedation and Hypnosis. |
|---|---|---|
| **Sedation** | **Dosage** | **Hypnosis** | **Dosage (at Bedtime)** |
| Alprazolam (Xanax) | 0.25–0.5 mg 2–3 times daily | Chloral hydrate | 500–1000 mg |
| Buspirone (BuSpar) | 5–10 mg 2–3 times daily | Estazolam (ProSom) | 0.5–2 mg |
| Chlordiazepoxide (Librium) | 10–20 mg 2–3 times daily | Flurazepam (Dalmane) | 15–30 mg |
| Clorazepate (Tranxene) | 5–7.5 mg twice daily | Lorazepam (Ativan) | 2–4 mg |
| Diazepam (Valium) | 5 mg twice daily | Quazepam (Doral) | 7.5–15 mg |
| Halazepam (Paxipam) | 20–40 mg 3–4 times daily | Secobarbital | 100–200 mg |
| Lorazepam (Ativan) | 1–2 mg once or twice daily | Temazepam (Restoril) | 7.5–30 mg |
| Oxazepam (Serax) | 15–30 mg 3–4 times daily | Triazolam (Halcion) | 0.125–0.5 mg |
| Phenobarbital | 15–30 mg 2–3 times daily | Zaleplon (Sonata) | 5–20 mg |
| Prazepam (Centrax) | 10–20 mg 2–3 times daily | Zolpidem (Ambien) | 5–10 mg |

**Other Therapeutic Uses**

Table 22–2 summarizes several other important clinical uses of drugs in the sedative-hypnotic class. Drugs used in the management of seizure disorders and as intravenous agents in anesthesia are discussed in Chapter 24: Antiseizure Drugs and Chapter 25: General Anesthetics.

For sedative and possible amnestic effects during medical or surgical procedures such as endoscopy and bronchoscopy—as well as for premedication prior to anesthesia—oral formulations of shorter-
acting drugs are preferred.

Long-acting drugs such as chlordiazepoxide and diazepam and, to a lesser extent, phenobarbital are administered in progressively decreasing doses to patients during withdrawal from physiologic dependence on ethanol or other sedative-hypnotics.

Meprobamate and, more recently, the benzodiazepines have frequently been used as central muscle relaxants, though evidence for general efficacy without accompanying sedation is lacking. A possible exception is diazepam, which has useful relaxant effects in skeletal muscle spasticity of central origin (see Chapter 27: Skeletal Muscle Relaxants).

Psychiatric uses of benzodiazepines other than treatment of anxiety states include the initial management of mania, the control of drug-induced hyperexcitability states (eg, phencyclidine intoxication), and possibly the treatment of major depressive disorders with alprazolam. Sedative-hypnotics are also used occasionally as diagnostic aids in neurology and psychiatry.

Clinical Toxicology of Sedative-Hypnotics

Direct Toxic Actions

Many of the common adverse effects of drugs in this class are those resulting from dose-related depression of central nervous system functions. Relatively low doses may lead to drowsiness, impaired judgment, and diminished motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships. Benzodiazepines may cause a significant dose-related anterograde amnesia; they can significantly impair ability to learn new information, particularly that involving effortful cognitive processes, while leaving the retrieval of previously learned information intact. This effect is utilized to clinical advantage in uncomfortable procedures, eg, endoscopy, since the appropriate dose leaves the patient able to cooperate during the procedure but amnesic regarding it afterward. The criminal use of benzodiazepines in cases of "date rape" is based on their dose-dependent amnestic effects. Hangover effects are not uncommon following use of hypnotic drugs with long elimination half-lives. Because elderly patients are more sensitive to the effects of sedative-hypnotics, doses approximately half of those used in younger adults are safer and usually as effective. The most common reversible cause of confusional states in the elderly is overuse of sedative-hypnotics. At higher doses, toxicity may present as lethargy or a state of exhaustion or, alternatively, in the form of gross symptoms equivalent to those of ethanol intoxication. The titration of useful therapeutic effects against such unwanted effects is usually more difficult with sedative-hypnotics that exhibit steep dose-response relationships of the type shown in Figure 22–1 (drug A), including the barbiturates, chloral hydrate, and piperidinediones. The physician should be aware of variability among patients in terms of doses causing adverse effects. An increased sensitivity to sedative-hypnotics is more common in patients with cardiovascular disease, respiratory disease, or hepatic impairment and in older patients. Sedative-hypnotics can exacerbate breathing problems in patients with chronic pulmonary disease and in those with symptomatic sleep apnea.

Sedative-hypnotics are the drugs most frequently involved in deliberate overdoses, in part because of their general availability as very commonly prescribed pharmacologic agents. The benzodiazepines are considered to be "safer" drugs in this respect, since they have flatter dose-response curves. Epidemiologic studies on the incidence of drug-related deaths support this general assumption—eg, 0.3 deaths per million tablets of diazepam prescribed versus 11.6 deaths per million capsules of secobarbital in one study. Of course, many factors other than the specific sedative-hypnotic could influence such data—particularly the presence of other central nervous
system depressants, including ethanol. In fact, most serious cases of drug overdosage, intentional or accidental, do involve polypharmacy; and when combinations of agents are taken, the practical safety of benzodiazepines may be less than the foregoing would imply.

The lethal dose of any sedative-hypnotic varies with the patient and the circumstances (see Chapter 59: Management of the Poisoned Patient). If discovery of the ingestion is made early and a conservative treatment regimen is started, the outcome is rarely fatal, even following very high doses. On the other hand, for most sedative-hypnotics—with the exception of benzodiazepines—a dose as low as ten times the hypnotic dose may be fatal if the patient is not discovered or does not seek help in time. With severe toxicity, the respiratory depression from central actions of the drug may be complicated by aspiration of gastric contents in the unattended patient—an even more likely occurrence if ethanol is present. Loss of brain stem vasomotor control, further complicates successful resuscitation. In such patients, treatment consists of ensuring a patent airway, with mechanical ventilation if needed, and maintenance of plasma volume, renal output, and cardiac function. Use of a positive inotropic drug such as dopamine, which preserves renal blood flow, is sometimes indicated. Hemodialysis or hemoperfusion may be used to hasten elimination of some of these drugs.

Flumazenil reverses the sedative actions of benzodiazepines. However, its duration of action is short and its antagonism of respiratory depression unpredictable. Therefore, the use of flumazenil in benzodiazepine overdose must be accompanied by adequate monitoring and support of respiratory function.

The extensive clinical use of triazolam has led to reports of serious central nervous system effects including behavioral disinhibition, delirium, aggression, and violence. While behavioral disinhibition may occur with sedative-hypnotic drugs, it does not appear to be more prevalent with triazolam than with other benzodiazepines. Disinhibitory reactions during benzodiazepine treatment are more clearly associated with the use of very high doses and the pretreatment level of patient hostility.

Adverse effects of the sedative-hypnotics that are not referable to their CNS actions occur infrequently. Hypersensitivity reactions, including skin rashes, occur only occasionally with most drugs of this class. Reports of teratogenicity leading to fetal deformation following use of piperidinediones and certain benzodiazepines justify caution in the use of these drugs during pregnancy. Because barbiturates enhance porphyrin synthesis, they are absolutely contraindicated in patients with a history of acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, or symptomatic porphyria.

Alterations in Drug Response

Depending on the dosage and the duration of use, tolerance occurs in varying degrees to many of the pharmacologic effects of sedative-hypnotics. However, it should not be assumed that the degree of tolerance achieved is identical for all pharmacologic effects. There is evidence that the lethal dose range is not altered significantly by the chronic use of sedative-hypnotics. Cross-tolerance between the different sedative-hypnotics, including ethanol, can lead to an unsatisfactory therapeutic response when standard doses of a drug are used in a patient with a recent history of excessive use of these agents. However, there have been few reports of tolerance development when zolpidem or zaleplon was used for less than 4 weeks.

With the chronic use of sedative-hypnotics, especially if doses are increased, a state of physiologic dependence can occur. This may develop to a degree unparalleled by any other drug group,
including the opioids. Withdrawal from a sedative-hypnotic can have severe and life-threatening manifestations. Withdrawal symptoms range from restlessness, anxiety, weakness, and orthostatic hypotension to hyperactive reflexes and generalized seizures. The severity of withdrawal symptoms depends to a large extent on the dosage range used immediately prior to discontinuance but also on the particular drug. Symptoms of withdrawal are usually more severe following discontinuance of sedative-hypnotics with shorter half-lives. (Zolpidem and zaleplon appear to be exceptions to this, because withdrawal symptoms are minimal following abrupt discontinuance of these newer short-acting agents.) Symptoms are less pronounced with longer-acting drugs, which may partly accomplish their own "tapered" withdrawal by virtue of their slow elimination. Cross-dependence, defined as the ability of one drug to suppress abstinence symptoms from discontinuance of another drug, is quite marked among sedative-hypnotics. This provides the rationale for therapeutic regimens in the management of withdrawal states: Longer-acting drugs such as chlordiazepoxide, diazepam, and phenobarbital can be used to alleviate withdrawal symptoms of shorter-acting drugs, including ethanol.

Drug Interactions

The most frequent drug interactions involving sedative-hypnotics are interactions with other central nervous system depressant drugs, leading to additive effects. These interactions have some therapeutic utility with respect to the use of these drugs as premedicants or anesthetic adjuvants. However, if not anticipated, they can lead to serious consequences, including enhanced depression with concomitant use of many other drugs. Additive effects can be predicted with concomitant use of alcoholic beverages, opioid analgesics, anticonvulsants, and phenothiazines. Less obvious but just as important is enhanced central nervous system depression with a variety of antihistamines, antihypertensive agents, and antidepressant drugs of the tricyclic class.

Interactions involving changes in the activity of hepatic drug-metabolizing enzyme systems have been discussed (see also Chapter 4: Drug Biotransformation and Appendix II).

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Preparations Available

Benzodiazepines

Alprazolam (generic, Xanax)
Oral: 0.25, 0.5, 1, 2 mg tablets; 0.1, 1.0 mg/mL solution

Chlordiazepoxide (generic, Librium)
Oral: 5, 10, 25 mg capsules; 10, 25 mg tablets
Parenteral: 100 mg powder for injection

Clorazepate (generic, Tranxene)
Oral: 3.75, 7.5, 15 mg tablets and capsules
Oral sustained-release: 11.25, 22.5 mg tablets
Clonazepam (Klonopin)
Oral: 0.5, 1, 2 mg tablets

Diazepam (generic, Valium)
Oral: 2, 5, 10 mg tablets; 1, 5 mg/mL solutions
Parenteral: 5 mg/mL for injection

Estazolam (generic, ProSom)
Oral: 1, 2 mg tablets

Flurazepam (generic, Dalmane)
Oral: 15, 30 mg capsules

Halazepam (Paxipam)
Oral: 20, 40 mg tablets

Lorazepam (generic, Ativan, Alzapam)
Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution
Parenteral: 2, 4 mg/mL for injection

Midazolam (Versed)
Oral: 2 mg/mL syrup
Parenteral: 1, 5 mg/mL in 1, 2, 5, 10 mL vials for injection

Oxazepam (generic, Serax)
Oral: 10, 15, 30 mg capsules, 15 mg tablets

Quazepam (Doral)
Oral: 7.5, 15 mg tablets

Temazepam (generic, Restoril)
Oral: 7.5, 15, 30 mg capsules

Triazolam (generic, Halcion)
Oral: 0.125, 0.25 mg tablets
Benzodiazepine Antagonist

**Flumazenil** (Romazicon)
Parenteral: 0.1 mg/mL for IV injection

Barbiturates

**Amobarbital** (Amytal)
Parenteral: powder in 250, 500 mg vials to reconstitute for injection

**Pentobarbital** (generic, Nembutal Sodium)
Oral: 50, 100 mg capsules; 4 mg/mL elixir
Rectal: 30, 60, 120, 200 mg suppositories
Parenteral: 50 mg/mL for injection

**Phenobarbital** (generic, Luminal Sodium)
Oral: 15, 16, 30, 60, 90, 100 mg tablets; 16 mg capsules; 15, 20 mg/5 mL elixirs
Parenteral: 30, 60, 65, 130 mg/mL for injection

**Secobarbital** (generic, Seconal)
Oral: 100 mg capsules

Miscellaneous Drugs

**Buspirone** (BuSpar)
Oral: 5, 10, 15 mg tablets

**Chloral hydrate** (generic, Aquachloral Supprettes)
Oral: 500 mg capsules; 250, 500 mg/5 mL syrups
Rectal: 324, 500, 648 mg suppositories

**Ethchlorvynol** (Placidyl)
Oral: 200, 500, 750 mg capsules

**Hydroxyzine** (generic, Atarax, Vistaril)
Oral: 10, 25, 50, 100 mg tablets; 25, 50, 100 mg capsules; 10 mg/5 mL syrup; 25 mg/5 mL suspension
Parenteral: 25, 50 mg/mL for injection

**Meprobamate** (generic, Equanil, Miltown)

Oral: 200, 400 mg tablets

Oral sustained-release: 200, 400 mg capsules

**Paraldehyde** (generic)

Oral, rectal liquids

**Zaleplon** (Sonata)

Oral: 5, 10 mg capsules

**Zolpidem** (Ambien)

Oral: 5, 10 mg tablets

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**Chapter 23. The Alcohols**

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The Alcohols: Introduction

Alcohol, primarily in the form of ethyl alcohol (ethanol), has occupied an important place in the history of humankind for at least 8000 years. In Western society, beer and wine were a main staple of daily life until the 19th century. These relatively dilute alcoholic beverages were preferred over water, which was known to be associated with acute and chronic illness. They provided important calories and nutrients and served as a main source of daily liquid intake. As systems for improved sanitation and water purification were introduced in the 1800s, beer and wine became less important as components of the human diet, and the consumption of alcoholic beverages, including distilled preparations with higher concentrations of alcohol, shifted toward their present-day role (in many societies) as a socially acceptable form of recreation.

Today, alcohol is widely consumed. Like other sedative-hypnotic drugs, alcohol in low to moderate amounts relieves anxiety and fosters a feeling of well-being or even euphoria. However, alcohol is also the most commonly abused drug in the world, a cause of vast medical and societal costs. In the United States, approximately 75% of the adult population drinks alcohol regularly. The majority of this drinking population is able to enjoy the pleasurable effects of alcohol without allowing their alcohol consumption to become a health risk. However, about 10% of the general population in the United States are unable to limit their ethanol consumption, a condition known as alcohol abuse.
People who continue to drink alcohol in spite of adverse medical or social consequences related directly to their alcohol consumption suffer from **alcoholism**, a complex disorder that appears to have genetic as well as environmental determinants. The societal and medical costs of alcohol abuse are staggering. It is estimated that about 30% of all people admitted to hospitals have coexisting alcohol problems. Once in the hospital, people with chronic alcoholism generally have poorer outcomes. In addition, each year thousands of children are born in the USA with morphologic and functional defects resulting from prenatal exposure to ethanol. Despite the investment of many resources and much basic research, alcoholism remains a common chronic disease that is difficult to treat.

Ethanol and many other alcohols with potentially toxic effects are used in industry, some in enormous quantities. In addition to ethanol, methanol and ethylene glycol toxicity occur with sufficient frequency to warrant discussion in this chapter.

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#### Basic Pharmacology of Ethanol

**Pharmacokinetics**

Ethanol is a small water-soluble molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the gut delays absorption by slowing gastric emptying. Distribution is rapid, with tissue levels approximating the concentration in blood. The volume of distribution for ethanol approximates total body water (0.5–0.7 L/kg). For an equivalent oral dose of alcohol, women have a higher peak concentration than men, in part because women have a lower total body water content. In the central nervous system, the concentration of ethanol rises quickly since the brain receives a large proportion of blood flow and ethanol readily crosses biologic membranes.

Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine. The excretion of a small but consistent proportion of alcohol by the lungs is utilized for breath alcohol tests that serve as a basis for a legal definition of "driving under the influence" in many countries. At levels of ethanol usually achieved in blood, the rate of oxidation follows zero-order kinetics, ie, it is independent of time and concentration of the drug. The typical adult can metabolize 7–10 g (150–220 mmol) of alcohol per hour, the equivalent of approximately 10 oz of beer, 3.5 oz of wine, or 1 oz of distilled 80 proof spirits.

Two major pathways of alcohol metabolism to acetaldehyde have been identified (Figure 23–1). Acetaldehyde is then oxidized by a third metabolic process.

![Figure 23–1.](image-url)
Metabolism of ethanol by alcohol dehydrogenase and the microsomal ethanol-oxidizing system (MEOS). Alcohol dehydrogenase and aldehyde dehydrogenase are inhibited by fomepizole and disulfiram, respectively.

Alcohol Dehydrogenase Pathway

The primary pathway for alcohol metabolism involves alcohol dehydrogenase (ADH), a cytosolic enzyme that catalyzes the conversion of alcohol to acetaldehyde (Figure 23–1, left). This enzyme is located mainly in the liver, but it is also found in other organs such as brain and stomach.

A significant amount of ethanol metabolism by gastric ADH occurs in the stomach in men, but a smaller amount occurs in women, who appear to have lower levels of the gastric enzyme. This difference in gastric metabolism of alcohol in women probably contributes to the sex-related differences in blood alcohol concentrations noted above.

During conversion of ethanol to acetaldehyde, hydrogen ion is transferred from alcohol to the cofactor nicotinamide adenine dinucleotide (NAD\(^+\)) to form NADH. As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH. The excess NADH production appears to underlie a number of metabolic disorders that accompany chronic alcoholism.

Microsomal Ethanol Oxidizing System (MEOS)

This enzyme system, also known as the mixed function oxidase system (see Chapter 4: Drug Biotransformation), uses NADPH as a cofactor in the metabolism of ethanol (Figure 23–1, right).

At blood concentrations below 100 mg/dL (22 mmol/L), the MEOS system, which has a relatively high K\(_m\) for alcohol, contributes little to the metabolism of ethanol. However, when large amounts of ethanol are consumed, the alcohol dehydrogenase system becomes saturated owing to depletion of the required cofactor, NAD\(^+\). As the concentration of ethanol increases above 100 mg/dL, there is increased contribution from the MEOS system, which does not rely upon NAD\(^+\) as a cofactor.

During chronic alcohol consumption, MEOS activity increases. As a result, chronic alcohol
consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs eliminated by the MEOS system. Similarly, other inducing drugs such as barbiturates may also enhance the rate of blood alcohol clearance slightly. However, the effect of other enzyme-inducing drugs on ethanol clearance is less important because the MEOS is not the primary pathway for ethanol metabolism.

Acetaldehyde Metabolism

Much of the acetaldehyde formed from alcohol appears to be oxidized in the liver in a reaction catalyzed by mitochondrial NAD-dependent aldehyde dehydrogenase. The product of this reaction is acetate (Figure 23–1), which can be further metabolized to CO₂ and water.

Oxidation of acetaldehyde is inhibited by disulfiram, a drug that has been used to deter drinking by alcohol-dependent patients undergoing treatment. When ethanol is consumed in the presence of disulfiram, acetaldehyde accumulates and causes an unpleasant reaction of facial flushing, nausea, vomiting, dizziness, and headache. Several other drugs (eg, metronidazole, cefotetan, trimethoprim) inhibit aldehyde dehydrogenase and can cause a disulfiram-like reaction if combined with ethanol.

Some people, primarily of Asian descent, have a genetic deficiency in the activity of the mitochondrial form of aldehyde dehydrogenase. When these individuals drink alcohol, they develop high blood acetaldehyde concentrations and experience a flushing reaction similar to that seen with the combination of disulfiram and ethanol.

Pharmacodynamics of Acute Ethanol Consumption

Central Nervous System

The central nervous system is markedly affected by acute alcohol consumption. Alcohol causes sedation and relief of anxiety and, at higher concentrations, slurred speech, ataxia, impaired judgment, and disinhibited behavior, a condition usually called intoxication or drunkenness (Table 23–1). These central nervous system effects are most marked as the blood level is rising, because acute tolerance to the effects of alcohol occurs after a few hours of drinking. For chronic drinkers who are tolerant to the effects of alcohol, much higher concentrations are needed to elicit these central nervous system effects. For example, a chronic alcoholic may appear sober or only slightly intoxicated with a blood alcohol concentration of 300–400 mg/dL, whereas this level is associated with marked intoxication or even coma in a nontolerant individual. The propensity of moderate doses of alcohol to inhibit the attention and information processing skills as well as the motor skills required for operation of motor vehicles has profound effects. Approximately half of all traffic accidents resulting in a fatality in the United States involve at least one person with a blood alcohol near or above the legal level of intoxication, and drunken driving is a leading cause of death in young adults.

<table>
<thead>
<tr>
<th>BAC (mg/dL)</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–100</td>
<td>Sedation, subjective &quot;high,&quot; increased reaction times</td>
</tr>
<tr>
<td>100–200</td>
<td>Impaired motor function, slurred speech, ataxia</td>
</tr>
<tr>
<td>Blood Concentration</td>
<td>Effect</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
</tr>
<tr>
<td>200–300</td>
<td>Emesis, stupor</td>
</tr>
<tr>
<td>300–400</td>
<td>Coma</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>Respiratory depression, death</td>
</tr>
</tbody>
</table>

In many parts of the USA, a blood level above 80–100 mg/dL for adults or 10 mg/dL for persons under 21 is sufficient for conviction of driving while "under the influence."

Like other sedative-hypnotic drugs, alcohol is a central nervous system depressant. At high blood concentrations, it induces coma, respiratory depression, and death.

No specific receptor for ethanol has been identified. Instead, ethanol has been shown to affect a large number of membrane proteins that participate in signaling pathways, including neurotransmitter receptors for amines, amino acids, and opioids; enzymes such as Na⁺/K⁺ ATPase, adenylyl cyclase, phosphoinositide-specific phospholipase C; and ion channels such as those for Ca²⁺. Much attention has focused on alcohol's effects upon neurotransmission by glutamate and GABA, the main excitatory and inhibitory neurotransmitters in the central nervous system. Acute ethanol exposure enhances the action of GABA at GABA_A receptors, which is consistent with the ability of GABA-mimetics to intensify many of the acute effects of alcohol and of GABA_A antagonists to attenuate some of the actions of ethanol. Ethanol also inhibits the ability of glutamate to open the cation channel associated with the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. The NMDA receptor is implicated in many aspects of cognitive function, including learning and memory. "Blackouts"—periods of memory loss that occur with high levels of alcohol—may result from inhibition of NMDA receptor activation.

Heart

Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol, ie, at a blood concentration above 100 mg/dL. Myocardial biopsies in humans before and after infusion of small amounts of alcohol have shown ultrastructural changes that may be associated with impaired myocardial function. Acetaldehyde is implicated as a cause of cardiac dysfunction by altering myocardial stores of catecholamines.

Smooth Muscle

Ethanol is a vasodilator, probably as a result of both central nervous system effects (depression of the vasomotor center) and direct smooth muscle relaxation caused by its metabolite, acetaldehyde. In cases of severe overdose, hypothermia—caused by vasodilation—may be marked in cold environments. Ethanol also relaxes the uterus and—before the introduction of more effective and safer uterine relaxants (eg, calcium blockers, magnesium ion, NSAIDs, and β_2-adrenoceptor stimulants)—was used intravenously for the suppression of premature labor.

Consequences of Chronic Alcohol Consumption

Chronic alcohol consumption profoundly affects the function of several vital organs—particularly the liver and skeletal muscle—and the nervous, gastrointestinal, cardiovascular, and immune systems. Since ethanol has low potency, it requires concentrations thousands of times higher than other misused drugs (eg, cocaine, opiates, amphetamines) to produce its intoxicating effects. As a result, ethanol is consumed in quantities that are unusually large for a pharmacologically active drug. The tissue damage caused by chronic alcohol ingestion results directly from toxic effects of
ethanol and acetaldehyde and indirectly by making tissues more susceptible to injury. Mechanisms implicated in tissue damage include increased oxidative stress coupled with depletion of glutathione, damage to mitochondria, growth factor dysregulation, and potentiation of cytokine-induced injury.

Chronic consumption of large amounts of alcohol is associated with an increased risk of death. Deaths linked to alcohol consumption are caused by liver disease, cancer, accidents, and suicide.

Liver and Gastrointestinal Tract

Liver disease is the most common medical complication of alcohol abuse; it is estimated that 15–30% of chronic heavy drinkers eventually develop severe liver disease. Clinically significant alcoholic liver disease may be insidious in onset and progress without evidence of overt nutritional abnormalities. Alcoholic fatty liver, a reversible condition, may progress to alcoholic hepatitis and finally to cirrhosis and liver failure. In the USA, chronic alcohol abuse is the leading cause of liver cirrhosis and of the need for liver transplantation. The risk of developing liver disease is related both to the average amount of daily consumption and to the duration of alcohol abuse. Women appear to be more susceptible to alcohol hepatotoxicity than men. Another factor that increases the risk of severe liver disease is concurrent infection with hepatitis B or C virus.

Other portions of the gastrointestinal tract can also be injured. Chronic alcohol ingestion is by far the most common cause of chronic pancreatitis in the Western world. In addition to its direct toxic effect on pancreatic acinar cells, alcohol alters pancreatic epithelial permeability and promotes the formation of protein plugs and calcium carbonate-containing stones.

Chronic alcoholics are prone to develop gastritis and have increased susceptibility to blood and plasma protein loss during drinking, which may contribute to anemia and protein malnutrition. Alcohol also reversibly injures the small intestine, leading to diarrhea, weight loss, and multiple vitamin deficiencies.

Malnutrition from dietary deficiency and vitamin deficiencies due to malabsorption are common in alcoholic individuals. Malabsorption of water-soluble vitamins is especially severe.

Nervous System

Tolerance and Physical Dependence

The consumption of alcohol in high doses over a long period results in tolerance and in physical and psychologic dependence. Tolerance to the intoxicating effects of alcohol is a complex process involving poorly understood changes in the nervous system as well as the metabolic changes described earlier. As with other sedative-hypnotic drugs, there is a limit to tolerance, so that only a relatively small increase in the lethal dose occurs with increasing alcohol use.

Chronic alcohol drinkers, when forced to reduce or discontinue alcohol, experience a withdrawal syndrome, which indicates the existence of physical dependence. Alcohol withdrawal symptoms classically consist of hyperexcitability in mild cases and seizures, toxic psychosis, and delirium tremens in severe ones. The dose, rate, and duration of alcohol consumption determine the intensity of the withdrawal syndrome. When consumption has been very high, merely reducing the rate of consumption may lead to signs of withdrawal.

Psychologic dependence upon alcohol is characterized by a compulsive desire to experience the
rewarding effects of alcohol and, for current drinkers, a desire to avoid the negative consequences of withdrawal. People who have recovered from alcoholism and become abstinent still experience periods of intense craving for alcohol that can be set off by environmental cues associated in the past with drinking, such as familiar places, groups of people, or events.

The molecular basis of alcohol tolerance and dependence is not known, nor is it known if the two phenomena reflect opposing effects upon a shared molecular pathway. Tolerance may result from ethanol-induced up-regulation of a pathway in response to the continuous presence of ethanol. Dependence may result from overactivity of that same pathway once the ethanol effect dissipates and before the system has time to return to a normal ethanol-free state. Chronic exposure of animals or cultured cells to alcohol elicits a multitude of adaptive responses involving neurotransmitters and their receptors, ion channels, and enzymes that participate in signal transduction pathways. Up-regulation of the NMDA subtype of glutamate receptors and voltage-sensitive Ca^{2+} channels may underlie the seizures that accompany the alcohol withdrawal syndrome. Based on the ability of sedative-hypnotic drugs that enhance GABAergic neurotransmission to substitute for alcohol during alcohol withdrawal and evidence of down-regulation of GABA_{A}-mediated responses with chronic alcohol exposure, changes in GABA neurotransmission are believed to play a central role in tolerance and withdrawal.

Neurotransmission events involved in the sensation of reward are also important. Alcohol affects local concentrations of serotonin, opioids, and dopamine—neurotransmitters involved in brain reward circuits. Alcohol also has complex effects on the expression of receptors for these neurotransmitters and their signaling pathways. The discovery that naltrexone, a nonselective opioid receptor antagonist, helps patients who are recovering from alcoholism abstain from drinking supports the idea that the neurochemical reward system is shared by drugs associated with physical and psychological dependence.

Neurotoxicity

Consumption of large amounts of alcohol over extended periods (usually years) often leads to neurologic deficits. The most frequent neurologic abnormality in chronic alcoholism is generalized symmetric peripheral nerve injury that begins with distal paresthesias of the hands and feet. Chronic alcoholics may also exhibit gait disturbances and ataxia that are due to degenerative changes in the central nervous system. Other neurologic disturbances associated with alcoholism include dementia and, rarely, demyelinating disease.

Wernicke-Korsakoff syndrome is a relatively uncommon but important entity characterized by paralysis of the external eye muscles, ataxia, and a confused state that can progress to coma and death. It is associated with thiamin deficiency but is rarely seen in the absence of alcoholism. Wernicke's encephalopathy represents the acute phase of this disease; it may be difficult to distinguish from the acute confused state created by acute alcohol intoxication, which later blends in with the perceptual and behavioral problems associated with alcohol withdrawal. A distinguishing feature of Wernicke's encephalopathy is the longer duration of confusion and the relative absence of the agitation that would be expected during withdrawal. Because of the importance of thiamin in this pathologic condition, all patients suspected of having Wernicke-Korsakoff syndrome should receive thiamine therapy. Often, the ocular signs, ataxia, and confusion improve upon prompt administration of thiamine. However, most patients are left with a chronic disabling memory disorder known as Korsakoff's psychosis.

Alcohol may also impair visual acuity, with painless blurring that occurs over several weeks of heavy alcohol consumption. Changes are usually bilateral and symmetric and may be followed by
optic nerve degeneration. Ingestion of ethanol substitutes such as methanol (see below) causes severe visual disturbances.

Cardiovascular System

Alcohol has complex effects upon the cardiovascular system. Heavy alcohol consumption of long duration is associated with a dilated cardiomyopathy with ventricular hypertrophy and fibrosis. In animals and humans, alcohol induces a number of changes in heart cells that may contribute to cardiomyopathy. They include membrane disruption, depressed function of mitochondria and sarcoplasmic reticulum, intracellular accumulation of phospholipids and fatty acids, and up-regulation of voltage-dependent calcium channels. There is evidence that patients with alcohol-induced dilated cardiomyopathy do significantly worse than patients with idiopathic dilated cardiomyopathy, even though cessation of drinking is associated with a reduction in cardiac size and improved function. The poorer prognosis for patients who continue to drink appears to be due in part to interference of ethanol with the beneficial effects of β-blockers and ACE inhibitors.

Heavy drinking—and especially "binge" drinking—are associated with both atrial and ventricular arrhythmias. Patients undergoing alcohol withdrawal syndrome can develop severe arrhythmias that may reflect abnormalities of potassium or magnesium metabolism as well as enhanced release of catecholamines. Seizures, syncope, and sudden death during alcohol withdrawal may be due to these arrhythmias.

A link between heavier alcohol consumption (more than three drinks per day) and hypertension has been firmly established in epidemiologic studies. Alcohol is estimated to be responsible for approximately 5% of cases of hypertension, making it one of the most common causes of reversible hypertension. This association is independent of obesity, salt intake, coffee drinking, or cigarette smoking. The mechanisms responsible for the sustained increase in blood pressure have not been identified. A reduction in alcohol intake appears to be effective in lowering blood pressure in hypertensives who are also heavy drinkers; the hypertension seen in this population is also responsive to standard blood pressure medications.

While the deleterious effects of excessive alcohol use on the cardiovascular system are well established, there is controversy over the effects of moderate drinking (one to three drinks a day) on the incidence of coronary heart disease (CHD). A number of observational studies concluded that moderate alcohol consumption actually prevents CHD and even reduces mortality. This type of relationship between mortality and the dose of a drug is called a "J-shaped" relationship. Results of these clinical studies are supported by ethanol's ability to raise serum levels of high-density lipoprotein (HDL) cholesterol, the form of cholesterol that appears to protect against atherosclerosis (see Chapter 35: Agents Used in Hyperlipidemia), its ability to inhibit some of the inflammatory processes that underlie atherosclerosis, and the presence in alcoholic beverages (especially red wine) of antioxidants and other substances that may protect against atherosclerosis. More recently, the relationship between moderate drinking and CHD has been called into question (Corrao et al, 2000) based on further investigation of confounders that affected the outcome of earlier epidemiologic studies. For example, moderate drinkers, especially wine drinkers, come from a higher socioeconomic level and may have healthier dietary habits; consumption tends to decrease with age; abstinence often is associated with ill health; and documenting precise amounts of consumption is difficult. Therefore, definitive conclusions regarding a cardioprotective effect of alcohol must await better clinical evidence.
Alcohol indirectly affects hematopoiesis through metabolic and nutritional effects and may also directly inhibit the proliferation of all cellular elements in bone marrow. The most common hematologic disorder seen in chronic drinkers is mild anemia resulting from alcohol-related folic acid deficiency. Iron deficiency anemia may result from gastrointestinal bleeding. Alcohol has also been implicated as a cause of several hemolytic syndromes, some of which are associated with hyperlipidemia and severe liver disease.

Endocrine System and Electrolyte Balance

Chronic alcohol use has important effects on the endocrine system and on fluid and electrolyte balance. Clinical reports of gynecomastia and testicular atrophy in alcoholics with or without cirrhosis suggest a derangement in steroid hormone balance.

Alcoholics with chronic liver disease may have disorders of fluid and electrolyte balance, including ascites, edema, and effusions. These factors may be related to decreased protein synthesis and portal hypertension. Alterations of whole body potassium induced by vomiting and diarrhea, as well as severe secondary aldosteronism, may contribute to muscle weakness and can be worsened by diuretic therapy. Some alcoholic patients develop hypoglycemia, probably as a result of impaired hepatic gluconeogenesis. Some alcoholics also develop ketosis, caused by excessive lipolytic factors, especially increased cortisol and growth hormone.

Fetal Alcohol Syndrome

Chronic maternal alcohol abuse during pregnancy is associated with teratogenic effects, and alcohol appears to be a leading cause of mental retardation and congenital malformation. The abnormalities that have been characterized as fetal alcohol syndrome include (1) intrauterine growth retardation, (2) microcephaly, (3) poor coordination, (4) underdevelopment of midfacial region (appearing as a flattened face), and (5) minor joint anomalies. More severe cases may include congenital heart defects and mental retardation. Heavy drinking in the first trimester of pregnancy produces the facial features associated with fetal alcohol syndrome. The consequences of heavy drinking in the second and third trimesters are not well defined, but animal studies suggest that the brain is vulnerable to ethanol throughout development. While the level of alcohol intake required for causing serious neurologic deficits appears quite high, the threshold for causing more subtle neurologic deficits is uncertain.

The mechanisms that underlie ethanol's teratogenic effects are unknown. Ethanol rapidly crosses the placenta and reaches concentrations in the fetus that are similar to those in maternal blood. The fetal liver has little or no alcohol dehydrogenase activity, so the fetus must rely upon maternal and placental enzymes for elimination of alcohol.

The neuropathologic abnormalities seen in humans and in animal models of fetal alcohol syndrome indicate that ethanol triggers apoptotic neurodegeneration and also causes aberrant neuronal and glial migration in the developing nervous system. In tissue culture systems, ethanol causes a striking reduction in neurite outgrowth. Alcohol's toxicity to the developing brain may be due to selective interference with the synthesis or function of molecules that are critical for cell recognition and migration, such as L1, an immunoglobulin cell adhesion molecule and gangliosides, major structural components of neuronal plasma membranes.

Immune System

The effects of alcohol on the immune system are complex—immune function in some tissues is
inhibited (eg, the lung), while immune function in other tissues is enhanced (eg, liver, pancreas). In addition, acute and chronic exposure to alcohol have widely different effects on immune function. The types of immunologic changes reported include suppression of the function of alveolar macrophages, inhibition of chemotaxis of granulocytes, and reduced number and function of T cells. In the liver, there is enhanced function of Kupffer cells. What is clear is that chronic heavy alcohol use predisposes to the development of infections, especially of the lung, and that it worsens the morbidity and increases the mortality risk of patients with pneumonia.

Increased Risk of Cancer

Chronic alcohol use increases the risk for cancer of the mouth, pharynx, larynx, esophagus, and liver. Evidence also points to a small increase in the risk of breast cancer in women. Although the methodologic problems of studies relating cancer to alcohol use have been formidable, the consistency of results showing an increase in the risk of gastrointestinal tract cancer is impressive. Much more information is required before a threshold level for alcohol consumption as it relates to cancer can be established. In fact, alcohol itself does not appear to be a carcinogen in most test systems. However, alcoholic beverages may carry potential carcinogens produced in fermentation or processing and may alter liver function so that the activity of potential carcinogens is increased.

Alcohol-Drug Interactions

Interactions between ethanol and other drugs can have important clinical effects that result from alterations in the pharmacokinetics or pharmacodynamics of the second drug.

The most frequent pharmacokinetic alcohol-drug interactions occur as a result of alcohol-induced increases of drug-metabolizing enzymes in liver cells as described in Chapter 4: Drug Biotransformation. Thus, prolonged intake of alcohol without damage to the liver may enhance the metabolic biotransformation of other drugs. Ethanol-mediated induction of hepatic cytochrome P450 enzymes is particularly important with regard to acetaminophen. Chronic consumption at the level of three or more drinks per day increases the risk of hepatotoxicity due to toxic or even high therapeutic levels of acetaminophen. This is probably due to increased P450-mediated conversion of acetaminophen to reactive hepatotoxic metabolites (see Chapter 4: Drug Biotransformation). In 1998, the FDA announced that all OTC products containing acetaminophen must carry a warning about the relationship between chronic ethanol consumption and acetaminophen-induced hepatotoxicity.

In contrast, acute alcohol use may inhibit metabolism of other drugs. This inhibition may be due to decreased enzyme activity or decreased liver blood flow. This acute alcohol effect may contribute to the commonly recognized danger of mixing alcohol with other drugs when performing activities requiring some skill, especially driving. Phenothiazines, tricyclic antidepressants, and sedative-hypnotic drugs are the most important drugs that may interact with alcohol by this pharmacokinetic mechanism.

Pharmacodynamic alcohol interactions are also of great clinical significance. Additive central nervous system depression with other sedative-hypnotics is most important. Alcohol also potentiates the pharmacologic effects of many nonsedative drugs, including vasodilators and oral hypoglycemic agents. There is some evidence that alcohol also enhances the antiplatelet action of aspirin.

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Clinical Pharmacology of Ethanol

Ethanol is the cause of more preventable morbidity and mortality than all other drugs combined with the exception of tobacco. The search for specific etiologic factors or the identification of significant predisposing variables for alcohol abuse has generally led to disappointing results. Personality type, severe life stresses, psychiatric disorders, and parental role models are not reliable predictors of alcohol abuse. While environmental factors clearly play a role, evidence suggests that there is a large genetic contribution to the development of alcoholism. Using new genetic markers for humans and animals, an intensive search for genes that predispose toward alcohol dependence is under way (Crabbe, 1999). Not surprisingly, polymorphisms in alcohol dehydrogenase and aldehyde dehydrogenase that lead to increased aldehyde accumulation (and therefore more severe hangover symptoms) appear to protect against alcoholism. Much attention in genetic mapping experiments has focused on membrane-signaling proteins known to be affected by ethanol and on protein constituents of reward pathways in the brain. Early reports of an association of an allele of the dopamine D2 receptor with alcohol dependence have not been confirmed. Other candidate genes for susceptibility to alcoholism identified in genome-wide screens in humans include the dopamine D4 receptor, the B1 subunit of the GABA_A receptor, and tyrosine hydroxylase, an enzyme involved in the synthesis of dopamine, norepinephrine, and epinephrine (see Chapter 6: Introduction to Autonomic Pharmacology).

Genetic mapping studies have also been performed in rodents selectively bred to exhibit high or low voluntary alcohol consumption and to show differences in the severity of alcohol withdrawal seizures. A number of candidate genes have been identified, including neurotransmitter receptors, ion channels, amino acid transporters, and enzymes involved in neurotransmitter synthesis and metabolism. One intriguing candidate is neuropeptide Y (NPY), a small protein expressed in the brain and implicated in the regulation of a variety of behaviors. The role of NPY in behavior related to ethanol has been explored by development of a strain of mice that lack the gene for NPY—NPY knockout mice—and a strain of mice that overexpress NPY. The NPY knockout mice voluntarily consume more ethanol than control mice and are less sensitive to the sedative effects of ethanol. In contrast, mice overexpressing NPY drink less alcohol than the controls even though their total consumption of food and liquid is normal. Much more work is needed to investigate the role of NPY in animal models and in human alcoholism, but these findings illustrate the application of modern genetic techniques for the study of differences in behavioral responses to drugs.

Management of Acute Alcohol Intoxication

Nontolerant individuals who consume alcohol in large quantities develop typical effects of acute sedative-hypnotic drug overdose along with the cardiovascular effects described above (vasodilation, tachycardia) and gastrointestinal irritation. Since tolerance is not absolute, even chronic alcoholics may become severely intoxicated. The degree of intoxication depends upon three factors: the blood ethanol concentration, the rapidity of the rise of the alcohol level, and the time during which the blood level is maintained. The pattern of drinking, the state of the absorptive surface of the gastrointestinal tract, and the presence in the body of other medications also affect the apparent degree of intoxication.

The most important goals in the treatment of acute alcohol intoxication are to prevent severe respiratory depression and aspiration of vomitus. Even with very high blood ethanol levels, survival is probable as long as the respiratory and cardiovascular systems can be supported. The average blood alcohol concentration in fatal cases is above 400 mg/dL; however, the lethal dose of alcohol varies because of varying degrees of tolerance.
Metabolic alterations may require treatment of hypoglycemia and ketosis by administration of glucose. Thiamine is given to protect against the Wernicke-Korsakoff syndrome. Alcoholic patients who are dehydrated and vomiting should also receive electrolyte solutions. If vomiting is severe, large amounts of potassium may be required as long as renal function is normal. Especially important is recognition of decreased serum concentrations of phosphate, which may be aggravated by glucose administration. Low phosphate stores may contribute to poor wound healing, neurologic deficits, and an increased risk of infection.

Management of Alcohol Withdrawal Syndrome

Abrupt alcohol withdrawal leads to a characteristic syndrome of motor agitation, anxiety, insomnia, and reduction of seizure threshold. The severity of the syndrome is usually proportionate to the degree and duration of alcohol abuse. However, this can be greatly modified by the use of other sedatives as well as by associated factors (eg, diabetes, injury). In its mildest form, the alcohol withdrawal syndrome of tremor, anxiety, and insomnia occurs 6–8 hours after alcohol is stopped. These effects usually abate in 1–2 days. In some patients, more severe withdrawal reactions occur in which visual hallucinations, total disorientation, and marked abnormalities of vital signs occur. Alcohol withdrawal is one of the most common causes of seizures in adults. The more severe the withdrawal syndrome, the greater the need for meticulous investigation of possible underlying medical complications. The mortality risks of severe alcohol withdrawal have been overstated in the past. The prognosis is probably related chiefly to the underlying medical complications.

The major objective of drug therapy in the alcohol withdrawal period is prevention of seizures, delirium, and arrhythmias. Potassium, magnesium, and phosphate balance should be restored as rapidly as is consistent with renal function. Thiamine therapy is initiated in all cases. Persons in mild alcohol withdrawal do not need any other pharmacologic assistance.

Specific drug treatment for detoxification in severe cases involves two basic principles: substituting a long-acting sedative-hypnotic drug for alcohol and then gradually reducing ("tapering") the dose of the long-acting drug. Because of their wide margin of safety, benzodiazepines are preferred for treatment of alcohol withdrawal syndrome, though barbiturates such as phenobarbital were used in the past. Since any benzodiazepine will prevent symptoms of alcohol withdrawal, the choice of a specific agent in this class is generally based upon pharmacokinetic or economic considerations. Long-acting benzodiazepines, including clorazepate, clorazepate, and diazepam, have the advantage of requiring less frequent dosing. Since their pharmacologically active metabolites are eliminated slowly, the long-acting drugs provide a built-in tapering effect. A disadvantage of the long-acting drugs is that they and their pharmacologically active metabolites may accumulate, especially in patients with compromised liver function. Short-acting drugs such as lorazepam and oxazepam are rapidly converted to inactive water-soluble metabolites that will not accumulate, and for this reason the short-acting drugs are especially useful in alcoholic patients with liver disease. Benzodiazepines can be administered orally in mild or moderate cases, or parenterally for patients with more severe withdrawal reactions.

Phenothiazine medications for alcohol withdrawal have potentially serious adverse effects (eg, increasing seizures) that probably outweigh their benefits. Antihistamines have been used but with little justification.

After the alcohol withdrawal syndrome has been treated acutely, sedative-hypnotic medications must be tapered slowly over several weeks. Complete detoxification is not achieved with just a few days of alcohol abstinence. Several months may be required for restoration of normal nervous
system function, especially sleep.

Pharmacotherapy of Alcoholism

Following detoxification, psychosocial therapy either in intensive inpatient or in outpatient rehabilitation programs serves as the primary treatment for alcohol dependence. Since these programs have been only moderately successful, with about 50% of patients relapsing within the first year, there is much interest in finding drugs that can be useful adjuncts to psychosocial counseling. The first approach to pharmacotherapy was to deter drinking with drugs that cause a noxious reaction to alcohol by blocking its metabolism. Disulfiram, an inhibitor of aldehyde dehydrogenase, is the drug most commonly used for this purpose in the USA. More recently, research has focused on identifying drugs that alter brain responses to alcohol, eg, by decreasing the craving of abstinent alcoholics for alcohol or by blunting the pleasurable "high" that comes with renewed drinking. Naltrexone, an inhibitor of opioid receptors, was the first drug of this type to be approved by the FDA for treatment of alcohol dependence.

Other psychiatric problems, most commonly depressive or anxiety disorders, often coexist with alcoholism and, if untreated, can contribute to the tendency of detoxified alcoholics to relapse. Treatment of these associated disorders with counseling and drugs can help decrease the rate of relapse for alcoholic patients.

Disulfiram

Disulfiram (tetraethylthiuram), a widely used antioxidant in the rubber industry, causes extreme discomfort to patients who drink alcoholic beverages. Disulfiram given by itself to nondrinkers has little effect; however, flushing, throbbing headache, nausea, vomiting, sweating, hypotension, and confusion occur within a few minutes after drinking alcohol. The effect may last 30 minutes in mild cases or several hours in severe ones. Disulfiram acts by inhibiting aldehyde dehydrogenase. Thus, alcohol is metabolized as usual, but acetaldehyde accumulates.

Disulfiram is rapidly and completely absorbed from the gastrointestinal tract; however, a period of 12 hours is required for its full action. Its elimination rate is slow, so that its action may persist for several days after the last dose. The drug inhibits the metabolism of many other therapeutic agents, including phenytoin, oral anticoagulants, and isoniazid.

Compliance with disulfiram therapy is often low, and both compliance and clinical outcome can be improved by supervised administration. When the drug is prescribed, the alcohol content of common nonprescription medications should be communicated to the patient; some of these are listed in Table 64–3. Management with disulfiram should be initiated only when the patient has been free of alcohol for at least 24 hours. The drug may cause mild changes in liver function tests. The safety of disulfiram in pregnancy has not been demonstrated. The duration of disulfiram treatment should be individualized and determined by the patient's responsiveness and clinical improvement. The usual oral dose is 250 mg daily taken at bedtime.

Several other drugs, eg, metronidazole, certain cephalosporins, sulfonylurea hypoglycemic drugs, and chloral hydrate, have disulfiram-like effects on ethanol metabolism. Patients should be warned to avoid drinking ethanol while taking these drugs and for several days after they discontinue them.

Naltrexone

Naltrexone is an orally available opioid receptor antagonist that blocks the effects of exogenous
and, presumably, endogenous opioids (see Chapter 31: Opioid Analgesics & Antagonists). Studies in experimental animals first suggested a link between alcohol consumption and opioids. Injection of small amounts of opioids was followed by an increase in alcohol drinking, whereas administration of opioid antagonists inhibited self-administration of alcohol. Several double-blind, placebo-controlled clinical trials showed that the combination of naltrexone with psychosocial therapy decreased the rate of relapse and reduced alcohol craving (see Manipulating Brain Neurotransmitter Systems to Treat Alcoholism). The subjects taking naltrexone who "slipped," that is, who sampled alcohol during the trial, were better able to control their drinking and avoid relapsing into heavy drinking. The lower alcohol consumption in naloxone-treated subjects was associated with a diminution of the subjective "high" associated with alcohol (Volpicelli et al, 1995). The durability of naltrexone's effect in alcoholism is not clear, since the initial clinical trials were only for 12 weeks. In a follow-up study, the decrease in relapse after 12 weeks of treatment continued for only one month after discontinuation of the naltrexone (O'Malley et al, 1996).

Naltrexone is taken once a day in a dose of 50 mg for treatment of alcoholism. The drug should be used with caution in alcoholic patients with evidence of mild abnormalities in serum aminotransferase activity. The combination of naltrexone plus disulfiram should be avoided since both drugs are potential hepatotoxins. Administration of naltrexone to patients who are physically dependent upon opioids will precipitate an acute withdrawal syndrome so patients must be opioid-free before initiating naltrexone therapy. Naltrexone also blocks the therapeutic effects of usual doses of opioids.

Other Drugs

Preliminary evidence suggests that topiramate, a drug used for partial and generalized tonic-clonic seizures (Chapter 24: Antiseizure Drugs), may be effective in reducing craving in chronic alcoholics.

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**Pharmacology of Other Alcohols**

Other alcohols related to ethanol have wide applications as industrial solvents and occasionally cause severe poisoning. Of these, methanol and ethylene glycol are two of the most common causes of intoxication.

**Methanol**

Methanol (methyl alcohol, wood alcohol) is widely used in the industrial production of synthetic organic compounds and as a constituent of many commercial solvents. In the home, methanol is most frequently found in the form of "canned heat" or in windshield-washing products. Poisonings occur from accidental ingestion of methanol-containing products or when it is used by alcoholics as an ethanol substitute.

Methanol can be absorbed through the skin or from the respiratory or gastrointestinal tract and is then distributed in body water. The primary mechanism of elimination of methanol in humans is by oxidation to formaldehyde, formic acid, and CO₂:
Animal species show great variability in mean lethal doses of methanol. The special susceptibility of humans to methanol toxicity is probably due to folate-dependent production of formate and not to methanol itself or to formaldehyde, the intermediate metabolite.

The most characteristic symptom in methanol poisoning is a visual disturbance, frequently described as "like being in a snowstorm." A complaint of blurred vision with a relatively clear sensorium should strongly suggest the diagnosis of methanol poisoning. Since much of the toxicity is due to metabolites of methanol, there is often a delay of up to 30 hours before development of visual disturbances and other signs of severe intoxication.

Physical findings in methanol poisoning are generally nonspecific. In severe cases, the odor of formaldehyde may be present on the breath or in the urine. Changes in the retina may sometimes be detected on examination, but these are usually late. The development of bradycardia, prolonged coma, seizures, and resistant acidosis all imply a poor prognosis. The cause of death in fatal cases is sudden cessation of respiration.

It is critical that the blood methanol level be determined as soon as possible if the diagnosis is suspected. Methanol concentrations in excess of 50 mg/dL are thought to be an absolute indication for hemodialysis and ethanol treatment, though formate blood levels are a better indication of clinical pathology. Additional laboratory evidence includes metabolic acidosis with an elevated anion gap and osmolar gap (see Chapter 59: Management of the Poisoned Patient). A decrease in serum bicarbonate is a uniform feature of severe methanol poisoning.

The first treatment for methanol poisoning, as in all critical poisoning situations, is support of respiration. For hospitalized patients, gastric lavage should be carried out after the airway has been protected by endotracheal intubation. Activated charcoal is not useful.

There are three specific modalities of treatment for severe methanol poisoning: suppression of metabolism by alcohol dehydrogenase to toxic products, dialysis to enhance removal of methanol and its toxic products, and alkalinization to counteract metabolic acidosis.

The enzyme chiefly responsible for methanol oxidation in the liver is alcohol dehydrogenase. Ethanol has a higher affinity than methanol for alcohol dehydrogenase; thus, saturation of the enzyme with ethanol reduces formate production. Ethanol is often used intravenously as treatment for methanol poisoning. The dose-dependent characteristics of ethanol metabolism and the variability of ethanol metabolism require frequent monitoring of blood ethanol levels to ensure appropriate alcohol concentration. *Fomepizole*, an alcohol dehydrogenase inhibitor, is approved for the treatment of ethylene glycol poisoning (see below) and methanol poisoning.

Hemodialysis rapidly eliminates both methanol and formate. However, ethanol will also be eliminated in the dialysate, requiring alterations in the dose of ethanol. Hemodialysis is discussed in Chapter 59: Management of the Poisoned Patient.

Two other measures are commonly taken. Because of profound metabolic acidosis in methanol poisoning, treatment with bicarbonate often is necessary. Since folate-dependent systems are
responsible for the oxidation of formic acid to CO₂ in humans, it is probably useful to administer folic acid to patients poisoned with methanol, though this has never been fully tested in clinical studies.

Ethylene Glycol

Polyhydric alcohols such as ethylene glycol (CH₂OHCH₂OH) are used as heat exchangers, in antifreeze formulations, and as industrial solvents. Young children and animals are sometimes attracted by the sweet taste of ethylene glycol and, rarely, it is ingested intentionally as an ethanol substitute or in attempted suicide. While ethylene glycol itself is relatively harmless and eliminated by the kidney, it is metabolized to toxic aldehydes and oxalate.

Three stages of ethylene glycol overdose occur. Within the first few hours after ingestion, there is transient excitation followed by central nervous system depression. After a delay of 4–12 hours, severe metabolic acidosis develops from accumulation of acid metabolites and lactate. Finally, delayed renal insufficiency follows deposition of oxalate in renal tubules. The key to the diagnosis of ethylene glycol poisoning is recognition of anion gap acidosis, osmolar gap, and oxalate crystals in the urine in a patient without visual symptoms.

As with methanol poisoning, early ethanol infusion and hemodialysis are standard treatments for ethylene glycol poisoning. Fomepizole, an inhibitor of alcohol dehydrogenase, has FDA approval for treatment of ethylene glycol poisoning in adults based on its ability to decrease concentrations of toxic metabolites in blood and urine and to prevent renal injury. Intravenous treatment with fomepizole is initiated immediately and continued until the patient's serum ethylene glycol concentration drops below a toxic threshold (20 mg/dL). Adverse effects associated with fomepizole are not severe. Headache, nausea, and dizziness are the ones most frequently reported, and a few patients experience minor allergic reactions. Fomepizole is classified as an orphan drug (see Chapter 5: Basic & Clinical Evaluation of New Drugs) because ethylene glycol poisoning is relatively uncommon. Its cost—estimated to be $4000 per patient—is much higher than the cost of infusible ethanol, but fomepizole offers some advantages over ethanol as an antidote for this potentially fatal poisoning.

Manipulating Brain Neurotransmitter Systems to Treat Alcoholism

Advances in knowledge about the neurochemistry of the brain's reward system have increased the hope that pharmacologic manipulation of brain neurotransmitter systems can help people who become addicted to alcohol and other drugs. The apparent utility of naltrexone, an opioid antagonist, in reducing craving and the incidence of relapse in alcoholic patients provides evidence that the opioid system is an important player in the alcohol response system. The glutamate neurotransmitter system also appears to be important. Acamprosate, a competitive inhibitor of the NMDA glutamate receptor, reduces the incidence of relapse and prolongs abstinence. It is widely available in Europe and is being tested in the USA.

Several other neurotransmitter systems are leading targets in studies of pharmacotherapy for alcoholism. Considerable evidence from animal studies indicates that serotonergic and dopaminergic systems participate in the regulation of alcohol consumption. One intriguing clinical trial found that ondansetron reduced drinking in patients with early-onset alcoholism (Johnson et al, 2000). Ondansetron is an antagonist of 5-HT₃ serotonin receptors and a commonly used antiemetic
Other clinical trials are focusing on selective serotonin reuptake inhibitors (SSRI) such as fluoxetine as well as selective serotonin receptor ligands such as buspirone, a 5-HT1A receptor partial agonist; and ritanserin, a 5-HT2 receptor antagonist. Of these other drugs, the SSRI drugs have been most thoroughly studied. Results from clinical trials have been mixed, with some studies showing favorable results and others failing to find that SSRIs attenuate alcohol consumption in nondepressed heavy drinkers. A number of dopamine receptor antagonists are also being studied, including selective antagonists of D1 and D2 dopamine receptors. Because of their importance in alcohol-related effects, drugs that modify neurotransmission through GABA and glutamate systems are also under investigation. Alcoholism is a heterogeneous disorder. As efforts to classify alcoholic patients into specific subtypes become more sophisticated, it may be possible to identify the subtypes that respond best to specific pharmacotherapies.

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Preparations Available

Drugs for the Treatment of Acute Alcohol Withdrawal Syndrome

**Diazepam** (generic, Valium, others)

Oral: 2, 3, 10 mg tablets; 5 mg/5 mL solutions (see also Chapter 22: Sedative-Hypnotic Drugs)

Parenteral: 5 mg/mL for injection

**Lorazepam** (generic, Alzapam, Ativan)

Oral: 0.5, 1, 2 mg tablets

Parenteral: 2, 4 mg/mL for injection

**Oxazepam** (generic, Serax)

Oral: 10, 15, 30 mg capsules, 15 mg tablets

**Thiamine** (generic)

Parenteral: 100 mg/mL for IV injection

Drugs for the Prevention of Alcohol Abuse

**Disulfiram** (generic, Antabuse)

Oral: 250, 500 mg tablets

**Naltrexone** (ReVia)

Oral: 50 mg tablets
Chapter 24. Antiseizure Drugs*

Antiseizure Drugs: Introduction

* The authors wish to thank Philip Mayer, PhD, for his assistance in reviewing the pharmacokinetic data in this chapter.

Approximately 1% of the world's population has epilepsy, the second most common neurologic disorder after stroke. Although standard therapy permits control of seizures in 80% of these patients, millions (500,000 people in the USA alone) have uncontrolled epilepsy. Epilepsy is a heterogeneous symptom complex—a chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures are many and include the full range of neurologic diseases, from infection to neoplasm and head injury. In some subgroups, heredity has proved to be a major contributing factor.

The antiseizure drugs described in this chapter are also used in patients with febrile seizures or with seizures occurring as part of an acute illness such as meningitis. The term "epilepsy" is not usually applied to such patients unless chronic seizures develop later. Seizures are occasionally caused by an acute underlying toxic or metabolic disorder, in which case appropriate therapy should be directed toward the specific abnormality, eg, hypocalcemia. In most cases of epilepsy, however, the choice of medication depends on the empiric seizure classification.

Drug Development for Epilepsy

For a long time it was assumed that a single drug could be developed for the treatment of all forms of epilepsy, but the causes of epilepsy are extremely diverse, encompassing genetic and developmental defects and infective, traumatic, neoplastic, and degenerative disease processes, and drug therapy to date shows little evidence of etiologic specificity. There is, however, some specificity according to seizure type. This is most clearly seen with generalized seizures of the
absence type (see Table 24–1), typically with 2–3 Hz spike-and-wave discharges on the electroencephalogram, which respond to ethosuximide and valproate but can be exacerbated by phenytoin and carbamazepine. Drugs acting selectively on absence seizures can be identified by animal screens, using either threshold pentylentetrazol clonic seizures in mice or rats or mutant mice showing absence-like episodes (so-called lethargic, star-gazer, or tottering mutants). In contrast, the maximal electroshock (MES) test, with suppression of the tonic extensor phase, identifies drugs such as phenytoin, carbamazepine, and lamotrigine that are active against generalized tonic-clonic seizures or complex partial seizures. Use of the maximal electroshock test as the major primary screen for new drugs has probably led to the identification of drugs with a common mechanism of action involving prolonged inactivation of the voltage-sensitive sodium channel. Limbic seizures induced in rats by the process of electrical kindling (involving repeated episodes of focal electrical stimulation) probably provides a better screen for predicting efficacy in complex partial seizures.

Table 24–1. Classification of Seizure Types.

<table>
<thead>
<tr>
<th>Partial seizures</th>
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<tbody>
<tr>
<td>Simple partial seizures</td>
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<tr>
<td>Complex partial seizures</td>
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<tr>
<td>Partial seizures secondarily generalized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalized seizures</th>
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</thead>
<tbody>
<tr>
<td>Generalized tonic-clonic (grand mal) seizures</td>
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<tr>
<td>Absence (petit mal) seizures</td>
</tr>
<tr>
<td>Tonic seizures</td>
</tr>
<tr>
<td>Atonic seizures</td>
</tr>
<tr>
<td>Clonic and myoclonic seizures</td>
</tr>
<tr>
<td>Infantile spasms‡</td>
</tr>
</tbody>
</table>

‡ An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

Existing antiseizure drugs provide adequate seizure control in about two thirds of patients. A fraction of the epileptic population is resistant to all available drugs and this may be due to increased expression of the multidrug transporter P-glycoprotein 170, a product of the \( \text{ABCB1} \) gene (Siddiqui, 2003). In children, some severe seizure syndromes associated with progressive brain damage are very difficult to treat. In adults, some focal seizures are refractory to medications. Some, particularly in the temporal lobe, are amenable to surgical resection. Some of the drug-resistant population may respond to vagus-nerve stimulation (VNS), a nonpharmacologic treatment for epilepsy, that is now widely approved for treatment of patients with partial seizures. VNS is indicated for refractory cases or for patients in whom antiseizure drugs are poorly tolerated. Stimulating electrodes are implanted in the left vagus nerve and the pacemaker is implanted in the chest wall or axilla. Use of this device may permit seizure control with lower doses of drugs. New antiseizure drugs are being sought not only by the screening tests noted above but also by more rational approaches. Compounds are sought that act by one of three mechanisms: (1) enhancement
of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, or (3) modification of ionic conductances.

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**Basic Pharmacology of Antiseizure Drugs**

**Chemistry**

Up to 1990, approximately 16 antiseizure drugs were available, and 13 of them can be classified into five very similar chemical groups: barbiturates, hydantoins, oxazolidinediones, succinimides, and acetylureas. These groups have in common a similar heterocyclic ring structure with a variety of substituents (Figure 24–1). For drugs with this basic structure, the substituents on the heterocyclic ring determine the pharmacologic class, either anti-MES or antipentylenetetrazol. Very small changes in structure can dramatically alter the mechanism of action and clinical properties of the compound. The remaining drugs—carbamazepine, valproic acid, and the benzodiazepines—are structurally dissimilar, as are the newer compounds marketed since 1990, ie, felbamate, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin, and levetiracetam.

![Antiseizure heterocyclic ring structure. The "X" varies as follows: hydantoin derivatives, –N--; barbiturates, –C–N--; oxazolidinediones, –O--; succinimides, –C--; acetylureas, –NH2 (N connected to C2). R1, R2, and R3 vary within each subgroup.](image)

**Pharmacokinetics**

The antiseizure drugs exhibit many similar pharmacokinetic properties—even those whose structural and chemical properties are quite diverse. Although many of these compounds are only slightly soluble, absorption is usually good, with 80–100% of the dose reaching the circulation. Most antiseizure drugs are not highly bound to plasma proteins.

Antiseizure drugs are cleared chiefly by hepatic mechanisms, although they have low extraction ratios (see Chapter 3: Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action). Many are converted to active metabolites that are also cleared by the liver. These drugs are predominantly distributed into total body water. Plasma clearance is relatively slow; many anticonvulsants are therefore considered to be medium- to long-acting. For most, half-lives are greater than 12 hours. Phenobarbital and carbamazepine are potent inducers of hepatic microsomal enzyme activity.

**Drugs Used in Partial Seizures & Generalized Tonic-Clonic Seizures**

The major drugs for partial and generalized tonic-clonic seizures are phenytoin (and congeners), carbamazepine, valproate, and the barbiturates. However, the availability of newer drugs—lamotrigine, gabapentin, oxcarbazepine, topiramate, vigabatrin, and levetiracetam—is altering
clinical practice in countries where these compounds are available.

Phenytoin

Phenytoin is the oldest nonsedative antiseizure drug, introduced in 1938 following a systematic evaluation of compounds such as phenobarbital that altered electrically induced seizures in laboratory animals. It was known for decades as diphenylhydantoin.

Chemistry

Phenytoin is a diphenyl-substituted hydantoin with the structure shown below. It has much lower sedative properties than compounds with alkyl substituents at the 5 position. A more soluble prodrug of phenytoin, fosphenytoin, is available for parenteral use. This phosphate ester compound is rapidly converted to phenytoin in the plasma.

![Phenytoin structure](image)

Mechanism of Action

Phenytoin has major effects on several physiologic systems. It alters Na\(^+\), K\(^+\), and Ca\(^{2+}\) conductance, membrane potentials, and the concentrations of amino acids and the neurotransmitters norepinephrine, acetylcholine, and \(\gamma\)-aminobutyric acid (GABA). Studies with neurons in cell culture show that phenytoin blocks sustained high-frequency repetitive firing of action potentials (Figure 24–2). This effect is seen at therapeutically relevant concentrations. It is a use-dependent effect (see Chapter 14: Agents Used in Cardiac Arrhythmias) on Na\(^+\) conductance, arising from preferential binding to—and prolongation of—the inactivated state of the Na\(^+\) channel. This effect is also seen with therapeutically relevant concentrations of carbamazepine and valproate and probably contributes to their antiseizure action in the electroshock model and in partial seizures.

Figure 24–2.
Effects of three antiseizure drugs on sustained high-frequency firing of action potentials by cultured neurons. Intracellular recordings were made from neurons while depolarizing current pulses, approximately 0.75 s in duration, were applied (on-off step changes indicated by arrows). In the absence of drug, a series of high-frequency repetitive action potentials filled the entire duration of the current pulse. Phenytoin, carbamazepine, and sodium valproate all markedly reduced the number of action potentials elicited by the current pulses. (Modified and reproduced, with permission, from Macdonald RL, Meldrum BS: Principles of antiepileptic drug action. In: Levy RH, et al [editors]. Antiepileptic Drugs, 4th ed. Raven Press, 1995.)

At high concentrations, phenytoin also inhibits the release of serotonin and norepinephrine, promotes the uptake of dopamine, and inhibits monoamine oxidase activity. The drug interacts with membrane lipids; this binding might promote the stabilization of the membrane. In addition, phenytoin paradoxically causes excitation in some cerebral neurons. A reduction of calcium permeability, with inhibition of calcium influx across the cell membrane, may explain the ability of phenytoin to inhibit a variety of calcium-induced secretory processes, including release of hormones and neurotransmitters. The significance of these biochemical actions and their relationship to phenytoin's clinical activity are unclear.

The mechanism of phenytoin's action probably involves a combination of actions at several levels. At therapeutic concentrations, the major action of phenytoin is to block sodium channels and inhibit the generation of repetitive action potentials.

Clinical Use

Phenytoin is one of the most effective drugs against partial seizures and generalized tonic-clonic seizures. In the latter, it appears to be effective against attacks that are either primary or secondary to another seizure type.

Pharmacokinetics

Absorption of phenytoin is highly dependent on the formulation of the dosage form. Particle size and pharmaceutical additives affect both the rate and the extent of absorption. Absorption of phenytoin sodium from the gastrointestinal tract is nearly complete in most patients, although the time to peak may range from 3 hours to 12 hours. Absorption after intramuscular injection is unpredictable, and some drug precipitation in the muscle occurs; this route of administration is not recommended for phenytoin. In contrast, fosphenytoin, a more soluble phosphate prodrug of phenytoin, is well absorbed after intramuscular administration.

Phenytoin is highly bound to plasma proteins. It appears certain that the total plasma level decreases when the percentage that is bound decreases, as in uremia or hypoalbuminemia, but correlation of free levels with clinical states remains uncertain. Drug concentration in cerebrospinal fluid is
Phenytoin accumulates in brain, liver, muscle, and fat. Phenytoin is metabolized to inactive metabolites that are excreted in the urine. Only a very small portion of phenytoin is excreted unchanged.

The elimination of phenytoin is dose-dependent. At very low blood levels, phenytoin metabolism follows first-order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize phenytoin is approached (Figure 24–3). Further increases in dose, even though relatively small, may produce very large changes in phenytoin concentrations. In such cases, the half-life of the drug increases markedly, steady state is not achieved in routine fashion (since the plasma level continues to rise), and patients quickly develop symptoms of toxicity.

Figure 24–3.

![Graph showing the non-linear relationship of phenytoin dosage and plasma concentrations.](image)

Nonlinear relationship of phenytoin dosage and plasma concentrations. Five different patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]. Quantitative Analytic Studies in Epilepsy. Raven Press, 1977.)

The half-life of phenytoin varies from 12 hours to 36 hours, with an average of 24 hours for most patients in the low to mid therapeutic range. Much longer half-lives are observed at higher concentrations. At low blood levels, it takes 5–7 days to reach steady-state blood levels after every dosage change; at higher levels, it may be 4–6 weeks before blood levels are stable.

**Therapeutic Levels & Dosage**

The therapeutic plasma level of phenytoin for most patients is between 10 and 20 µg/mL. A loading dose can be given either orally or intravenously; the latter, using fosphenytoin, is the method of choice for convulsive status epilepticus (discussed later). When oral therapy is started, it is common
to begin adults at a dosage of 300 mg/d regardless of body weight. While this may be acceptable in some patients, it frequently yields steady-state blood levels below 10 μg/mL, the minimum therapeutic level for most patients. If seizures continue, higher doses are usually necessary to achieve plasma levels in the upper therapeutic range. Because of its dose-dependent kinetics, some toxicity may occur with only small increments in dose; the phenytoin dosage should be increased each time by only 25–30 mg in adults, and ample time should be allowed for the new steady state to be achieved before further increasing the dose. A common clinical error is to increase the dosage directly from 300 mg/d to 400 mg/d; toxicity frequently occurs at a variable time thereafter. In children, a dosage of 5 mg/kg/d should be followed by readjustment after steady-state plasma levels are obtained.

Two types of oral phenytoin sodium are currently available in the USA, differing in their respective rates of dissolution; one is absorbed rapidly and one more slowly. Only the slow-release extended action formulation can be given in a single daily dosage, and care must be used when changing brands (see Preparations Available). Although a few patients being given phenytoin on a chronic basis have been proved to have low blood levels from poor absorption or rapid metabolism, the most common cause of low levels is poor compliance. Fosphenytoin sodium is available for intravenous or intramuscular use and replaces intravenous phenytoin sodium, a much less soluble form of the drug.

Drug Interactions & Interference with Laboratory Tests

Drug interactions involving phenytoin are primarily related to protein binding or to metabolism. Since phenytoin is 90% bound to plasma protein, other highly bound drugs, such as phenylbutazone or sulfonamides, can displace phenytoin from its binding site. In theory, such displacement may cause a transient increase in free drug. A decrease in protein binding—e.g., from hypoalbuminemia—results in a decrease in the total plasma concentration of drug but not the free concentration; intoxication may occur if efforts are made to maintain total drug levels in the therapeutic range by increasing the dose. The protein binding of phenytoin is decreased in the presence of renal disease. The drug has an affinity for thyroid-binding globulin, which confuses some tests of thyroid function; the most reliable screening test of thyroid function in patients taking phenytoin appears to be measurement of TSH.

Phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs. Autostimulation of its own metabolism, however, appears to be insignificant. Other drugs, notably phenobarbital and carbamazepine, cause decreases in phenytoin steady-state concentrations through induction of hepatic microsomal enzymes. On the other hand, isoniazid inhibits the metabolism of phenytoin, resulting in increased steady-state concentrations when the two drugs are given together.

Toxicity

Dose-related adverse effects caused by phenytoin are unfortunately similar to other antiseizure drugs in this group, making differentiation difficult in patients receiving multiple drugs. Nystagmus occurs early, as does loss of smooth extraocular pursuit movements, but neither is an indication for decreasing the dose. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients; the latter can be especially unpleasant in women. Long-term use is associated in some patients with coarsening of facial features and with mild peripheral neuropathy, usually manifested by diminished deep tendon reflexes in the lower extremities. Long-term use may also result in abnormalities of vitamin D
metabolism, leading to osteomalacia. Low folate levels and megaloblastic anemia have been reported, but the clinical importance of this observation is unknown.

Idiosyncratic reactions to phenytoin are relatively rare. A skin rash may indicate hypersensitivity of the patient to the drug. Fever may also occur, and in rare cases the skin lesions may be severe and exfoliative. Lymphadenopathy may be difficult to distinguish from malignant lymphoma, and although some studies suggest a causal relationship between phenytoin and Hodgkin's disease, the data are far from conclusive. Hematologic complications are exceedingly rare, although agranulocytosis has been reported in combination with fever and rash.

Mephenytoin, Ethotoin, & Phenacemide

Many congeners of phenytoin have been synthesized, but only three have been marketed recently in the USA, and one of these (phenacemide) has been withdrawn from the market. The first two congeners, mephenytoin and ethotoin, like phenytoin, appear to be most effective against generalized tonic-clonic seizures and partial seizures. No well-controlled clinical trials have documented their effectiveness. The incidence of severe reactions such as dermatitis, agranulocytosis, or hepatitis is higher for mephenytoin than for phenytoin.

Ethotoin may be recommended for patients hypersensitive to phenytoin, but larger doses are required. The adverse effects and toxicity are generally less severe than those associated with phenytoin, but the drug appears to be less effective.

Both ethotoin and mephenytoin share with phenytoin the property of saturable metabolism within the therapeutic dosage range. Careful monitoring of the patient during dosage alterations with either drug is essential. Mephenytoin is metabolized to 5,5-ethylphenylhydantoin via demethylation. This metabolite, nirvanol, contributes most of the antiseizure activity of mephenytoin. Both mephenytoin and nirvanol are hydroxylated and undergo subsequent conjugation and excretion. Therapeutic levels for mephenytoin range from 5 μg/mL to 16 μg/mL, and levels above 20 μg/mL are considered toxic.

Therapeutic blood levels of nirvanol are between 25 and 40 μg/mL. A therapeutic range for ethotoin has not been established.

The third congener of phenytoin, phenacemide, is a straight-chain analog of phenytoin. It is a toxic drug of last resort for refractory partial seizures.

Carbamazepine

Closely related to imipramine and other antidepressants, carbamazepine is a tricyclic compound effective in treatment of bipolar depression. It was initially marketed for the treatment of trigeminal neuralgia but has proved useful for epilepsy as well.

Chemistry

Although not obvious from a two-dimensional representation of its structure, carbamazepine has many similarities to phenytoin. The ureide moiety (–N–CO–NH₂) present in the heterocyclic ring of most antiseizure drugs is also present in carbamazepine. Three-dimensional structural studies indicate that its spatial conformation is similar to that of phenytoin.
Mechanism of Action

The mechanism of action of carbamazepine appears to be similar to that of phenytoin. Like phenytoin, carbamazepine shows activity against maximal electroshock seizures. Carbamazepine, like phenytoin, blocks sodium channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons in culture (Figure 24–2). It also acts presynaptically to decrease synaptic transmission. These effects probably account for the anticonvulsant action of carbamazepine. Binding studies show that carbamazepine interacts with adenosine receptors, but the functional significance of this observation is not known. Carbamazepine also inhibits uptake and release of norepinephrine from brain synaptosomes but does not influence GABA uptake in brain slices. Recent evidence suggests that the postsynaptic action of GABA can be potentiated by carbamazepine.

Clinical Use

Carbamazepine is considered the drug of choice for partial seizures, and many physicians also use it first for generalized tonic-clonic seizures. It can be used with phenytoin in many patients who are difficult to control. Carbamazepine is not sedative in its usual therapeutic range. The drug is also very effective in some patients with trigeminal neuralgia, although older patients may tolerate higher doses poorly, with ataxia and unsteadiness. Carbamazepine is also useful in some patients with mania (bipolar disorder).

Pharmacokinetics

The rate of absorption of carbamazepine varies widely among patients, although almost complete absorption apparently occurs in all. Peak levels are usually achieved 6–8 hours after administration. Slowing absorption by giving the drug after meals helps the patient tolerate larger total daily doses.

Distribution is slow, and the volume of distribution is roughly 1 L/kg. The drug is only 70% bound to plasma proteins; no displacement of other drugs from protein binding sites has been observed.

Carbamazepine has a very low systemic clearance of approximately 1 L/kg/d at the start of therapy. The drug has a notable ability to induce microsomal enzymes. Typically, the half-life of 36 hours observed in subjects following an initial single dose decreases to much less than 20 hours in subjects receiving continuous therapy. Considerable dosage adjustments are thus to be expected during the first weeks of therapy. Carbamazepine also alters the clearance of other drugs (see below).

Carbamazepine is completely metabolized in humans to several derivatives. One of these, carbamazepine-10,11-epoxide, has been shown to have anticonvulsant activity. The contribution of this and other metabolites to the clinical activity of carbamazepine is unknown.
Therapeutic Levels & Dosage

Carbamazepine is considered the drug of choice in partial seizures. It is available only in oral form. The drug is effective in children, in whom a dosage of 15–25 mg/kg/d is appropriate. In adults, daily doses of 1 g or even 2 g are tolerated. Higher dosage is achieved by giving multiple divided doses daily. An extended-release preparation permits twice-daily dosing for most patients. In patients in whom the blood is drawn just before the morning dose (trough level), the therapeutic level is usually 4–8 µg/mL; although many patients complain of diplopia at drug levels above 7 µg/mL, others can tolerate levels above 10 µg/mL, especially with monotherapy.

Drug Interactions

Drug interactions involving carbamazepine are almost exclusively related to the drug’s enzyme-inducing properties. As noted previously, the increased metabolic capacity of the hepatic enzymes may cause a reduction in steady-state carbamazepine concentrations and an increased rate of metabolism of other drugs, eg, primidone, phenytoin, ethosuximide, valproic acid, and clonazepam. Other drugs such as propoxyphene, troleandomycin, and valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels. Other anticonvulsants, however, such as phenytoin and phenobarbital, may decrease steady-state concentrations of carbamazepine through enzyme induction. No clinically significant protein-binding interactions have been reported.

Toxicity

The most common dose-related adverse effects of carbamazepine are diplopia and ataxia. The diplopia often occurs first and may last less than an hour during a particular time of day. Rearrangement of the divided daily dose can often remedy this complaint. Other dose-related complaints include mild gastrointestinal upsets, unsteadiness, and, at much higher doses, drowsiness. Hyponatremia and water intoxication have occasionally occurred and may be dose-related.

Considerable concern exists regarding the occurrence of idiosyncratic blood dyscrasias with carbamazepine, including fatal cases of aplastic anemia and agranulocytosis. Most of these have been in elderly patients with trigeminal neuralgia, and most have occurred within the first 4 months of treatment. The mild and persistent leukopenia seen in some patients is not necessarily an indication to stop treatment but requires careful monitoring. The most common idiosyncratic reaction is an erythematous skin rash; other responses such as hepatic dysfunction are unusual.

Oxcarbazepine

Oxcarbazepine is closely related to carbamazepine and useful in the same seizure types, but it may have an improved toxicity profile. Oxcarbazepine has a half-life of only 1–2 hours. Its activity, therefore, resides almost exclusively in the 10-hydroxy metabolite, to which it is rapidly converted and which has a half-life similar to that of carbamazepine, ie, 8–12 hours. The drug is mostly excreted as the glucuronide of the 10-hydroxy metabolite. Oxcarbazepine is less potent than carbamazepine, both in animal models of epilepsy and in epileptic patients; clinical doses of oxcarbazepine may need to be 50% higher than those of carbamazepine to obtain equivalent seizure control. Some studies report fewer hypersensitivity reactions to oxcarbazepine, and cross-reactivity with carbamazepine does not always occur. Furthermore, the drug appears to induce hepatic enzymes to a lesser extent than carbamazepine, minimizing drug interactions. Those adverse effects—such as hyponatremia—that do occur with oxcarbazepine are similar in character to reactions reported with carbamazepine.
Phenobarbital

Aside from the bromides, phenobarbital is the oldest of the currently available antiseizure drugs. Although it has long been considered one of the safest of the antiseizure agents, the use of other medications with lesser sedative effects has been urged. Many consider the barbiturates the drugs of choice for seizures only in infants.

Chemistry

The four derivatives of barbituric acid clinically useful as antiseizure drugs are phenobarbital, mephobarbital, metharbital, and primidone (Figure 24–4). The first three are so similar that they will be considered together. Metharbital is methylated barbital, and mephobarbital is methylated phenobarbital; both are demethylated in vivo. The pKa's of these three weak acid compounds range from 7.3 to 7.9. Slight changes in the normal acid-base balance, therefore, can cause significant fluctuation in the ratio of the ionized to the un-ionized species. This is particularly important for phenobarbital, the most commonly used barbiturate, whose pKa is similar to the plasma pH of 7.4.

Figure 24–4.

Primidone and its active metabolites.
The three-dimensional conformations of phenobarbital and N-methylphenobarbital are similar to that of phenytoin. Both compounds possess a phenyl ring and are active against partial seizures.

Mechanism of Action

The exact mechanism of action of phenobarbital is unknown, but enhancement of inhibitory processes and diminution of excitatory transmission probably contribute importantly. Recent data indicate that phenobarbital may selectively suppress abnormal neurons, inhibiting the spread and suppressing firing from the foci. Like phenytoin, phenobarbital suppresses high-frequency repetitive firing in neurons in culture through an action on Na⁺ conductance, but only at high concentrations. Also at high concentrations, barbiturates block some Ca²⁺ currents (L-type and N-type). Phenobarbital binds to an allostERIC regulatory site on the GABA-benzodiazepine receptor, and it enhances the GABA receptor-mediated current by prolonging the openings of the Cl⁻ channels. Phenobarbital also blocks excitatory responses induced by glutamate, principally those mediated by activation of the AMPA receptor (see Chapter 21: Introduction to the Pharmacology of CNS Drugs). Both the enhancement of GABA-mediated inhibition and the reduction of glutamate-mediated excitation are seen with therapeutically relevant concentrations of phenobarbital.

Clinical Use

Phenobarbital is useful in the treatment of partial seizures and generalized tonic-clonic seizures, although the drug is often tried for virtually every seizure type, especially when attacks are difficult to control. There is little evidence for its effectiveness in generalized seizures such as absence, atonic attacks, or infantile spasms; it may worsen certain patients with these seizure types.

Some physicians prefer either metharbital or mephobarbital—especially the latter—to phenobarbital because of supposed decreased adverse effects. Only anecdotal data are available to support such comparisons.

Pharmacokinetics

See Chapter 22: Sedative-Hypnotic Drugs.

Therapeutic Levels & Dosage

The therapeutic levels of phenobarbital in most patients range from 10 μg/mL to 40 μg/mL. Documentation of effectiveness is best in febrile seizures, and levels below 15 μg/mL appear ineffective for prevention of febrile seizure recurrence. The upper end of the therapeutic range is more difficult to define, as many patients appear to tolerate chronic levels above 40 μg/mL.

Drug Interactions & Toxicity

See Chapter 22: Sedative-Hypnotic Drugs.

Primidone

Primidone, or 2-desoxyphenobarbital (Figure 24–4), was first marketed in the early 1950s. It was later reported that primidone was metabolized to phenobarbital and phenylethylmalonamide (PEMA). All three compounds are active anticonvulsants.
Mechanism of Action

Although primidone is converted to phenobarbital, the mechanism of action of primidone itself may be more like that of phenytoin.

Clinical Use

Primidone, like its metabolites, is effective against partial seizures and generalized tonic-clonic seizures and may be more effective than phenobarbital. It was previously considered to be the drug of choice for complex partial seizures, but the latest studies of partial seizures in adults strongly suggest that carbamazepine and phenytoin are superior to primidone. Attempts to determine the relative potencies of the parent drug and its two metabolites have been conducted in newborn infants, in whom drug-metabolizing enzyme systems are very immature and in whom primidone is only slowly metabolized. Primidone has been shown to be effective in controlling seizures in this group and in older patients beginning treatment with primidone; the latter show seizure control before phenobarbital concentrations reach the therapeutic range. Finally, studies of maximal electroshock seizures in animals suggest that primidone has an anticonvulsant action independent of its conversion to phenobarbital and PEMA (the latter is relatively weak).

Pharmacokinetics

Primidone is completely absorbed, usually reaching peak concentrations about 3 hours after oral administration, although considerable variation has been reported. Primidone is generally confined to total body water, with a volume of distribution of 0.6 L/kg. It is not highly bound to plasma proteins; approximately 70% circulates as unbound drug.

Primidone is metabolized by oxidation to phenobarbital, which accumulates very slowly, and by scission of the heterocyclic ring to form PEMA (Figure 24–4). Both primidone and phenobarbital also undergo subsequent conjugation and excretion.

Primidone has a larger clearance than most other antiseizure drugs (2 L/kg/d), corresponding to a half-life of 6–8 hours. PEMA clearance is approximately half that of primidone, but phenobarbital has a very low clearance. The appearance of phenobarbital corresponds to the disappearance of primidone. Phenobarbital therefore accumulates very slowly but eventually reaches therapeutic concentrations in most patients when therapeutic doses of primidone are administered. During chronic therapy, phenobarbital levels derived from primidone are usually two to three times higher than primidone levels. PEMA, which probably makes a minimal contribution to the efficacy of primidone, has a half-life of 8–12 hours and therefore reaches steady state more rapidly than phenobarbital.

Therapeutic Levels & Dosage

Primidone is most efficacious when plasma levels are in the range of 8–12 µg/mL. Concomitant levels of its metabolite, phenobarbital, at steady state will usually vary from 15 µg/mL to 30 µg/mL. Dosages of 10–20 mg/kg/d are necessary to obtain these levels. It is very important, however, to start primidone at low doses and gradually increase over days to a few weeks to avoid prominent sedation and gastrointestinal complaints. When adjusting doses of the drug, it is important to remember that the parent drug will rapidly reach steady state (30–40 hours), but the active metabolites phenobarbital (20 days) and PEMA (3–4 days) will reach steady state much more slowly.
Toxicity

The dose-related adverse effects of primidone are similar to those of its metabolite, phenobarbital, except that drowsiness occurs early in treatment and may be prominent if the initial dose is too large; gradual increments are indicated when starting the drug in either children or adults.

Vigabatrin

Current investigations that seek drugs to enhance the effects of GABA include efforts to find GABA agonists and prodrugs, GABA transaminase inhibitors, and GABA uptake inhibitors. Vigabatrin (γ-vinyl-GABA) is one of these new drugs and has been registered in Europe and South America.

\[
\begin{align*}
\text{CH}_2 & \equiv \text{CH} & \text{NH}_2 \\
\text{CH} & \equiv \text{CH}_2 & \text{COOH} \\
\text{CH}_2 & \equiv \text{CH} & \text{COOH}
\end{align*}
\]

Vigabatrin

Mechanism of Action

Vigabatrin is an irreversible inhibitor of GABA aminotransferase (GABA-T), the enzyme responsible for the degradation of GABA. It apparently acts by increasing the amount of GABA released at synaptic sites, thereby enhancing inhibitory effects. Vigabatrin may also potentiate GABA by inhibiting the GABA transporter. It is effective in a wide range of seizure models. Vigabatrin is marketed as a racemate; the \(S(+)\) enantiomer is active and the \(R(–)\) enantiomer appears to be inactive.

Clinical Use

Vigabatrin is useful in the treatment of partial seizures and West's syndrome. The half-life is approximately 6–8 hours, but considerable evidence suggests that the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life. In adults, vigabatrin should be started at an oral dosage of 500 mg twice daily; a total of 2–3 g (rarely more) daily may be required for full effectiveness. Typical toxicities include drowsiness, dizziness, and weight gain. Less common but more troublesome adverse reactions are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication. The drug was delayed in its worldwide introduction by the appearance in rats and dogs of a reversible intramyelinic edema; this phenomenon has not been observed in any patient to date. More recently, unfortunately, long-term therapy with vigabatrin has been associated with development of visual field defects in up to one third of patients. This adverse effect may not be reversible, and vigabatrin may therefore be relegated to use in patients—such as those with infantile spasms—who are refractory to other treatments.

Lamotrigine

Lamotrigine was developed when some investigators thought that the antifolate effects of certain antiseizure drugs (eg, phenytoin) may contribute to their effectiveness. Several phenyltriazines were developed, and although their antifolate properties were weak, some were active in seizure screening tests.
Mechanism of Action

Lamotrigine, like phenytoin, suppresses sustained rapid firing of neurons and produces a voltage- and use-dependent inactivation of sodium channels. This action probably explains lamotrigine's efficacy in focal epilepsy. It appears likely that lamotrigine has another mechanism of action to account for its efficacy in primary generalized seizures in childhood, including absence attacks; this mechanism may involve actions on voltage-activated Ca\textsuperscript{2+} channels.

Clinical Use

Although most controlled studies have evaluated lamotrigine as add-on therapy, some also suggest that the drug is effective as monotherapy for partial seizures. Some authorities feel that the drug is also active against absence and myoclonic seizures in children. Adverse effects include dizziness, headache, diplopia, nausea, somnolence, and skin rash. The rash is considered a typical hypersensitivity reaction. Although the risk of rash may be diminished by introducing the drug slowly, pediatric patients are at high risk; some studies suggest that a potentially life-threatening dermatitis will develop in 1–2% of pediatric patients.

Pharmacokinetics & Dosage

Lamotrigine is almost completely absorbed and has a volume of distribution in the range of 1−1.4 L/kg. Protein binding is only about 55%. The drug has linear kinetics and is metabolized primarily by glucuronidation to the 2-\textit{N}-glucuronide, which is excreted in the urine. Lamotrigine has a half-life of approximately 24 hours in normal volunteers; this decreases to 13−15 hours in patients taking enzyme-inducing drugs. Lamotrigine is effective against partial seizures in adults, with dosages typically between 100 mg/d and 300 mg/d and with a therapeutic blood level near 3 \textit{mg/mL}. Valproate causes a twofold increase in the drug's half-life; in patients receiving valproate, the initial dosage of lamotrigine must be reduced to 25 mg every other day.

Felbamate

Felbamate has been approved and marketed in the USA and in some European countries. Although it is effective in some patients with partial seizures, the drug causes aplastic anemia and severe hepatitis at unexpectedly high rates and has been relegated to the status of a third-line drug for refractory cases.
The mechanism of action of felbamate is not established. The strongest evidence suggests NMDA receptor blockade via the glycine binding site. Felbamate has a half-life of 20 hours (somewhat shorter when administered with either phenytoin or carbamazepine) and is metabolized by hydroxylation and conjugation; a significant percentage of the drug is excreted unchanged in the urine. When added to treatment with other antiseizure drugs, felbamate increases plasma phenytoin and valproic acid levels but decreases levels of carbamazepine.

In spite of the seriousness of the adverse effects, more than 10,000 patients worldwide remain on the medication. Usual dosages are 2000–4000 mg/d in adults, and effective plasma levels range from 30 μg/mL to 100 μg/mL. In addition to its usefulness in partial seizures, felbamate has proved effective against the seizures that occur in Lennox-Gastaut syndrome.

Gabapentin

Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures. Originally planned as a spasmolytic, it was found to be more effective as an antiseizure drug.

Mechanism of Action

In spite of its close structural relationship to GABA, gabapentin appears not to act on GABA receptors. It may, however, alter GABA metabolism, its nonsynaptic release, or its reuptake by GABA transporters. An increase in brain GABA concentration is observed in man. Gabapentin is transported into the brain by the L-amino acid transporter. Its anticonvulsant effect in the electroshock model is delayed relative to its peak plasma concentration. The drug also binds to the α2δ subunit of voltage-sensitive Ca2+ channels.

Clinical Use & Dosage

Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures at dosages that range up to 2400 mg/d in controlled clinical trials. Open follow-on studies permitted

\[
\text{GABA} \quad \text{Gabapentin}
\]
dosages up to 4800 mg/d, but data are inconclusive on the effectiveness or tolerability of such doses. Monotherapy studies also document some efficacy. Very high dosages have been needed by some clinicians to achieve improvement in seizure control. Effectiveness in other seizure types has not been well demonstrated. Gabapentin has also been found effective in the treatment of neuropathic pain and is now indicated for postherpetic neuralgia in adults at doses of 1800 mg and above. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor.

Pharmacokinetics

Gabapentin is not metabolized and does not induce hepatic enzymes. Absorption is nonlinear and dose-dependent at very high doses, but otherwise the elimination kinetics are linear. The drug is not bound to plasma proteins. Drug-drug interactions are negligible. Elimination is via renal mechanisms; the drug is excreted unchanged. The half-life is short, ranging from 5 hours to 8 hours; the drug is typically administered two or three times per day.

Topiramate

Topiramate is a substituted monosaccharide that is structurally different from all other antiseizure drugs.

![Topiramate](image)

Mechanism of Action

Topiramate blocks repetitive firing of cultured spinal cord neurons, as do phenytoin and carbamazepine. Its mechanism of action, therefore, is likely to involve blocking of voltage-dependent sodium channels. Topiramate also appears to potentiate the inhibitory effect of GABA, acting at a site different from the benzodiazepine or barbiturate sites. Topiramate also depresses the excitatory action of kainate on AMPA receptors. It is possible that all three of these actions contribute to topiramate's anticonvulsant effect.

Clinical Use

Clinical trials of topiramate demonstrated a dose-response relationship, and monotherapy trials (using a pseudoplacebo) showed the drug to be effective against partial and generalized tonic-clonic seizures. Some evidence suggests that the drug has a broader spectrum, with effectiveness against Lennox-Gestaut syndrome, West's syndrome, and even absence seizures. Dosages typically ranged from 200 mg/d to 600 mg/d, with a few patients tolerating dosages greater than 1000 mg/d. Most clinicians begin slowly (50 mg/d) and increase slowly to avoid adverse effects. Although no idiosyncratic reactions have been noted, dose-related side effects occur most frequently in the first 4 weeks and include somnolence, fatigue, dizziness, cognitive slowing, paresthesias, nervousness, and confusion. Acute myopia and glaucoma may require prompt drug withdrawal. Urolithiasis has also been reported. However, the discontinuation rate is apparently only about 15%. The drug is teratogenic in animal models, but no human fetal deformities have been noted in the very few
pregnancies that have occurred during the course of topiramate administration.

Pharmacokinetics

Topiramate is rapidly absorbed (about 2 hours) and is 80% bioavailable. There is no food effect on absorption, minimal (15%) plasma protein binding, and only moderate (20–50%) metabolism; no active metabolites are formed. The drug is primarily excreted unchanged in the urine. The half-life is about 20–30 hours. Although increased levels are seen with renal failure and hepatic impairment, there is no age or gender effect, no autoinduction, no inhibition of metabolism, and kinetics are linear. Drug interactions do occur and can be complex, but the major effect is on topiramate levels rather than on the levels of other antiseizure drugs. Birth control pills may be less effective in the presence of topiramate, and higher estrogen doses may be required.

Tiagabine

Tiagabine is a derivative of nipecotic acid and was "rationally designed" as an inhibitor of GABA uptake (as opposed to discovery through random screening).

\[
\text{Tiagabine}
\]

Mechanism of Action

Tiagabine is an inhibitor of GABA uptake in both neurons and glia. It preferentially inhibits the transporter isoform 1 (GAT-1) rather than GAT-2 or GAT-3 and increases extracellular GABA levels in the forebrain and hippocampus. It prolongs the inhibitory action of synaptically released GABA. In rodents it is potent against kindled seizures but weak against the maximum electroshock model.

Clinical Use

Tiagabine is indicated for the adjunctive treatment of partial seizures and is effective in doses ranging from 16 mg/d to 56 mg/d. Divided doses as often as four times per day are sometimes required. Some patients appear to do well with tiagabine monotherapy, which is generally well tolerated. Minor adverse events are dose-related and include nervousness, dizziness, tremor, difficulty in concentrating, and depression. Excessive confusion, somnolence, or ataxia may require discontinuation. Psychosis occurs rarely. Rash is an uncommon idiosyncratic adverse effect. Laboratory studies are usually normal.

Pharmacokinetics
Tiagabine is 90–100% bioavailable, has linear kinetics, and is highly protein-bound. The half-life is 5–8 hours and decreases in the presence of enzyme-inducing drugs. Food decreases the peak plasma concentration but not the area under the concentration curve (see Chapter 3: Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action). Hepatic impairment causes a slight decrease in clearance (and may necessitate a lower dose), but the drug does not cause inhibition or induction of hepatic enzymes. The drug is oxidized in the liver by CYP3A. Elimination is primarily in the feces (60–65%) and urine (25%).

Zonisamide

Zonisamide is a sulfonamide derivative. Its primary site of action appears to be on the sodium channel; it may also act on voltage-dependent calcium channels. The drug is effective against partial and generalized tonic-clonic seizures and may also be useful against infantile spasms and certain myoclonias. It has good bioavailability, linear kinetics, low protein-binding, renal excretion, and a half-life of 1–3 days. Doses range from 100 mg/d to 600 mg/d in adults and from 4 mg/d to 12 mg/d in children. Adverse effects include drowsiness, cognitive impairment, and potentially serious skin rashes. Zonisamide does not interact with other antiseizure drugs.

Levetiracetam

Levetiracetam is a piracetam analog that is ineffective against seizures induced by maximum electroshock or pentylenetetrazol but has prominent activity in the kindling model. Its mechanism of action is unknown. It has a brain-specific binding site and affects allosteric modulations of GABA receptors, high-voltage activated Ca2+ channels and some K+ channels. The drug is marketed for the treatment of partial seizures. Oral absorption is nearly complete; it is rapid and unaffected by food, with peak plasma concentrations in 1.3 hours. Kinetics are linear. Protein binding is less than 10%. The plasma half-life is 6–8 hours, and may be longer in the elderly. Two thirds of the drug is excreted unchanged in the urine. Drug interactions are minimal; levetiracetam is not metabolized by cytochrome P450. Dosing can begin with 500 mg orally twice daily; some patients require up to 3000 mg/d. Adverse effects include somnolence, asthenia, and dizziness. Idiosyncratic reactions are rare.

Drugs Used in Generalized Seizures
Ethosuximide

Ethosuximide was introduced in 1960 as the third of three marketed succinimides in the USA. Ethosuximide has very little activity against maximal electroshock but considerable efficacy against pentylenetetrazol seizures and was introduced as a "pure petit mal" drug. Its continued popularity is based on its safety and efficacy, and its role as the first choice anti-absence drug remains undiminished—in part because of the idiosyncratic hepatotoxicity of the alternative drug, valproic acid.

Chemistry

Ethosuximide is the last antiseizure drug to be marketed whose origin is in the cyclic ureide structure. The three antiseizure succinimides marketed in the USA are ethosuximide, phensuximide, and methsuximide. All three are substituted at the 2 position. (See structure below, and note the difference in numbering relative to Figure 24–1.) Methsuximide and phensuximide have phenyl substituents, while ethosuximide is 2-ethyl-2-methylsuccinimide.

![Structure of Ethosuximide](image)

Mechanism of Action

Ethosuximide has an important effect on Ca$^{2+}$ currents, reducing the low-threshold (T-type) current. This effect is seen at therapeutically relevant concentrations in thalamic neurons. The T-type calcium currents are thought to provide a pacemaker current in thalamic neurons responsible for generating the rhythmic cortical discharge of an absence attack. Inhibition of this current could therefore account for the specific therapeutic action of ethosuximide. Ethosuximide also inhibits Na$^+$/$K^+$ ATPase, depresses the cerebral metabolic rate, and inhibits GABA aminotransferase. However, none of these actions are seen at therapeutic concentrations.

Clinical Use

As predicted from its activity in laboratory models, ethosuximide is particularly effective against absence seizures. Documentation of its effectiveness required specific advances in quantitation of absence seizures; this was accomplished in the 1970s, when the characteristic generalized 3/s spike-wave electroencephalographic abnormality was correlated with a decrement in consciousness even when the abnormality occurs for only a few seconds. Long-term electroencephalographic recordings, therefore, provided the necessary quantitative method for determining the frequency of absence attacks and allowed rapid and effective evaluation of the efficacy of anti-absence drugs. Although ethosuximide was marketed in advance of the federal requirements for efficacy, these techniques were applied to later drugs such as clonazepam and valproic acid in documentation of their efficacy. This was accomplished by comparison with ethosuximide.

Pharmacokinetics
Absorption is complete following administration of the oral dosage forms. Peak levels are observed 3–7 hours after oral administration of the capsules. Animal studies indicate that chronic administration of the solution may prove irritating to the gastric mucosa. Ethosuximide is uniformly distributed in total body water, ie, 0.7 L/kg and does not penetrate fat. Ethosuximide is not protein-bound, and spinal fluid concentrations are therefore equal to plasma concentrations.

Ethosuximide is completely metabolized, principally by hydroxylation, to inactive metabolites. The drug has a very low total body clearance (0.25 L/kg/d). This corresponds to a half-life of approximately 40 hours, although values from 18 to 72 hours have been reported.

Therapeutic Levels & Dosage

Therapeutic levels of 60–100 μg/mL can be achieved in adults with dosages of 750–1500 mg/d, although lower or higher dosages and blood levels may be necessary and tolerated (up to 125 μg/mL) in some patients. Ethosuximide has a linear relationship between dose and steady-state plasma levels. The drug might be administered as a single daily dose were it not for its adverse gastrointestinal effects; twice-a-day dosage is common.

Drug Interactions

Administration of ethosuximide with valproic acid results in a decrease in ethosuximide clearance and higher steady-state concentrations owing to inhibition of metabolism. No other important drug interactions have been reported for the succinimides.

Toxicity

The most common dose-related adverse effect of ethosuximide is gastric distress, including pain, nausea, and vomiting. This can often be avoided by starting therapy at a low dose, with gradual increases into the therapeutic range. When the adverse effect does occur, temporary dosage reductions may allow adaptation. Ethosuximide is a highly efficacious and safe drug for absence seizures; the appearance of relatively mild, dose-related adverse effects should not immediately call for its abandonment. Other dose-related adverse effects include transient lethargy or fatigue and, much less commonly, headache, dizziness, hiccup, and euphoria. Behavioral changes are usually in the direction of improvement.

Non-dose-related or idiosyncratic adverse effects of ethosuximide are extremely uncommon. Skin rashes have been reported, including at least one case of Stevens-Johnson syndrome. A few patients have had eosinophilia, thrombocytopenia, leukopenia, or pancytopenia; it is not entirely certain that ethosuximide was the causal agent. The development of systemic lupus erythematosus has also been reported, but other drugs may have been involved.

Phensuximide & Methsuximide

Phensuximide and methsuximide are phenylsuccinimides that were developed and marketed before ethosuximide. They are used primarily as anti-absence drugs. Methsuximide is generally considered more toxic, and phensuximide less effective, than ethosuximide. Unlike ethosuximide, these two compounds have some activity against maximal electroshock seizures, and methsuximide has been used for partial seizures by some investigators. The desmethyl metabolite of methsuximide has a half-life of 25 hours or more and exerts the major antiseizure effect. The toxicity and reduced effectiveness of phensuximide when compared with methsuximide has been investigated, and the failure of the desmethyl metabolite to accumulate in the former probably explains its relatively
weak effect.

Valproic Acid & Sodium Valproate

Sodium valproate, also used as the free acid, valproic acid, was found to have antiseizure properties when it was used as a solvent in the search for other drugs effective against seizures. It was marketed in France in 1969 but was not licensed in the USA until 1978. Valproic acid is fully ionized at body pH, and for that reason the active form of the drug may be assumed to be the valproate ion regardless of whether valproic acid or a salt of the acid is administered.

Chemistry

Valproic acid is one of a series of fatty carboxylic acids that have antiseizure activity; this activity appears to be greatest for carbon chain lengths of five to eight atoms. Branching and unsaturation do not significantly alter the drug's activity but may increase its lipophilicity, thereby increasing its duration of action. The amides and esters of valproic acid are also active antiseizure agents.

\[
\begin{align*}
\text{CH}_3 \rightarrow \text{CH}_2 \rightarrow \text{CH}_2
\text{CH}_2 \rightarrow \text{COOH}
\end{align*}
\]

Valproic acid

Mechanism of Action

The time course of valproate's anticonvulsant activity appears to be poorly correlated with blood or tissue levels of the parent drug, an observation giving rise to considerable speculation regarding both the active species and the mechanism of action of valproic acid. Valproate is active against both pentylentetrazol and maximal electroshock seizures. Like phenytoin and carbamazepine, valproate blocks sustained high-frequency repetitive firing of neurons in culture at therapeutically relevant concentrations. Its action against partial seizures may be a consequence of this effect on Na⁺ currents. Blockade of NMDA receptor-mediated excitation may also be important. Much attention has been paid to the effects of valproate on GABA. Several studies have shown increased levels of GABA in the brain after administration of valproate, although the mechanism for this increase remains unclear. An effect of valproate to facilitate glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis, has been described. An inhibitory effect on the GABA transporter GAT-1 may contribute. At very high concentrations, valproate inhibits GABA-T in the brain, thus blocking degradation of GABA. However, at the relatively low doses of valproate needed to abolish pentylentetrazol seizures, brain GABA levels may remain unchanged. Valproate produces a reduction in the aspartate content of rodent brain, but the relevance of this effect to its anticonvulsant action is not known.

At high concentrations, valproate has been shown to increase membrane potassium conductance. Furthermore, low concentrations of valproate tend to hyperpolarize membrane potentials. These findings have led to speculation that valproate may exert an action through a direct effect on the potassium channels of the membrane.

Valproate probably owes its broad spectrum of action to more than one molecular mechanism. Its action against absence attacks remains to be explained.

Clinical Use
Valproate is very effective against absence seizures. Although ethosuximide is the drug of choice when absence seizures occur alone, valproate is preferred if the patient has concomitant generalized tonic-clonic attacks. The reason for preferring ethosuximide for uncomplicated absence seizures is valproate's idiosyncratic hepatotoxicity, described below. Valproate is unique in its ability to control certain types of myoclonic seizures; in some cases the effect is very dramatic. The drug is effective in generalized tonic-clonic seizures, especially those which are primarily generalized. A few patients with atonic attacks may also respond, and some evidence suggests that the drug is effective in partial seizures.

Other uses of valproate include management of bipolar disorder and migraine prophylaxis.

Pharmacokinetics

Valproate is well absorbed following an oral dose, with bioavailability greater than 80%. Peak blood levels are observed within 2 hours. Food may delay absorption, and decreased toxicity may result if the drug is given after meals.

Valproic acid is 90% bound to plasma proteins, although the fraction bound is somewhat reduced at blood levels greater than 150 \( \mu \text{g/mL} \). Since valproate is both highly ionized and highly protein-bound, its distribution is essentially confined to extracellular water, with a volume of distribution of approximately 0.15 L/kg.

Clearance for valproate is low; its half-life varies from 9 hours to 18 hours. At very high blood levels, the clearance of valproate is dose-dependent. There appear to be offsetting changes in the intrinsic clearance and protein binding at higher doses. Approximately 20% of the drug is excreted as a direct conjugate of valproate.

The sodium salt of valproate is marketed in Europe as a tablet protected by aluminum foil, as it is quite hygroscopic. In Central and South America, the magnesium salt is available, which is considerably less hygroscopic. An enteric-coated tablet of divalproex sodium is also marketed in the USA. This improved product, a 1:1 coordination compound of valproic acid and sodium valproate, is as bioavailable as the capsule but is absorbed much more slowly and is preferred by most patients. Peak concentrations following administration of the enteric-coated tablets are seen in 3–4 hours.

Therapeutic Levels & Dosage

Dosages of 25–30 mg/kg/d may be adequate in some patients, but others may require 60 mg/kg/d or even more. Therapeutic levels of valproate range from 50 \( \mu \text{g/mL} \) to 100 \( \mu \text{g/mL} \). In testing efficacy, this drug should not be abandoned until morning trough levels of at least 80 \( \mu \text{g/mL} \) have been attained; some patients may require and tolerate trough levels in excess of 100 \( \mu \text{g/mL} \).

Drug Interactions

As noted above, the clearance of valproate is dose-dependent, caused by changes in both the intrinsic clearance and protein binding. Valproate inhibits its own metabolism at low doses, thus decreasing intrinsic clearance. At higher doses, there is an increased free fraction of valproate, resulting in lower total drug levels than expected. It may be clinically useful, therefore, to measure both total and free drug levels. Valproate also displaces phenytoin from plasma proteins. In addition to binding interactions, valproate inhibits the metabolism of several drugs, including phenobarbital,
phenytoin, and carbamazepine, leading to higher steady-state concentrations of these agents. The side effects and toxicity of phenytoin are enhanced. The inhibition of phenobarbital metabolism may cause levels of the barbiturate to rise precipitously, causing stupor or coma.

Toxicity

The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn. The drug should be started gradually to avoid these symptoms; a temporary reduction in dose can usually alleviate the problems, and the patient will eventually tolerate higher doses. Sedation is uncommon with valproate alone but may be striking when valproate is added to phenobarbital. A fine tremor is frequently seen at higher levels. Other reversible adverse effects, seen in a small number of patients, include weight gain, increased appetite, and hair loss.

The idiosyncratic toxicity of valproate is largely limited to hepatotoxicity, but this may be severe; there seems little doubt that the hepatotoxicity of valproate has been responsible for more than 50 fatalities in the USA alone. The risk is greatest for patients under the age of 2 years and for those taking multiple medications. Initial aspartate aminotransferase values may not be elevated in susceptible patients, although these levels do eventually become abnormal. Most fatalities have occurred within 4 months after initiation of therapy. Careful monitoring of liver function is recommended when starting the drug; the hepatotoxicity is reversible in some cases if the drug is withdrawn. The other observed idiosyncratic response with valproate is thrombocytopenia, although documented cases of abnormal bleeding are lacking. It should be noted that valproate is an effective and popular antiseizure drug and that only a very small number of patients have had severe toxic effects from its use.

Epidemiologic studies of valproate suggest an increased incidence of spina bifida in the offspring of women who took the drug during pregnancy. In addition, an increased incidence of cardiovascular, orofacial, and digital abnormalities has been reported. These observations, although based on a small number of cases, must be strongly considered in the choice of drugs during pregnancy.

Oxazolidinediones

Trimethadione, the first oxazolidinedione, was introduced as an antiseizure drug in 1945 and remained the drug of choice for absence seizures until the introduction of succinimides in the 1950s. The use of the oxazolidinediones (trimethadione, paramethadione, and dimethadione) is now very limited.

Chemistry

The oxazolidinediones contain an oxazolidine heterocyclic ring (Figure 24–1) and are similar in structure to other antiseizure drugs introduced before 1960. The structure includes only short-chain alkyl substituents on the heterocyclic ring, with no attached phenyl group.
Mechanism of Action

These compounds are active against pentylenetetrazol-induced seizures. Trimethadione raises the threshold for seizure discharges following repetitive thalamic stimulation. It—or, more notably, its active metabolite dimethadione—has the same effect on thalamic Ca\(^{2+}\) currents as ethosuximide (reducing the T-type calcium current). Thus, suppression of absence seizures is likely to depend on inhibiting the pacemaker action of thalamic neurons.

Pharmacokinetics

Trimethadione is rapidly absorbed, with peak levels reached within an hour after drug administration. It is distributed to all perfused tissues, with a volume of distribution that approximates that of total body water. It is not bound to plasma proteins. Trimethadione is completely metabolized in the liver by demethylation to 5,5-dimethyl-2,4-oxazolidinedione (dimethadione), which may exert the major antiseizure activity. The clearance of dimethadione is 0.08 L/kg/d; this metabolite has an extremely long half-life (240 hours).

Therapeutic Levels & Dosage

The therapeutic plasma level range for trimethadione has never been established, although trimethadione blood levels above 20 \(\mu g/mL\) and dimethadione levels above 700 \(\mu g/mL\) have been suggested. A dosage of 30 mg/kg/d of trimethadione is necessary to achieve these levels in adults.

Drug Interactions

Relatively few drug interactions involving the oxazolidinediones have been reported, although trimethadione may competitively inhibit the demethylation of other drugs such as metharbital.

Toxicity

The most common and bothersome dose-related adverse effect of the oxazolidinediones is sedation. An unusual adverse effect is hemeralopia, a glare effect in which visual adaptation is impaired; it is reversible upon withdrawal of the drug. Accumulation of dimethadione has been reported to cause a very mild metabolic acidosis. Trimethadione has been associated with many other toxic adverse effects, some of which are severe. These drugs should not be used during pregnancy.

Other Drugs Used in Management of Epilepsy

Some drugs not classifiable by application to seizure type are discussed in this section.

Benzodiazepines
Six benzodiazepines play prominent roles in the therapy of epilepsy (see also Chapter 22: Sedative-Hypnotic Drugs). Although many benzodiazepines are quite similar chemically, subtle structural alterations result in differences in activity. They have two different mechanisms of antiseizure action, which are shown to different degrees by the six compounds. This is evident from the fact that diazepam is relatively more potent against electroshock and clonazepam against pentylenetetrazol (the latter effect correlating with an action at the GABA-benzodiazepine allosteric receptor site). Possible mechanisms of action are discussed in Chapter 22: Sedative-Hypnotic Drugs.

**Diazepam** given intravenously or rectally is highly effective for stopping continuous seizure activity, especially generalized tonic-clonic status epilepticus (see below). The drug is occasionally given orally on a chronic basis, although it is not considered very effective in this application, probably because of the rapid development of tolerance. A rectal gel is available for refractory patients who need acute control of bouts of seizure activity. **Lorazepam** appears in some studies to be more effective and longer-acting than diazepam in the treatment of status epilepticus.

**Clonazepam** is a long-acting drug with documented efficacy against absence seizures; it is one of the most potent antiseizure agents known. It is also effective in some cases of myoclonic seizures and has been tried in infantile spasms. Sedation is prominent, especially on initiation of therapy; starting doses should be small. Maximal tolerated doses are usually in the range of 0.1–0.2 mg/kg, but many weeks of gradually increasing daily dosage may be needed to achieve these doses in some patients. Therapeutic blood levels are usually less than 0.1 µg/mL and are not routinely measured in most laboratories. **Nitrazepam** is not marketed in the USA but is used in many other countries, especially for infantile spasms and myoclonic seizures. It is less potent than clonazepam, and its clinical advantages over that drug have not been documented.

**Clorazepate dipotassium** is approved in the USA as an adjunct to treatment of complex partial seizures in adults. Drowsiness and lethargy are common adverse effects, but as long as the drug is increased gradually, dosages as high as 45 mg/d can be given.

**Clobazam** is not available in the USA but is marketed in most countries and is widely used in a variety of seizure types. It is a 1,5-benzodiazepine (all other marketed benzodiazepines are 1,4-benzodiazepines) and reportedly has less sedative potential than benzodiazepines marketed in the USA. Whether the drug has significant clinical advantages is not clear. It has a half-life of 18 hours and is effective at dosages of 0.5–1 mg/kg/d. It does interact with some other antiseizure drugs and causes adverse effects typical of the benzodiazepines; efficacy, in some patients, is limited by the development of tolerance.

**Pharmacokinetics**

The pharmacokinetic properties of the benzodiazepines in part determine their clinical use. In general, the drugs are well absorbed, widely distributed, and extensively metabolized, with many active metabolites. The rate of distribution of benzodiazepines within the body is different from that of other antiseizure drugs. Diazepam and lorazepam in particular are rapidly and extensively distributed to the tissues, with volumes of distribution between 1 L/kg and 3 L/kg. The onset of action is very rapid. Total body clearances of the parent drug and its metabolites are low, corresponding to half-lives of 20–40 hours.

**Limitations**

Two prominent aspects of benzodiazepines limit their usefulness. The first is their pronounced
sedative effect, which is unfortunate both in the treatment of status epilepticus and in chronic therapy. Children may manifest a paradoxical hyperactivity, as with barbiturates. The second problem is tolerance, in which seizures may respond initially but recur within a few months. The remarkable antiseizure potency of these compounds often cannot be realized because of these limiting factors.

Acetazolamide

Acetazolamide is a diuretic whose main action is the inhibition of carbonic anhydrase (see Chapter 15: Diuretic Agents). Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizure activity; alternatively, the depolarizing action of bicarbonate ions moving out of neurons via GABA receptor ion channels will be diminished by carbonic anhydrase inhibition. Acetazolamide has been used for all types of seizures but is severely limited by the rapid development of tolerance, with return of seizures usually within a few weeks. The drug may have a special role in epileptic women who experience seizure exacerbations at the time of menses; seizure control may be improved and tolerance may not develop because the drug is not administered continuously. The usual dosage is approximately 10 mg/kg/d up to a maximum of 1000 mg/d.

Another carbonic anhydrase inhibitor, sulthiame, was not found to be effective as an anticonvulsant in clinical trials in the USA. It is marketed in some other countries.

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Clinical Pharmacology of Antisiezure Drugs

Seizure Classification

The type of medication utilized for epilepsy depends on the empiric nature of the seizure. For this reason, considerable effort has been expended to classify seizures so that clinicians will be able to make a "seizure diagnosis" and on that basis prescribe appropriate therapy. Errors in seizure diagnosis cause use of the wrong drugs, and an unpleasant cycle ensues in which poor seizure control is followed by increasing drug doses and medication toxicity. As noted above, seizures are divided into two groups: partial and generalized. Drugs used for partial seizures are more or less the same for the entire group, but drugs used for generalized seizures are determined by the individual seizure type. A summary of the international classification of epileptic seizures is presented in Table 24–1.

Partial Seizures

Partial seizures are those in which a localized onset of the attack can be ascertained, either by clinical observation or by electroencephalographic recording; the attack begins in a specific locus in the brain. There are three types of partial seizures, determined to some extent by the degree of brain involvement by the abnormal discharge.

The least complicated partial seizure is the simple partial seizure, characterized by minimal spread of the abnormal discharge such that normal consciousness and awareness are preserved. For example, the patient may have a sudden onset of clonic jerking of an extremity lasting 60–90 seconds; residual weakness may last for 15–30 minutes after the attack. The patient is completely aware of the attack and can describe it in detail. The electroencephalogram may show an abnormal discharge highly localized to the involved portion of the brain.
The complex partial seizure also has a localized onset, but the discharge becomes more widespread (usually bilateral) and almost always involves the limbic system. Most (not all) complex partial seizures arise from one of the temporal lobes, possibly because of the susceptibility of this area of the brain to insults such as hypoxia or infection. Clinically, the patient may have a brief warning followed by an alteration of consciousness during which some patients may stare and others may stagger or even fall. Most, however, demonstrate fragments of integrated motor behavior called automatisms for which the patient has no memory. Typical automatisms are lip smacking, swallowing, fumbling, scratching, or even walking about. After 30–120 seconds, the patient makes a gradual recovery to normal consciousness but may feel tired or ill for several hours after the attack.

The last type of partial seizure is the secondarily generalized attack, in which a partial seizure immediately precedes a generalized tonic-clonic (grand mal) seizure. This seizure type is described below.

Generalized Seizures

Generalized seizures are those in which there is no evidence of localized onset. The group is quite heterogeneous.

Generalized tonic-clonic (grand mal) seizures are the most dramatic of all epileptic seizures and are characterized by tonic rigidity of all extremities, followed in 15–30 seconds by a tremor that is actually an interruption of the tonus by relaxation. As the relaxation phases become longer, the attack enters the clonic phase, with massive jerking of the body. The clonic jerking slows over 60–120 seconds, and the patient is usually left in a stuporous state. The tongue or cheek may be bitten, and urinary incontinence is common. Primary generalized tonic-clonic seizures begin without evidence of localized onset, whereas secondary generalized tonic-clonic seizures are preceded by another seizure type, usually a partial seizure. The medical treatment of both primary and secondary generalized tonic-clonic seizures is the same and uses drugs appropriate for partial seizures.

The absence (petit mal) seizure is characterized by both sudden onset and abrupt cessation. Its duration is usually less than 10 seconds and rarely more than 45 seconds. Consciousness is altered; the attack may also be associated with mild clonic jerking of the eyelids or extremities, with postural tone changes, autonomic phenomena, and automatisms. The occurrence of automatisms can complicate the clinical differentiation from complex partial seizures in some patients. Absence attacks begin in childhood or adolescence and may occur up to hundreds of times a day. The electroencephalogram during the seizure shows a highly characteristic 2.5–3.5 Hz spike-and-wave pattern. Atypical absence patients have seizures with postural changes that are more abrupt, and such patients are often mentally retarded; the electroencephalogram may show a slower spike-and-wave discharge, and the seizures may be more refractory to therapy.

Myoclonic jerking is seen, to a greater or lesser extent, in a wide variety of seizures, including generalized tonic-clonic seizures, partial seizures, absence seizures, and infantile spasms. Treatment of seizures that include myoclonic jerking should be directed at the primary seizure type rather than at the myoclonus. Some patients, however, have myoclonic jerking as the major seizure type, and some have frequent myoclonic jerking and occasional generalized tonic-clonic seizures without overt signs of neurologic deficit. Many kinds of myoclonus exist, and much effort has gone into attempts to classify this entity.

Atonic seizures are those in which the patient has sudden loss of postural tone. If standing, the patient falls suddenly to the floor and may be injured. If seated, the head and torso may suddenly
drop forward. Although most often seen in children, this seizure type is not unusual in adults. Many patients with atonic seizures wear helmets to prevent head injury.

**Infantile spasms** are an epileptic syndrome and not a seizure type. The attacks, although sometimes fragmentary, are most often bilateral and are included for pragmatic purposes with the generalized seizures. These attacks are most often characterized clinically by brief, recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs; the forms of infantile spasms are, however, quite heterogeneous. Ninety percent of affected patients have their first attack before the age of 1 year. Most patients are mentally retarded, presumably from the same cause as the spasms. The cause is unknown in many patients, but such widely disparate disorders as infection, kernicterus, tuberous sclerosis, and hypoglycemia have been implicated. In some cases, the electroencephalogram is characteristic. Drugs used to treat infantile spasms are effective only in some patients; there is little evidence that the mental retardation is alleviated by therapy, even when the attacks disappear.

**Therapeutic Strategy**

For most antiseizure drugs, relationships between blood levels and therapeutic effects have been characterized to a high degree. The same is true for the pharmacokinetics of these drugs. These relationships provide significant advantages in the development of therapeutic strategies for the treatment of epilepsy. The therapeutic index for most antiseizure drugs is low, and toxicity is not uncommon. Thus, effective treatment of seizures requires an awareness of the therapeutic levels and pharmacokinetic properties as well as the characteristic toxicities of each agent. Measurements of antiseizure drug plasma levels are extremely useful when combined with clinical observations and pharmacokinetic data (Table 24–2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effective Level (µg/mL)</th>
<th>High Effective Level (µg/mL)</th>
<th>Toxic Level (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>4–12</td>
<td>7</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Primidone</td>
<td>5–15</td>
<td>10</td>
<td>&lt; 12</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10–20</td>
<td>18</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10–40</td>
<td>35</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>50–100</td>
<td>80</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Valproate</td>
<td>50–100</td>
<td>80</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>


2Level that should be achieved, if possible, in patients with refractory seizures, assuming that the blood samples are drawn before administration of the morning medication. Higher levels are often possible—without toxicity—when the drugs are used alone, ie, as monotherapy.

Management of Epilepsy
Partial Seizures & Generalized Tonic-Clonic Seizures

Until recently, the choice of drugs was usually limited to phenytoin, carbamazepine, or barbiturates. There has been a strong tendency in the past few years to limit the use of sedative antiseizure drugs such as barbiturates and benzodiazepines to patients who cannot tolerate other medications. In the 1980s, the trend was to increase the use of carbamazepine. Although the choice now appears to be divided between carbamazepine and phenytoin, all of the newer drugs have shown effectiveness against these seizures. The exact role of these drugs remains to be determined, making decisions for the individual patient more complex.

Generalized Seizures

The drugs used for generalized tonic-clonic seizures are the same as for partial seizures; in addition, valproate is clearly useful.

Three drugs are effective against absence seizures. Two are nonsedating and therefore preferred: ethosuximide and valproate. Clonazepam is also highly effective but has disadvantages of dose-related adverse effects and development of tolerance. The drug of choice is ethosuximide, although valproate is effective in some ethosuximide-resistant patients. Lamotrigine and topiramate may also be useful.

Specific myoclonic syndromes are usually treated with valproate; an intravenous formulation can be used acutely as needed. It is nonsedating and can be dramatically effective. Other patients respond to clonazepam, nitrazepam, or other benzodiazepines, although high doses may be necessary, with accompanying sedation and drowsiness. Zonisamide and levetiracetam may be useful. Another specific myoclonic syndrome, juvenile myoclonic epilepsy, can be aggravated by phenytoin or carbamazepine; valproate is the drug of choice followed by lamotrigine and topiramate.

Atonic seizures are often refractory to all available medications, although some reports suggest that valproate may be beneficial, as may lamotrigine. Benzodiazepines have been reported to improve seizure control in some of these patients but may worsen the attacks in others. Felbamate has been demonstrated to be effective in some patients, although the drug's idiosyncratic toxicity limits its use. If the loss of tone appears to be part of another seizure type (such as absence or complex partial seizures), every effort should be made to treat the other seizure type vigorously, hoping for simultaneous alleviation of the atonic component of the seizure. The ketogenic diet may also be useful.

Drugs Used in Infantile Spasms

The treatment of infantile spasms is unfortunately limited to improvement of control of the seizures rather than other features of the disorder, such as retardation. Most patients receive a course of intramuscular corticotropin, although some clinicians note that prednisone may be equally effective and can be given orally. Clinical trials have been unable to settle the matter. In either case, therapy must often be discontinued because of adverse effects. If seizures recur, repeat courses of corticotropin or corticosteroids can be given, or other drugs may be tried. Other drugs widely used are the benzodiazepines such as clonazepam or nitrazepam; their efficacy in this heterogeneous syndrome may be nearly as good as that of corticosteroids. Vigabatrin may also be effective. The mechanism of action of corticosteroids or corticotropin in the treatment of infantile spasms is unknown. Further details may be sought in more specialized texts.
Status Epilepticus

There are many forms of status epilepticus. The most common, generalized tonic-clonic status epilepticus, is a life-threatening emergency, requiring immediate cardiovascular, respiratory, and metabolic management as well as pharmacologic therapy. The latter virtually always requires intravenous administration of antiseizure medications. Diazepam is the most effective drug in most patients for stopping the attacks and is given directly by intravenous push to a maximum total dose of 20–30 mg in adults. Intravenous diazepam may depress respiration (less frequently, cardiovascular function), and facilities for resuscitation must be immediately at hand during its administration. The effect of diazepam is not lasting, but the 30- to 40-minute seizure-free interval allows more definitive therapy to be initiated. For patients who are not actually in the throes of a seizure, diazepam therapy can be omitted and the patient treated at once with a long-acting drug such as phenytoin. Some physicians prefer lorazepam, which is equivalent to diazepam in effect and perhaps somewhat longer-acting.

Until the introduction of fosphenytoin, the mainstay of continuing therapy for status epilepticus was intravenous phenytoin, which is effective and non-sedating. It should be given as a loading dose of 13–18 mg/kg in adults; the usual error is to give too little. Administration should be at a maximum rate of 50 mg/min. It is safest to give the drug directly by intravenous push, but it can also be diluted in saline; it precipitates rapidly in the presence of glucose. Careful monitoring of cardiac rhythm and blood pressure is necessary, especially in elderly people. At least part of the cardiotoxicity is from the propylene glycol in which the phenytoin is dissolved. Fosphenytoin, which is freely soluble in intravenous solutions without the need for propylene glycol or other solubilizing agents, is a better parenteral agent. Because of its greater molecular weight, this prodrug is two thirds to three quarters as potent as phenytoin on a milligram basis.

In previously treated epileptic patients, the administration of a large loading dose of phenytoin may cause some dose-related toxicity such as ataxia. This is usually a relatively minor problem during the acute status episode and is easily alleviated by later adjustment of plasma levels.

For patients who do not respond to phenytoin, phenobarbital can be given in large doses: 100–200 mg intravenously to a total of 400–800 mg. Respiratory depression is a common complication, especially if benzodiazepines have already been given, and there should be no hesitation in instituting intubation and ventilation.

Although other drugs such as lidocaine have been recommended for the treatment of generalized tonic-clonic status epilepticus, general anesthesia is usually necessary in highly resistant cases.

For patients in absence status, benzodiazepines are still drugs of first choice. Rarely, intravenous valproate may be required.

Special Aspects of the Toxicology of Antiseizure Drugs

Teratogenicity

The potential teratogenicity of antiseizure drugs is controversial and important. It is important because teratogenicity resulting from long-term drug treatment of millions of people throughout the world may have a profound effect even if the effect occurs in only a small percentage of cases. It is controversial because both epilepsy and antiseizure drugs are heterogeneous, and few epileptic patients are available for study who are not receiving these drugs. Furthermore, patients with severe epilepsy, in whom genetic factors rather than drug factors may be of greater importance in the
occurrence of fetal malformations, are often receiving multiple antiseizure drugs in high doses.

In spite of these limitations, it appears—from whatever cause—that children born to mothers taking antiseizure drugs have an increased risk, perhaps twofold, of congenital malformations. Phenytoin has been implicated in a specific syndrome called fetal hydantoin syndrome, although not all investigators are convinced of its existence and a similar syndrome has been attributed both to phenobarbital and to carbamazepine. Valproate, as noted above, has also been implicated in a specific malformation, spina bifida. It is estimated that a pregnant woman taking valproic acid or sodium valproate has a 1–2% risk of having a child with spina bifida. To-piramate has shown some teratogenicity in animal testing.

In dealing with the clinical problem of a pregnant woman with epilepsy, most epileptologists agree that while it is important to minimize exposure to antiseizure drugs, both in numbers and dosages, it is also important not to allow maternal seizures to go unchecked.

Withdrawal

Withdrawal of antiseizure drugs, whether by accident or by design, can cause increased seizure frequency and severity. There are two factors to consider: the effects of the withdrawal itself and the need for continued drug suppression of seizures in the individual patient. In many patients, both factors must be considered. It is important to note, however, that the abrupt discontinuance of antiseizure drugs ordinarily does not cause seizures in nonepileptic patients provided the drug levels are not above the usual therapeutic range when the drug is stopped.

Some drugs are more easily withdrawn than others. In general, withdrawal of anti-absence drugs is easier than withdrawal of drugs needed for partial or generalized tonic-clonic seizures. Barbiturates and benzodiazepines are the most difficult to discontinue; weeks or months may be required, with very gradual dosage decrements, to accomplish their complete removal, especially if the patient is not hospitalized.

Because of the heterogeneity of epilepsy, complete discontinuance of antiseizure drug administration is an especially difficult problem. If a patient is seizure-free for 3 or 4 years, gradual discontinuance is usually warranted.

Overdose

Antiseizure drugs are central nervous system depressants but are rarely lethal. Very high blood levels are usually necessary before overdoses can be considered life-threatening. The most dangerous effect of antiseizure drugs after large overdoses is respiratory depression, which may be potentiated by other agents, such as alcohol. Treatment of antiseizure drug overdose is supportive; stimulants should not be used. Efforts to hasten removal of antiseizure drugs, such as alkalization of the urine (phenytoin is a weak acid), are usually ineffective.

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Preparations Available

Carbamazepine (generic, Tegretol)

Oral: 200 mg tablets; 100 mg chewable tablets; 100 mg/5 mL suspension
Oral extended-release: 100, 200, 400 mg tablets; 200, 300 mg capsules

**Clonazepam** (generic, Klonopin)
Oral: 0.5, 1, 2 mg tablets

**Clorazepate dipotassium** (generic, Tranxene)
Oral: 3.75, 7.5, 15 mg tablets, capsules
Oral sustained-release (Tranxene-SD): 11.25, 22.5 mg tablets

**Diazepam** (generic, Valium, others)
Oral: 2, 5, 10 mg tablets; 5 mg/5 mL, 5 mg/mL solutions
Parenteral: 5 mg/mL for IV injection
Rectal: 2.5, 5, 10, 15, 20 mg diazepam viscous rectal solution

**Ethosuximide** (generic, Zarontin)
Oral: 250 mg capsules; 250 mg/5 mL syrup

**Ethotoin** (Peganone)
Oral: 250, 500 mg tablets

**Felbamate** (Felbatol)
Oral: 400, 600 mg tablets; 600 mg/5 mL suspension

**Fosphenytoin** (Cerebyx)
Parenteral: 75 mg/mL for IV or IM injection

**Gabapentin** (Neurontin)
Oral: 100, 300, 400 mg capsules; 600, 800 mg filmtabs; 50 mg/mL solution

**Lamotrigine** (Lamictal)
Oral: 25, 100, 150, 200 mg tablets; 2, 5, 25 mg chewable tablets

**Levetiracetam** (Keppra)
Oral: 250, 500, 750 mg tablets

**Lorazepam** (generic, Ativan)
Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution

Parenteral: 2, 4 mg/mL for IV or IM injection

**Mephenytoin** (Mesantoin)
Oral: 100 mg tablets

**Mephobarbital** (Mebaral)
Oral: 32, 50, 100 mg tablets

**Oxycarbazepine** (Trileptal)
Oral: 100, 300, 600 mg tablets; 60 mg/mL suspension

**Pentobarbital sodium** (generic, Nembutal)
Parenteral: 50 mg/mL for IV or IM injection

**Phenobarbital** (generic, Luminal Sodium, others)
Oral: 15, 16, 30, 60, 90, 100 mg tablets; 16 mg capsules; 15, 20 mg/5 mL elixirs
Parenteral: 30, 60, 65, 130 mg/mL for IV or IM injection

**Phenytoin** (generic, Dilantin, others)
Oral (prompt release): 100 mg capsules; 50 mg chewable tablets; 30, 125 mg/5 mL suspension
Oral extended-action: 30, 100 mg capsules
Oral slow release (Phenytek): 200, 300 mg capsules
Parenteral: 50 mg/mL for IV injection

**Primidone** (generic, Mysoline)
Oral: 50, 250 mg tablets; 250 mg/5 mL suspension

**Tiagabine** (Gabitril)
Oral: 4, 12, 16, 20 mg tablets

**Topiramate** (Topamax)
Oral: 25, 100, 200 mg tablets; 15, 25 mg sprinkle capsules

**Trimethadione** (Tridione)
Valproic acid (generic, Depakene)

Oral: 150 mg chewable tablets; 300 mg capsules; 40 mg/mL solution

Oral: 250 mg capsules; 250 mg/5 mL syrup (sodium valproate)

Oral sustained-release (Depakote): 125, 250, 500 mg tablets (as divalproex sodium)

Parenteral (Depacon): 100 mg/mL in 5 mL vial for IV injection

Chapter 25. General Anesthetics

General Anesthetics: Introduction

The physiologic state of general anesthesia typically includes analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes, and skeletal muscle relaxation. The extent to which any individual anesthetic drug can exert these effects varies with the drug, the dosage, and the clinical situation.

An ideal anesthetic drug would induce anesthesia smoothly and rapidly while allowing for prompt recovery after its administration is discontinued. The drug would also possess a wide margin of safety and be devoid of adverse effects. No single anesthetic agent is capable of achieving all of these desirable effects without some disadvantages when used alone. The modern practice of anesthesiology most commonly involves the use of combinations of intravenous and inhaled drugs, taking advantage of their individual favorable properties while attempting to minimize their potential for causing adverse reactions.

The anesthetic technique will vary depending on the proposed type of diagnostic, therapeutic, or surgical intervention. For minor procedures, so-called monitored anesthesia care or conscious sedation is used, employing oral or parenteral sedatives in conjunction with local anesthetics (see Chapter 26: Local Anesthetics). These techniques provide profound analgesia, but with retention of the patient's ability to maintain a patent airway and to respond to verbal commands. For more extensive surgical procedures, anesthesia frequently includes the use of preoperative benzodiazepines, induction of anesthesia with intravenous thiopental or propofol, and maintenance of anesthesia with a combination of inhaled and intravenous anesthetic drugs. Such protocols also often include the use of neuromuscular blocking drugs (see Chapter 27: Skeletal Muscle Relaxants).

Types of General Anesthetics

General anesthetics are usually given by inhalation or by intravenous injection.

Inhaled Anesthetics
The chemical structures of the currently available inhaled anesthetics are shown in Figure 25–1. Nitrous oxide, a gas at ambient temperature and pressure, continues to be an important component of many anesthesia regimens. Halothane, enflurane, isoflurane, desflurane, sevoflurane, and methoxyflurane are volatile liquids.

Intravenous Anesthetics

Several drugs are used intravenously, alone or in combination with other drugs, to achieve an anesthetic state (as components of balanced anesthesia) or to sedate patients in intensive care units who must be mechanically ventilated. These drugs include the following: (1) barbiturates (thiopental, methohexital); (2) benzodiazepines (midazolam, diazepam); (3) opioid analgesics (morphine, fentanyl, sufentanil, alfentanil, remifentanil); (4) propofol; (5) ketamine; and (6) miscellaneous drugs (droperidol, etomidate, dexmedetomidine). Figure 25–2 shows the structures of...
commonly used intravenous anesthetics.

**Figure 25–2.**

Intravenous anesthetics.

**Signs & Stages of Anesthesia**

The traditional description of the signs and stages of anesthesia (Guedel's signs) were derived from observations of the effects of diethyl ether, which has a slow onset of central action owing to its high solubility in blood. With these signs, anesthetic effects can be divided into four stages of increasing depth of central nervous system depression.

I. Stage of Analgesia: The patient initially experiences analgesia without amnesia. Later in stage I, both analgesia and amnesia are produced.

II. Stage of Excitement: During this stage, the patient often appears to be delirious and excited but definitely is amnesic. Respiration is irregular both in volume and rate, and retching and vomiting may occur. The patient may struggle and is sometimes incontinent. For these reasons, efforts are made to limit the duration and severity of this stage, which ends with the reestablishment of regular breathing.

III. Stage of Surgical Anesthesia: This stage begins with the recurrence of regular respiration
and extends to complete cessation of spontaneous respiration. Four planes of stage III have been described in terms of changes in ocular movements, eye reflexes, and pupil size, which under specified conditions may represent signs of increasing depth of anesthesia.

IV. Stage of Medullary Depression: This stage of anesthesia includes severe depression of the vasomotor center in the medulla as well as the respiratory center. Without full circulatory and respiratory support, death rapidly ensues.

In modern anesthesia practice, the distinctive signs of each of the four stages described above are usually obscured. Reasons for this include the relatively rapid onset of action of many intravenous and inhaled anesthetics compared with ether and the fact that respiratory activity is often controlled mechanically with muscle relaxants. In addition, the practice of administering other pharmacologic agents preoperatively or intraoperatively can also alter the clinical signs of anesthesia. Atropine and glycopyrrolate are used to decrease secretions; however, they also dilate the pupils. Drugs such as tubocurarine and succinylcholine affect muscle tone, and the opioid analgesics exert depressant effects on respiration. The most reliable indication that stage III (surgical anesthesia) has been achieved is loss of the eyelash reflex and establishment of a regular respiratory pattern. The adequacy of depth of anesthesia for the specific surgical requirements is assessed by changes in respiratory and cardiovascular responses with surgical stimulation.

While vital sign monitoring remains a common method of assessing depth of anesthesia during surgery, newer techniques involving computer-assisted monitoring of cerebral function appear to offer some advantages. Automated techniques available include those based on the bispectral index (BIS), the physical state index (PSI) and the middle-latency auditory evoked potential (MLAEP), all of which are processed variables derived from established effects of anesthetics on the electroencephalogram. The application of such real-time cerebral monitoring techniques has been shown to reduce the volatile anesthetic requirement, contributing to a more rapid recovery from general anesthesia.

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Inhaled Anesthetics

Pharmacokinetics

Depth of anesthesia is dependent upon the concentration of anesthetic in the central nervous system. The rate at which an effective brain concentration is reached (the rate of induction of anesthesia) depends on multiple pharmacokinetic factors that influence the uptake and distribution of the anesthetic. Certain of these factors also influence the rate of recovery from anesthesia when the anesthetic is discontinued.

Uptake & Distribution

The concentration of an individual gas in a mixture of gases is proportionate to its partial pressure or tension. These terms are often used interchangeably in discussing the various transfer processes of anesthetic gases in the body. Achievement of a brain concentration of an inhaled anesthetic adequate to cause anesthesia requires transfer of that anesthetic from the alveolar air to blood and then to brain. The rate at which a given concentration of anesthetic in the brain is reached depends on the solubility properties of the anesthetic, its concentration in the inspired air, pulmonary ventilation rate, pulmonary blood flow, and the partial pressure gradient of the anesthetic between arterial and mixed venous blood.
Solubility

One of the most important factors influencing the transfer of an anesthetic from the lungs to the arterial blood is its solubility. The blood:gas partition coefficient is a useful index of solubility and defines the relative affinity of an anesthetic for the blood compared to air. The partition coefficients for desflurane and nitrous oxide, which are not very soluble in the blood, are low (< 0.5). Halothane has a value greater than 2, and methoxyflurane, which is rarely used, has a coefficient of more than 10 (Table 25–1). When an anesthetic with low blood solubility diffuses from the lung into the arterial blood, relatively few molecules are required to raise its partial pressure, and therefore the arterial tension rises quickly (Figure 25–3, top, nitrous oxide). Conversely, for anesthetics with moderate to high solubility, more molecules dissolve before partial pressure changes significantly, and arterial tension of the gas increases less rapidly (Figure 25–3, bottom, halothane). This inverse relationship between the blood solubility of an anesthetic and the rate of rise of its tension in arterial blood is illustrated in Figure 25–4. Nitrous oxide with low solubility in blood, reaches high arterial tensions rapidly, which in turn results in rapid equilibration with the brain and fast onset of action. A rapid onset of anesthetic action is also characteristic of desflurane and sevoflurane, compounds that also have a low blood:gas partition coefficient.

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood:Gas Partition Coefficient</th>
<th>Brain:Blood Partition Coefficient</th>
<th>Minimal Alveolar Conc (MAC) (%)</th>
<th>Metabolism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>0.47</td>
<td>1.1</td>
<td>&gt; 100</td>
<td>None</td>
<td>Incomplete anesthetic; rapid onset and recovery</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>1.3</td>
<td>6–7</td>
<td>&lt; 0.05%</td>
<td>Low volatility; poor induction agent; rapid recovery</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
<td>1.7</td>
<td>2.0</td>
<td>2–5% (fluoride)</td>
<td>Rapid onset and recovery; unstable in soda-lime</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.40</td>
<td>2.6</td>
<td>1.4</td>
<td>&lt; 2%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.80</td>
<td>1.4</td>
<td>1.7</td>
<td>8%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.30</td>
<td>2.9</td>
<td>0.75</td>
<td>&gt; 40%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>12</td>
<td>2.0</td>
<td>0.16</td>
<td>&gt; 70%</td>
<td>Slow onset and recovery</td>
</tr>
</tbody>
</table>
Partition coefficients (at 37 °C) are from multiple literature sources.

MAC is the anesthetic concentration that produces immobility in 50% of patients exposed to a noxious stimulus.

Figure 25–3.

Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

Figure 25–4.
Tensions of three anesthetic gases in arterial blood as a function of time after beginning inhalation. Nitrous oxide is relatively insoluble (blood:gas partition coefficient = 0.47); methoxyflurane is much more soluble (coefficient = 12); and halothane is intermediate (2.3).

Anesthetic Concentration in the Inspired Air

The concentration of an inhaled anesthetic in the inspired gas mixture has direct effects on both the maximum tension that can be achieved in the alveoli and the rate of increase in its tension in arterial blood. Increases in the inspired anesthetic concentration will increase the rate of induction of anesthesia by increasing the rate of transfer into the blood according to Fick's law (see Chapter 1: Introduction). Advantage is taken of this effect in anesthetic practice with inhaled anesthetics of moderate blood solubility such as enflurane, isoflurane, and halothane, which have a relatively slow onset of anesthetic effect. For example, a 3–4% concentration of halothane may be administered initially to increase the rate of induction; this is reduced to 1–2% for maintenance when adequate anesthesia is achieved. In addition, these anesthetics are often administered in combination with a less soluble agent (eg, nitrous oxide) to reduce the time required for loss of consciousness.

Pulmonary Ventilation

The rate of rise of anesthetic gas tension in arterial blood is directly dependent on both the rate and depth of ventilation (ie, minute ventilation). The magnitude of the effect varies according to the blood:gas partition coefficient. An increase in pulmonary ventilation is accompanied by only a slight increase in arterial tension of an anesthetic with low blood solubility or low coefficient but can significantly increase tension of agents with moderate or high blood solubility (Figure 25–5). For example, a fourfold increase in ventilation rate almost doubles the arterial tension of halothane during the first 10 minutes of anesthesia but increases the arterial tension of nitrous oxide by only 15%. Therefore, hyperventilation increases the speed of induction of anesthesia with inhaled anesthetics that would normally have a slow onset. Depression of respiration by opioid analgesics will slow the onset of anesthesia of some inhaled anesthetics if ventilation is not assisted.
Changes in blood flow to and from the lungs influence transfer processes of the anesthetic gases. An increase in pulmonary blood flow (increased cardiac output) slows the rate of rise in arterial tension, particularly for those anesthetics with moderate to high blood solubility. This is because increased pulmonary blood flow exposes a larger volume of blood to the anesthetic; thus, blood "capacity" increases and the anesthetic tension rises slowly. A decrease in pulmonary blood flow has the opposite effect and increases the rate of rise of arterial tension of inhaled anesthetics. In a patient with circulatory shock, the combined effects of decreased cardiac output (resulting in decreased pulmonary flow) and increased ventilation will accelerate the induction of anesthesia with halothane and isoflurane. This is not likely to occur with nitrous oxide, desflurane, or sevoflurane because of their low blood solubility.

Arteriovenous Concentration Gradient

The anesthetic concentration gradient between arterial and mixed venous blood is dependent mainly on uptake of the anesthetic by the tissues, including nonneural tissues. Depending on the rate and extent of tissue uptake, venous blood returning to the lungs may contain significantly less anesthetic than arterial blood. The greater this difference in anesthetic tensions, the more has been taken up by viscera, muscle, etc, and the more time it will take to achieve equilibrium with brain tissue. Anesthetic entry into tissues is influenced by factors similar to those that determine transfer from lung to blood, including tissue:blood partition coefficient, rates of blood flow to the tissues, and
concentration gradients.

During the induction phase of anesthesia, the tissues that exert greatest influence on the arterial-venous anesthetic concentration gradient are those which are highly perfused. These include the brain, heart, liver, kidneys, and splanchnic bed, which together receive over 75% of the resting cardiac output. In the case of anesthetics with relatively high solubility in these tissues, venous blood concentration will initially be very low, and equilibrium with arterial blood is achieved slowly.

During maintenance of anesthesia with inhaled anesthetics, these drugs may continue to be transferred between various tissues at rates dependent on solubility and blood flow. Muscle and skin, which together constitute 50% of body mass, accumulate anesthetics more slowly than the highly vascularized tissues (eg, brain), since they receive only one-fifth the blood flow of the latter groups. Although most anesthetic gases have high solubility in adipose tissues, low blood perfusion rates to these tissues delay accumulation, and equilibrium is unlikely to occur with most anesthetics during the time usually required for surgery.

Elimination

The time to recovery from inhalation anesthesia depends on the rate of elimination of anesthetics from the brain after the inspired concentration of anesthetic has been decreased. Many of the processes of anesthetic transfer during recovery are similar to those that occur during induction of anesthesia. One of the most important factors governing rate of recovery is the blood:gas partition coefficient of the anesthetic agent (see below). Other factors controlling rate of recovery include the pulmonary blood flow, the magnitude of ventilation, and the solubility of the anesthetic in the tissues. Two features of recovery, however, are quite different from what happens during induction of anesthesia. First, while transfer of an anesthetic from the lungs to blood can be enhanced by increasing its concentration in inspired air, the reverse transfer process cannot be enhanced, since the concentration in the lungs cannot be reduced below zero. Second, at the beginning of recovery, the anesthetic gas tension in different tissues may be quite variable, depending on the specific agent and the duration of anesthesia. With induction of anesthesia, the initial anesthetic tension in all tissues is zero.

Inhaled anesthetics that are relatively insoluble in blood (low blood:gas partition coefficient) and brain are eliminated at faster rates than more soluble anesthetics. The washout of nitrous oxide, desflurane, and sevoflurane occurs at a rapid rate, which leads to a more rapid recovery from their anesthetic effects compared to halothane and isoflurane. Halothane is approximately twice as soluble in brain tissue and five times more soluble in blood than nitrous oxide and desflurane; its elimination therefore takes place more slowly, and recovery from halothane anesthesia is predictably less rapid. The duration of exposure to the anesthetic can also have a marked effect on the time of recovery, especially in the case of more soluble anesthetics. Accumulation of anesthetics in tissues, including muscle, skin, and fat, increases with continuous inhalation (especially in obese patients), and blood tension may decline slowly during recovery as the anesthetic is gradually eliminated from these tissues. Thus, if exposure to the anesthetic is short, recovery may be rapid even with the more soluble agents. However, after prolonged anesthesia, recovery may be delayed even with anesthetics of moderate solubility such as isoflurane.

Clearance of inhaled anesthetics by the lungs into the expired air is the major route of their elimination from the body. However, metabolism by enzymes of the liver and other tissues may also contribute to the elimination of volatile anesthetics. For example, the elimination of halothane during recovery is more rapid than that of enflurane, which would not be predicted from their concentration gradients.
respective solubilities. However, over 40% of inspired halothane is metabolized during an average anesthetic procedure, while less than 10% of enflurane is metabolized over the same period. Oxidative metabolism of halothane results in the formation of trifluoroacetic acid and release of bromide and chloride ions. Under conditions of low oxygen tension, halothane is metabolized to the chlorotrifluoroethyl free radical, which is capable of reacting with hepatic membrane components. Isoflurane and desflurane are the least metabolized of the fluorinated anesthetics, only traces of trifluoroacetic acid appearing in the urine even after prolonged administration. The metabolism of enflurane and sevoflurane results in the formation of fluoride ion, which does not appear to reach toxic levels under normal circumstances. In addition, sevoflurane is degraded by contact with the carbon dioxide absorbent in anesthesia machines, yielding a vinyl ether called "compound A" that can cause renal damage if high concentrations are absorbed. (See Do We Need Another Inhaled Anesthetic?) Over 70% of absorbed methoxyflurane is metabolized by the liver with the release of fluoride ions at concentrations that can be nephrotoxic. In terms of the extent of metabolism of inhaled anesthetics, the rank order is: methoxyflurane > halothane > enflurane > sevoflurane > isoflurane > desflurane > nitrous oxide (Table 25–1). Nitrous oxide is probably not metabolized by human tissues.

Pharmacodynamics

Mechanism of Action

The inhaled anesthetics—and most of the intravenous agents—depress spontaneous and evoked activity of neurons in many regions of the brain. Older concepts of the mechanism of anesthesia invoked nonspecific interactions of these agents with the lipid matrix of the nerve membrane (the Meyer-Overton principle)—interactions that were thought to lead to secondary changes in ion flux. More recently, evidence has accumulated suggesting that the modification of ion currents by anesthetics results from more specific interactions with nerve membrane components. The ionic mechanisms involved for different anesthetics may vary, but at clinically relevant concentrations they appear to involve interactions with members of the ligand-gated ion channel family.

In the past decade, considerable evidence has accumulated that a primary molecular target of many general anesthetics is the GABA$_A$ receptor-chloride channel, a major mediator of inhibitory synaptic transmission. Inhaled anesthetics, barbiturates, benzodiazepines, etomidate, and propofol facilitate GABA-mediated inhibition at GABA$_A$ receptor sites. These receptors are sensitive to clinically relevant concentrations of the anesthetic agents and exhibit the appropriate stereospecific effects in the case of enantiomeric drugs. The GABA$_A$ receptor-chloride channel is a pentameric assembly of five proteins derived from several polypeptide subclasses (see Chapter 22: Sedative-Hypnotic Drugs). Combinations of three major subunits—a, b, and g—are necessary for normal physiologic and pharmacologic functions. GABA$_A$ receptors in different areas of the central nervous system contain different subunit combinations conferring different pharmacologic properties on each receptor subtype. Inhaled anesthetics and intravenous agents with general anesthetic properties directly activate GABA$_A$ receptors, but at low concentrations they can also facilitate the action of GABA to increase chloride ion flux. In contrast, sedative benzodiazepines lacking general anesthetic properties (e.g., midazolam) facilitate GABA action but have no direct actions on GABA$_A$ receptors even at high concentrations in the absence of GABA.

Reconstitution studies with transfected cells utilizing chimeric and mutated GABA$_A$ receptors reveal that anesthetic molecules do not interact directly with the GABA binding site but with specific sites in the transmembrane domains of both a and b subunits. Two specific amino acid residues in transmembrane segments 2 and 3 of the GABA$_A$ receptor a2 subunit, Ser270 and Ala291, are critical for the enhancement of GABA$_A$ receptor function by inhaled anesthetics. One
consequence of the interaction of isoflurane with this domain is an alteration in the gating of the chloride ion channel. However, differences occur in the precise binding sites of individual anesthetics. For example, a specific aspartate residue within transmembrane segment 2 of the GABA<sub>A</sub> receptor α<sub>2</sub> subunit is required for etomidate activity but is not essential for the activity of barbiturates or propofol.

Ketamine does not produce its effects via facilitation of GABA<sub>A</sub> receptor functions, but it may function via antagonism of the action of the excitatory neurotransmitter glutamic acid on the NMDA receptor.

In addition to actions on GABA<sub>A</sub> chloride channels, inhaled anesthetics have been reported to cause membrane hyperpolarization (an inhibitory action) via their activation of ligand-gated potassium channels. These channels are ubiquitous in the central nervous system and are linked to several neurotransmitters, including acetylcholine, dopamine, norepinephrine, and serotonin. Electrophysiologic analyses of membrane ion flux in cultured cells have shown that inhaled anesthetics decrease the duration of opening of nicotinic receptor-activated cation channels—an action that decreases the excitatory effects of acetylcholine at cholinergic synapses. Most inhaled anesthetics inhibit nicotinic acetylcholine receptor isoforms, particularly those containing the α<sub>4</sub> subunit, though such actions do not appear to be involved in their immobilizing actions. The strychnine-sensitive glycine receptor is another ligand-gated ion channel that may function as a target for inhaled anesthetics which can elicit channel opening directly and independently of their facilitatory effects on neurotransmitter binding.

The neuropharmacologic basis for the effects that characterize the stages of anesthesia appears to be differential sensitivity of specific neurons or neuronal pathways to the anesthetic drugs. Neurons in the substantia gelatinosa of the dorsal horn of the spinal cord are very sensitive to relatively low anesthetic concentrations. Interaction with neurons in this region interrupts sensory transmission in the spinothalamic tract, including transmission of nociceptive (pain) stimuli. These effects contribute to stage I analgesia and conscious sedation. The disinhibitory effects of general anesthetics (stage II), which occur at higher brain concentrations, result from complex neuronal actions including blockade of many small inhibitory neurons such as Golgi type II cells, together with a paradoxical facilitation of excitatory neurotransmitters. A progressive depression of ascending pathways in the reticular activating system occurs during stage III of anesthesia, together with suppression of spinal reflex activity, which contributes to muscle relaxation. Neurons in the respiratory and vasomotor centers of the medulla are relatively insensitive to the effects of the general anesthetics, but at high concentrations their activity is depressed, leading to cardiorespiratory collapse (stage IV). It remains to be determined whether regional variation in anesthetic actions corresponds with the regional variation in the subtypes of GABA<sub>A</sub> receptor. The differential sensitivity of specific neurons or neuronal pathways to anesthetics could reflect their interactions with other molecules in the fast ligand-gated ion channel family or could represent the existence of other molecular targets that have yet to be characterized.

Dose-Response Characteristics: The Minimum Alveolar Anesthetic Concentration (MAC)

Inhaled anesthetics are delivered to the lungs in gas mixtures in which concentrations and flow rates are easy to measure and control. However, dose-response characteristics of gaseous anesthetics are difficult to measure. Although achievement of an anesthetic state depends on the concentration of the anesthetic in the brain, that concentration is impossible to measure under clinical conditions. Furthermore, neither the lower nor the upper ends of the graded dose-response curve can be ethically determined, since at very low concentrations severe pain might be experienced while at high concentrations there would be a high risk of fatal cardiovascular and respiratory depression.
Nevertheless, a useful estimate of anesthetic potency can be obtained using quantal dose-response principles.

During general anesthesia, the partial pressure of an inhaled anesthetic in the brain equals that in the lung when steady state is reached. Therefore, at a given level of anesthesia, the measurement of the steady-state alveolar concentrations of different anesthetics provides a comparison of their relative potencies. The minimum alveolar anesthetic concentration (MAC) is defined as the median concentration (ie, the percentage of the alveolar gas mixture, or partial pressure of the anesthetic as a percentage of 760 mm Hg) that results in immobility in 50% of patients when exposed to a noxious stimulus (eg, surgical incision). Therefore, MAC represents one point (the ED$_{50}$) on a conventional quantal dose-response curve (see Figure 2–16). Table 25–1 shows some properties of the common inhaled anesthetics, permitting comparison of their relative anesthetic potencies. The MAC value greater than 100% for nitrous oxide demonstrates that it is the least potent anesthetic, since at normal barometric pressure even 760 mm Hg partial pressure of nitrous oxide (100% of the inspired gas) is still not equal to 1 MAC.

The dose of anesthetic gas that is being administered can be stated in multiples of MAC. While a dose of 1 MAC of any anesthetic prevents movement in response to surgical incision in 50% of patients, individual patients may require 0.5–1.5 MAC. Unfortunately, the MAC gives no information about the slope of the dose-response curve. In general, however, the dose-response relationship for inhaled anesthetics is very steep. Therefore, over 95% of patients may fail to respond to a noxious stimulus at 1.1 MAC. The measurement of MAC values under controlled conditions has permitted quantitation of the effects of a number of variables on anesthetic requirements. For example, MAC values decrease in elderly patients and with hypothermia, but are not affected greatly by sex, height, and weight. Of particular importance is the presence of adjuvant drugs, which can change anesthetic requirement. For example, when drugs such as the opioid analgesics, sympatholytics, or sedative-hypnotics are present, the MAC is decreased in a dose-related fashion. The inspired concentration of anesthetic should be decreased in these situations. MAC values of the inhaled anesthetics are additive. For example, nitrous oxide can be used as a "carrier" gas at 40% of its MAC, decreasing the anesthetic requirement of other inhaled anesthetics; 70% of their MAC would yield a total of 110% of one MAC, which is sufficient for surgical anesthesia in most patients.

Organ System Effects of Inhaled Anesthetics

Effects on Cardiovascular System

Halothane, desflurane, enflurane, sevoflurane, and isoflurane all decrease mean arterial pressure in direct proportion to their alveolar concentration. With halothane and enflurane, the reduced arterial pressure appears to be caused by a reduction in cardiac output because there is little change in systemic vascular resistance despite marked changes in individual vascular beds (eg, increase in cerebral blood flow). In contrast, isoflurane, desflurane, and sevoflurane have a depressant effect on arterial pressure as a result of a decrease in systemic vascular resistance with minimal effect on cardiac output.

Inhaled anesthetics change heart rate either directly by altering the rate of sinus node depolarization or indirectly by shifting the balance of autonomic nervous system activity. Bradycardia is often seen with halothane, probably through vagal stimulation. In contrast, enflurane, and sevoflurane have little effect, and both desflurane and isoflurane increase heart rate. In the case of desflurane, cardiovascular responses include a transient sympathetic activation that can lead to marked increases in heart rate and blood pressure when high inspired gas concentrations are administered.
All inhaled anesthetics tend to increase right atrial pressure in a dose-related fashion, which reflects depression of myocardial function. In general, enflurane and halothane have greater myocardial depressant effects than isoflurane and the newer less soluble halogenated anesthetics. Inhaled anesthetics reduce myocardial oxygen consumption, primarily by decreasing the variables that control oxygen demand, such as arterial blood pressure and contractile force. Although certainly less depressant than the other inhaled anesthetics, nitrous oxide has also been found to depress the myocardium in a dose-dependent manner. However, nitrous oxide in combination with potent inhaled anesthetics produces sympathetic stimulation that minimizes cardiac depressant effects. The combination of nitrous oxide with halothane or enflurane, for example, appears to produce less cardiac depression at a given depth of anesthesia than either of the more potent anesthetics given alone.

Several factors influence the cardiovascular effects of inhaled anesthetics. Surgical stimulation, volume status, ventilatory status, and duration of anesthesia will alter the depressant effects of these drugs. Hypercapnia releases catecholamines, which attenuate the decrease in blood pressure. The blood pressure decrease after 5 hours of anesthesia is less than it is after 1 hour; concomitant use of beta-blockers reduces this adaptive effect. Halothane (and, to a lesser extent, isoflurane) sensitizes the myocardium to catecholamines. Ventricular arrhythmias may occur in patients with cardiac disease who are given sympathomimetic drugs or have high circulating levels of endogenous catecholamines (eg, anxious patients, patients with pheochromocytoma). The newer, less soluble inhaled anesthetics appear to be less arrhythmogenic.

Effects on the Respiratory System

With the exception of nitrous oxide, all inhaled anesthetics in current use cause a dose-dependent decrease in tidal volume and an increase in respiratory rate. However, the increase in rate is insufficient to compensate for the decrease in volume, resulting in a decrease in minute ventilation. All inhaled anesthetics are respiratory depressants, as indicated by a reduced response to increased levels of carbon dioxide. The degree of ventilatory depression varies among the volatile agents, with isoflurane and enflurane being the most depressant. All inhaled anesthetics in current use increase the resting level of PaCO₂ (the partial pressure of carbon dioxide in arterial blood).

Inhaled anesthetics increase the apneic threshold (PaCO₂ level below which apnea occurs through lack of CO₂-driven respiratory stimulation) and decrease the ventilatory response to hypoxia. The latter effect is especially important because subanesthetic concentrations (ie, those that exist during recovery) depress the normal compensating increase in ventilation that occurs during hypoxia. Respiratory depressant effects of anesthetics are overcome by assisting or controlling ventilation mechanically. Furthermore, the ventilatory depressant effects of the inhaled anesthetics are lessened by surgical stimulation.

Inhaled anesthetics also depress mucociliary function in the airway. Thus, prolonged anesthesia may lead to pooling of mucus and then result in atelectasis and postoperative respiratory infections. However, inhaled anesthetics tend to be bronchodilators, an effect of value in the treatment of status asthmaticus. The bronchodilating action of halothane and sevoflurane makes them the induction agents of choice in patients with underlying airway problems. Airway irritation, which may provoke coughing or breath holding, is rarely a problem with most inhaled anesthetics. However, it is relatively common with desflurane, making induction of anesthesia more difficult to accomplish with this anesthetic despite its low blood:gas partition coefficient. Similarly, the pungency of enflurane may elicit breath holding, which can decrease the speed of induction.

Effects on Brain
Inhaled anesthetics decrease the metabolic rate of the brain. Nevertheless, most volatile agents increase cerebral blood flow because they decrease cerebral vascular resistance. The increase in cerebral blood flow is often clinically undesirable. For example, in patients who have an increased intracranial pressure because of a brain tumor or head injury, administration of a volatile anesthetic may increase cerebral blood flow, which in turn will increase cerebral blood volume and further increase intracranial pressure.

Of the inhaled anesthetics, nitrous oxide increases cerebral blood flow the least. However, when 60% nitrous oxide is added to halothane anesthesia, cerebral blood flow usually increases more than with halothane alone. At low doses, all of the halogenated agents have similar effects on cerebral blood flow. At larger doses, enflurane and isoflurane increase cerebral blood flow less than halothane. If the patient is hyperventilated before the anesthetic is given (reducing PaCO₂), the increase in intracranial pressure from inhaled anesthetics can be minimized.

Halothane, isoflurane, and enflurane have similar effects (eg, burst suppression) on the EEG up to doses of 1–1.5 MAC. At higher doses, the cerebral irritant effects of enflurane may lead to development of a spike-and-wave pattern during which auditory stimuli can precipitate mild generalized muscle twitching that is augmented by hyperventilation. Enflurane-induced EEG seizure activity has never been shown to have any adverse clinical consequences, though it may be prudent to avoid the use of enflurane in patients with a history of seizure disorders. This effect is not seen clinically with the newer volatile anesthetics. Although nitrous oxide has low anesthetic potency, it does exert analgesic and amnesic actions, desirable properties when used in combination with other agents in general anesthesia and dental anesthesia.

Effects on the Kidney

To varying degrees, all inhaled anesthetics decrease glomerular filtration rate and effective renal plasma flow and increase filtration fraction. All the anesthetics tend to increase renal vascular resistance. Since renal blood flow decreases during general anesthesia in spite of well-maintained or even increased perfusion pressures, autoregulation of renal flow is probably impaired.

Effects on the Liver

All volatile anesthetics cause a decrease in hepatic blood flow, ranging from 15% to 45% of the preanesthetic flow rate. Despite transient intraoperative changes in liver function tests, permanent changes in liver function rarely occur from the use of these agents. The hepatotoxicity of halothane is discussed below.

Effects on Uterine Smooth Muscle

Nitrous oxide appears to have little effect on uterine musculature. However, the halogenated hydrocarbon anesthetics are potent uterine muscle relaxants. This pharmacologic effect can be used to advantage when profound uterine relaxation is required for intrauterine fetal manipulation or manual extraction of a retained placenta during delivery.

Toxicity

Hepatotoxicity (Halothane)

Postoperative hepatic dysfunction is usually associated with factors such as blood transfusions, hypovolemic shock, and other surgical stresses rather than anesthetic toxicity. However, a very
small subset of individuals exposed to halothane may develop a potentially severe and life-threatening hepatitis. The incidence of severe hepatotoxicity following exposure to halothane is probably in the range of one in 20,000–35,000. Obese patients having more than one exposure to halothane during a short time interval may be more susceptible. There is no specific treatment for halothane hepatitis, and liver transplantation may ultimately be required.

The mechanisms underlying hepatotoxicity from halothane remain unclear, but studies in animals have implicated the formation of reactive metabolites that either cause direct hepatocellular damage (eg, free radical intermediates) or initiate immune-mediated responses. With regard to the latter mechanism, serum from patients with halothane hepatitis contains a variety of autoantibodies against hepatic proteins, many of which are in a trifluoroacetylated form. These trifluoroacetylated proteins could be formed in the hepatocyte during the biotransformation of halothane by liver drug-metabolizing enzymes. However, TFA proteins have also been identified in the sera of patients who did not develop hepatitis after halothane anesthesia.

Nephrotoxicity

Metabolism of enflurane and sevoflurane leads to the formation of fluoride ions, and this has raised questions concerning the potential nephrotoxicity of these anesthetics. Changes in renal concentrating ability have been observed with prolonged exposure to enflurane but not sevoflurane. Differences between the two agents may be related to the fact that enflurane (but not sevoflurane) is metabolized in part by renal enzymes, generating fluoride ions intrarenally. Sevoflurane degradation by carbon dioxide absorbents in anesthesia machines leads to formation of a haloalkene, compound A, that causes a proximal tubular necrosis when administered to rats. However, there have been no reports of renal injury in humans undergoing sevoflurane anesthesia, and the anesthetic does not appear to change standard markers of renal function. Renal dysfunction following methoxyflurane is caused by inorganic fluoride released during the extensive metabolism of this anesthetic by hepatic and renal enzymes. As a result, methoxyflurane is considered obsolete for most purposes.

Malignant Hyperthermia

Malignant hyperthermia is an autosomal dominant genetic disorder of skeletal muscle that occurs in susceptible individuals undergoing general anesthesia with inhaled agents and muscle relaxants (eg, succinylcholine). The malignant hyperthermia syndrome consists of the rapid onset of tachycardia and hypertension, severe muscle rigidity, hyperthermia, hyperkalemia, and acid-base imbalance with acidosis, following exposure to a triggering agent. Malignant hyperthermia is a rare but important cause of anesthetic morbidity and mortality. The specific biochemical abnormality is an increase in free calcium concentration in skeletal muscle cells. Treatment includes administration of dantrolene (which prevents calcium release from the sarcoplasmic reticulum) and appropriate measures to reduce body temperature and restore electrolyte and acid-base balance.

Malignant hyperthermia susceptibility is characterized by genetic heterogeneity, and several predisposing clinical myopathies have been identified. It has been associated with mutations in the gene loci corresponding to the skeletal muscle ryanodine receptor (RYR1), the calcium release channel of the sarcoplasmic reticulum. Mutations in the ryanodine receptor gene are inherited as mendelian dominant characteristics. Other chromosomal loci for malignant hyperthermia susceptibility include mutant alleles of the gene encoding the α1 subunit of the human skeletal muscle dihydropyridine-sensitive L-type voltage-dependent calcium channel. However, the genetic loci identified to date account for no more than 50% of malignant hyperthermia-susceptible individuals. Given such genetic heterogeneity, it seems premature to utilize genetic testing methods
for malignant hyperthermia susceptibility at this time. Currently, the most reliable test to establish such susceptibility is the in vitro caffeine-halothane contracture test utilizing skeletal muscle biopsy tissue.

Chronic Toxicity

Mutagenicity

Under normal conditions, most modern and many older inhaled anesthetics are neither mutagens nor carcinogens.

Carcinogenicity

Some epidemiologic studies have suggested an increase in the cancer rate in operating room personnel who have been exposed to trace concentrations of anesthetic agents. However, no study has demonstrated the existence of a cause-and-effect relationship between anesthetics and cancer. Many other factors might account for the questionably positive results seen after a careful review of epidemiologic data. Most operating room theaters remove trace concentrations of anesthetics released from anesthetic machines via vents to the outdoors.

Effects on Reproduction

The most consistent finding reported from surveys conducted to determine the reproductive performance of female operating room personnel has been a higher than expected incidence of miscarriages. However, there are several problems in interpreting these studies, and the evidence is not strong.

The association of obstetric problems with surgery and anesthesia in pregnant patients is an important consideration. In the USA, at least 50,000 pregnant women each year undergo anesthesia and surgery for indications unrelated to pregnancy. The risk of abortion is clearly higher following this experience. It is not obvious whether the underlying disease, surgery, anesthesia, or a combination of these factors is the cause of the increased risk. Another concern is that anesthesia during pregnancy may lead to an increased incidence of congenital anomalies. Since anesthetics do not appear to be teratogenic, the risk must be very small.

Hematotoxicity

Prolonged exposure to nitrous oxide decreases methionine synthase activity and causes megaloblastic anemia. This is a potential occupational hazard for staff working in poorly ventilated dental operating suites.

Clinical Use of Inhaled Anesthetics

Volatile anesthetics are rarely used as the sole agents for both induction and maintenance of anesthesia. Most commonly, they are combined with intravenous agents in regimens of so-called balanced anesthesia. Of the inhaled anesthetics, nitrous oxide, desflurane, sevoflurane, and isoflurane are the most commonly used in the USA. Use of the more soluble volatile anesthetics has declined during the last decade as more surgical procedures are performed on an outpatient ("short-stay") basis. The low blood:gas coefficients of desflurane and sevoflurane afford more rapid recovery and fewer postoperative adverse effects than halothane or isoflurane. Although halothane is still used in pediatric anesthesia, sevoflurane is rapidly replacing halothane in this setting. As
indicated previously, nitrous oxide lacks sufficient potency to produce surgical anesthesia by itself and therefore is used with volatile or intravenous anesthetics to produce a general anesthetic state.

Despite the advantages of the inhaled anesthetics now available, there is reason to believe that better ones might be developed. (See Do We Need Another Inhaled Anesthetic?)

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Do We Need Another Inhaled Anesthetic?

For almost 30 years, from its introduction in 1956, halothane was the standard of comparison for inhaled anesthetics. However, the onset of its anesthetic action is slow compared with many intravenous agents, and the rate of recovery from its anesthetic effects is not rapid. In addition, its hepatic metabolism to a reactive compound may lead to development of halothane-associated hepatitis.

The newer inhaled anesthetics, desflurane and sevoflurane, have physicochemical characteristics (low blood:gas partition coefficients) favorable to a more rapid onset and a shorter duration of anesthetic actions than older agents such as isoflurane and halothane. However, both of these newer agents also have certain limitations. The low volatility of desflurane necessitates the use of a specialized vaporizer, and the pungency of the drug leads to a high incidence of coughing—and sometimes laryngospasm—such that it cannot be used for induction of anesthesia. In addition, desflurane causes a centrally mediated sympathetic activation leading to elevations of blood pressure and heart rate.

In the case of the newest agent, sevoflurane, induction of anesthesia is achieved rapidly and smoothly, and recovery is more rapid than most other inhaled anesthetics including isoflurane. However, sevoflurane is chemically unstable when exposed to carbon dioxide absorbents, degrading to an olefinic compound (fluoromethyl-2,2-difluoro-1-[trifluoromethyl]vinyl ether, compound A) that is potentially nephrotoxic. In addition, sevoflurane is metabolized by the liver to release fluoride ions, raising concerns about possible renal damage similar to that caused by methoxyflurane. Sevoflurane comes close to having the characteristics of an ideal gas anesthetic, but a relatively insoluble compound that has greater chemical stability could be a useful alternative in the future.

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Intravenous Anesthetics

In the last 2 decades there has been increasing use of intravenous drugs in anesthesia, both as adjuncts to inhaled anesthetics and in techniques that do not include inhaled anesthetics (eg, total intravenous anesthesia). Unlike inhaled anesthetics, intravenous agents do not require specialized vaporizer equipment for their delivery or expensive facilities for the recovery and disposal of exhaled gases. Intravenous drugs such as thiopental, etomidate, ketamine, and propofol have an onset of anesthetic action faster than the fastest of the inhaled gaseous agents such as desflurane and sevoflurane. Therefore, intravenous agents are commonly used for induction of anesthesia. Recovery is sufficiently rapid with many intravenous drugs to permit their extensive use for short ambulatory (outpatient) surgical procedures. In the case of propofol, recovery times are similar to those seen with the shortest-acting inhaled anesthetics. The anesthetic potency of intravenous anesthetics, including thiopental, ketamine, and propofol, is adequate to permit their use as the sole anesthetic in short surgical procedures when combined with nitrous oxide and opioid analgesics.
Adjunctive use of potent opioids (e.g., fentanyl and related compounds) contributes cardiovascular stability, enhanced sedation, and profound analgesia. Other intravenous agents such as the benzodiazepines (e.g., midazolam, diazepam) have slower onset and recovery features and are rarely used for induction of anesthesia. However, preanesthetic administration of benzodiazepines can be used to provide a basal level of sedation and amnesia when used in conjunction with other anesthetic agents.

Pharmacokinetic properties of the intravenous anesthetics are summarized in Table 25–2.

**Table 25–2. Characteristics of Intravenous Anesthetics.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Induction and Recovery</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>Rapid onset and moderately fast recovery</td>
<td>Cardiovascular stability; decreased steroidogenesis; involuntary muscle movements</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Moderately rapid onset and recovery</td>
<td>Cardiovascular stimulation; increased cerebral blood flow; emergence reactions impair recovery</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Slow onset and recovery; flumazenil reversal available</td>
<td>Used in balanced anesthesia and conscious sedation; cardiovascular stability; marked amnesia</td>
</tr>
<tr>
<td>Propofol</td>
<td>Rapid onset and rapid recovery</td>
<td>Used in induction and for maintenance; hypotension; useful antiemetic action</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Rapid onset and rapid recovery (bolus dose)—slow recovery following infusion</td>
<td>Standard induction agent; cardiovascular depression; avoid in porphyrias</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Slow onset and recovery; naloxone reversal available</td>
<td>Used in balanced anesthesia and conscious sedation; marked analgesia</td>
</tr>
</tbody>
</table>

**Short-Acting Barbiturates**

Thiopental is a short-acting barbiturate commonly used for induction of anesthesia. The general pharmacology of the barbiturates is discussed in Chapter 22: Sedative-Hypnotic Drugs.

Following an intravenous bolus injection, thiopental rapidly crosses the blood-brain barrier and, if given in sufficient dosage, produces loss of consciousness (hypnosis) in one circulation time. Similar effects occur with another short-acting barbiturate, methohexital. With these barbiturates, plasma:brain equilibrium occurs rapidly (< 1 minute) because of their high lipid solubility. Thiopental rapidly diffuses out of the brain and other highly vascular tissues and is redistributed to muscle, fat, and eventually all body tissues (Figure 25–6). It is because of this rapid removal from brain tissue that a single dose of thiopental is so short-acting. Thiopental is metabolized at the rate of 12–16% per hour in humans following a single dose. Less than 1% of an administered dose of thiopental is excreted unchanged by the kidney.

**Figure 25–6.**
Redistribution of thiopental after an intravenous bolus administration. Note that the time axis is not linear.

With large doses, thiopental causes dose-dependent decreases in arterial blood pressure, stroke volume, and cardiac output. This is due primarily to its myocardial depressant effect and increased venous capacitance; there is little change in total peripheral resistance. Thiopental is also a potent respiratory depressant, lowering the sensitivity of the medullary respiratory center to carbon dioxide.

Cerebral metabolism and oxygen utilization are decreased after thiopental administration in proportion to the degree of cerebral depression. Cerebral blood flow is also decreased, but much less so than oxygen consumption. This makes thiopental a desirable drug for use in patients with cerebral swelling (e.g., head trauma, brain tumors), since intracranial pressure and blood volume are not increased (in contrast to the volatile anesthetics).

Thiopental may reduce hepatic blood flow and glomerular filtration rate, but it produces no lasting effects on hepatic and renal function. Barbiturates may exacerbate acute intermittent porphyria by inducing the synthesis of hepatic ALA synthase (see Chapter 22: Sedative-Hypnotic Drugs). Thiopental has precipitated porphyric crisis when used as an induction agent in susceptible individuals.

Benzodiazepines

Diazepam, lorazepam, and midazolam are used in anesthetic procedures. The primary indication is for premedication because of their sedative and amnestic properties. (The basic pharmacology of benzodiazepines is discussed in Chapter 22: Sedative-Hypnotic Drugs.) Diazepam and lorazepam are not water-soluble, and their intravenous use necessitates nonaqueous vehicles, which may cause local irritation. Midazolam formulations are water-soluble and thus produce less irritation, but the drug becomes lipid-soluble at physiologic pH and readily crosses the blood-brain barrier.

Compared with intravenous barbiturates, benzodiazepines produce a slower onset of central nervous
system effects and induce a plateau of central depression less than that required for a true anesthetic state. Large doses of benzodiazepines can prolong the postanesthetic recovery period (an undesirable effect), but they can produce a high incidence of anterograde amnesia which is clinically useful. Because it causes a high incidence of amnesia (>50%), midazolam is frequently given intravenously before induction of general anesthesia. Midazolam has a more rapid onset, a shorter elimination half-life (2–4 hours), and a steeper dose-response curve than do the other benzodiazepines used in anesthesia.

The benzodiazepine antagonist flumazenil is sometimes used to accelerate recovery from excessive sedative actions of intravenous benzodiazepines, but reversal of respiratory depression by flumazenil is less predictable. Its short duration of action (<90 minutes) may necessitate multiple doses to prevent recurrence of central nervous system depressant effects of longer-acting benzodiazepines.

Opioid Analgesics

Large doses of opioid analgesics have been used to achieve general anesthesia, particularly in patients undergoing cardiac surgery or other major surgery when their circulatory reserve is minimal. Intravenous morphine, 1–3 mg/kg, or the high-potency opioid fentanyl, 100–150 μg/kg, have been used in such situations with minimal evidence of cardiovascular deterioration. More recently, several congeners of fentanyl, namely sufentanil, alfentanil, and remifentanil, have also been used. Despite the use of high doses of these potent opioids (see Table 31–2 for conventional analgesic doses), awareness during anesthesia and unpleasant postoperative recall have occurred. Furthermore, high intravenous doses of opioids can cause chest wall rigidity, thereby acutely impairing ventilation, as well as postoperative respiratory depression requiring prolonged assisted ventilation and the administration of opioid antagonists (eg, naloxone). Low doses of fentanyl have been used as premedication and as an adjunct to both intravenous and inhaled anesthetics. Alfentanil and remifentanil have been used as induction agents since they both have a rapid onset of action. Remifentanil has an extremely short duration of action because it is rapidly metabolized by esterases in the blood (not plasma cholinesterase) and muscle tissues. The metabolism of remifentanil is not subject to genetic variability, and the drug does not interfere with the clearance of compounds metabolized by plasma cholinesterase (eg, esmolol, mivacurium, or succinylcholine). Rapid recovery following remifentanil is important regarding its potential utility in anesthesia regimens for ambulatory surgery. Fentanyl and droperidol (a butyrophenone related to haloperidol) together produce analgesia and amnesia and are sometimes used with nitrous oxide to provide a state of neuroleptanalgesia.

Opioid analgesics can also be used at low doses by the epidural and spinal routes of administration to produce excellent postoperative analgesia.

Propofol

Propofol (2,6-diisopropylphenol) is an extremely popular intravenous anesthetic. Its rate of onset of action is similar to that of the intravenous barbiturates; recovery is more rapid; and patients are able to ambulate sooner after propofol. Furthermore, patients subjectively "feel better" in the immediate postoperative period after propofol as compared with other intravenous anesthetics. Postoperative nausea and vomiting is less common because propofol has antiemetic actions. Propofol is used for both induction and maintenance of anesthesia; however, cumulative effects can delay arousal following prolonged infusion. These favorable properties are responsible for the extensive use of propofol as a component of balanced anesthesia and for its great popularity as an anesthetic for use
in day surgery outpatient procedures. The drug is also effective in producing prolonged sedation in patients in critical care settings (see Conscious Sedation and Deep Sedation). However, use of propofol for the sedation of children under intensive care has led to severe acidosis in the presence of respiratory infections and possible neurological sequelae on withdrawal.

After intravenous administration of propofol, the distribution half-life is 2–8 minutes; the elimination half-life is approximately 30–60 minutes. The drug is rapidly metabolized in the liver (ten times faster than thiopental) and excreted in the urine as glucuronide and sulfate conjugates. Less than 1% of the drug is excreted unchanged. Total body clearance of the anesthetic is greater than hepatic blood flow, suggesting that its elimination includes extrahepatic mechanisms in addition to metabolism by liver enzymes. This property is useful in patients with impaired ability to metabolize other sedative-anesthetic drugs.

Effects on respiration are similar to those of thiopental at usual anesthetic doses. However, propofol causes a marked decrease in systemic blood pressure during induction of anesthesia, primarily through decreased peripheral resistance. In addition, propofol has greater negative inotropic effects on the heart than etomidate and thiopental. Apnea and pain at the site of injection are common adverse effects of bolus administration. Muscle movements, hypotonus, and (rarely) tremors have also been reported following its use. Clinical infections due to bacterial contamination of the propofol emulsion have led to the addition of antimicrobial adjuvants (eg, ethylenediaminetetraacetic acid and metabisulfite).

Etomidate

Etomidate is a carboxylated imidazole that can be used for induction of anesthesia in patients with limited cardiovascular reserve. Its major advantage over other intravenous agents is that it causes minimal cardiovascular and respiratory depression. Etomidate produces a rapid loss of consciousness, with minimal hypotension. The heart rate is usually unchanged, and the incidence of apnea is low. The drug has no analgesic effects, and coadministration of opioids may be required to decrease cardiac responses during tracheal intubation and to lessen spontaneous muscle movements. Following an induction dose, recovery is rapid (< 5 minutes).

Distribution of etomidate is rapid, with a biphasic plasma concentration curve showing distribution half-lives of 3 and 29 minutes. Redistribution of the drug from brain to highly perfused tissues appears to be responsible for the short duration of its anesthetic effects. Etomidate is extensively metabolized in the liver and plasma to inactive metabolites with only 2% of the drug excreted unchanged in the urine.

Etomidate causes a high incidence of pain on injection, myoclonus, and postoperative nausea and vomiting. The involuntary muscle movements are not associated with electroencephalographic epileptiform activity. Etomidate may also cause adrenocortical suppression via inhibitory effects on steroidogenesis, with decreased plasma levels of hydrocortisone after a single dose. Prolonged infusion of etomidate in critically ill patients may result in hypotension, electrolyte imbalance, and oliguria due to its adrenal suppressive effects.

Ketamine

Ketamine (Figure 25–2) produces dissociative anesthesia, which is characterized by catatonia, amnesia, and analgesia, with or without actual loss of consciousness. The drug is an arylcyclohexylamine chemically related to phencyclidine (PCP), a drug frequently abused because of its psychoactive properties. The mechanism of action of ketamine may involve blockade of the
membrane effects of the excitatory neurotransmitter glutamic acid at the NMDA (N-methyl-D-aspartate) receptor subtype (see Chapter 21: Introduction to the Pharmacology of CNS Drugs).

Ketamine is a highly lipophilic drug and is rapidly distributed into highly vascular organs, including the brain, and subsequently redistributed to less well perfused tissues with concurrent hepatic metabolism and both urinary and biliary excretion.

Ketamine is the only intravenous anesthetic that possesses analgesic properties and produces cardiovascular stimulation. Heart rate, arterial blood pressure, and cardiac output are usually significantly increased. The peak increases in these variables occur 2–4 minutes after intravenous injection and then slowly decline to normal over the next 10–20 minutes. Ketamine produces its cardiovascular stimulation by excitation of the central sympathetic nervous system and possibly by inhibition of the reuptake of norepinephrine at sympathetic nerve terminals. Increases in plasma epinephrine and norepinephrine levels occur as early as 2 minutes after intravenous ketamine and return to baseline levels 15 minutes later.

Ketamine markedly increases cerebral blood flow, oxygen consumption, and intracranial pressure. In this regard ketamine resembles the volatile anesthetics as a potentially dangerous drug when intracranial pressure is elevated. In most patients, ketamine decreases the respiratory rate. However, upper airway muscle tone is well maintained, and airway reflexes are usually preserved.

Although it is a desirable anesthetic in many respects, ketamine has been associated with postoperative disorientation, sensory and perceptual illusions, and vivid dreams (so-called emergence phenomena). Diazepam, 0.2–0.3 mg/kg, or midazolam, 0.025–0.05 mg intravenously, given prior to the administration of ketamine reduces the incidence of these adverse effects. Because of the high incidence of postoperative psychic phenomena associated with its use, ketamine is not commonly used in general surgery in the USA. It is considered useful for poor-risk geriatric patients and in unstable patients (eg, cardiogenic or septic shock) because of its cardiostimulatory properties. It is also used in low doses for outpatient anesthesia in combination with propofol and in children undergoing painful procedures (eg, dressing changes for burns).

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Conscious Sedation & Deep Sedation

Many diagnostic, therapeutic, and minor surgical procedures require neither general anesthesia nor the availability of specialized equipment and facilities necessary for inhaled anesthesia. In this setting, regional or local anesthesia supplemented with midazolam or propofol and opioid analgesics may be a more appropriate and safer approach than general anesthesia.

Another approach has been the development of protocols to provide a state of conscious sedation or drug-induced alleviation of anxiety and pain in combination with an altered level of consciousness, but with retention of the ability of the patient to maintain a patent airway and to respond to verbal commands. A wide variety of intravenous anesthetic agents have proved to be useful drugs in conscious sedation techniques. For example, intravenous benzodiazepines, propofol, and opioid analgesics can provide amnestic, sedative, and analgesic effects without loss of consciousness. Use of benzodiazepines and opioid analgesics in conscious sedation protocols has the advantage of being reversible by the specific receptor antagonist drugs (eg, flumazenil and naloxone, respectively).

A special form of conscious sedation is sometimes needed in the ICU, when patients are under
severe stress and often require mechanical ventilation for long periods (days) with an endotracheal tube in place. In this situation, sedative drugs or intravenous anesthetics in low dosage, neuromuscular blockers, and **dexmedetomidine** may be combined. Dexmedetomidine is an α₂ agonist with strong sedative properties. It has a half-life of 2–3 hours and is metabolized in the liver and excreted, mainly as metabolites, in the urine.

**Deep sedation** is a controlled state of anesthesia involving decreased consciousness from which the patient is not easily aroused. Since deep sedation is often accompanied by a loss of protective reflexes, an inability to maintain a patent airway, and lack of response to surgical stimuli, the state may be indistinguishable from that of general anesthesia. Intravenous agents used in deep sedation protocols include thiopental, ketamine, propofol, and certain intravenous opioid analgesics.

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**Preparations Available**

**Desflurane** (Suprane)
- Liquid: 240 mL for inhalation

**Dexmedetomidine** (Precedex)
- Parenteral: 100 μg/mL for IV infusion

**Diazepam** (generic, Valium)
- Oral: 2, 5, 10 mg tablets; 5 mg/5 mL and 5 mg/mL solution
- Oral sustained-release: 15 mg capsules
- Parenteral: 5 mg/mL for injection

**Droperidol** (generic, Inapsine)
- Parenteral: 2.5 mg/mL for IV or IM injection

**Enflurane** (Enflurane, Ethrane)
- Liquid: 125, 250 mL for inhalation

**Etomidate** (Amidate)
- Parenteral: 2 mg/mL for injection

**Halothane** (generic, Fluothane)
- Liquid: 125, 250 mL for inhalation

**Isoflurane** (Isoflurane, Forane)
Liquid: 100 mL for inhalation

**Ketamine** (generic, Ketalar)

Parenteral: 10, 50, 100 mg/mL for injection

**Lorazepam** (generic, Ativan)

Oral: 0.5, 1, 2 mg tablets; 2 mg/mL solution

Parenteral: 2, 4 mg/mL for injection

**Methohexital** (Brevital Sodium)

Parenteral: 0.5, 2.5, 5 g powder to reconstitute for injection

**Methoxyflurane** (Penthrane)

Liquid: 15, 125 mL for inhalation

**Midazolam** (generic, Versed)

Parenteral: 1, 5 mg/mL for injection in 1, 2, 5, 10 mL vials

Oral: 2 mg/mL syrup

**Nitrous oxide** (gas, supplied in blue cylinders)

**Propofol** (generic, Diprivan)

Parenteral: 10 mg/mL for IV injection

**Sevoflurane** (Ultane)

Liquid: 250 mL for inhalation

**Thiopental** (generic, Pentothal)

Parenteral: powder to reconstitute 20, 25 mg/mL for IV injection

1See Chapter 31: Opioid Analgesics & Antagonists for formulations of opioid agents used in anesthesia.

**Chapter 26. Local Anesthetics**
Local anesthetics reversibly block impulse conduction along nerve axons and other excitable membranes that utilize sodium channels as the primary means of action potential generation. This action can be used clinically to block pain sensation from—or sympathetic vasoconstrictor impulses to—specific areas of the body. Cocaine, the first such agent, was isolated by Niemann in 1860. It was introduced into clinical use by Koller in 1884 as an ophthalmic anesthetic. Cocaine was soon found to be strongly addicting but was widely used, nevertheless, for 30 years, since it was the only local anesthetic drug available. In an attempt to improve the properties of cocaine, Einhorn in 1905 synthesized procaine, which became the dominant local anesthetic for the next 50 years. Since 1905, many local anesthetic agents have been synthesized. The goals of these efforts were reduction of local irritation and tissue damage, minimization of systemic toxicity, faster onset of action, and longer duration of action. Lidocaine, still a popular agent, was synthesized in 1943 by Löfgren and may be considered the prototype local anesthetic agent.

None of the currently available local anesthetics are ideal, and development of newer agents continues. However, while it is relatively easy to synthesize a chemical with local anesthetic effects, it is very difficult to reduce the toxicity significantly below that of the current agents. The major reason for this difficulty is the fact that the much of the serious toxicity of local anesthetics represents extensions of the therapeutic effect on the brain and the circulatory system. However, new research into the mechanisms of cardiac and spinal toxicity and alternative drug targets for spinal analgesia (eg, &eta; receptors) suggest that it may be possible to find better drugs, at least for spinal anesthesia. In an attempt to extend the duration of the local anesthetic action, a variety of novel delivery systems are in development (eg, polymers). Transdermal local anesthetic delivery systems are also being investigated.

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**Basic Pharmacology of Local Anesthetics**

**Chemistry**

Most local anesthetic agents consist of a lipophilic group (frequently an aromatic ring) connected by an intermediate chain (commonly including an ester or amide) to an ionizable group (usually a tertiary amine; Table 26–1). In addition to the general physical properties of the molecules, specific stereochemical configurations are associated with differences in the potency of stereoisomers for a few compounds, eg, bupivacaine, ropivacaine. Since ester links (as in procaine) are more prone to hydrolysis than amide links, esters usually have a shorter duration of action.
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<th>Lipophilic Group</th>
<th>Intermediate Chain</th>
<th>Amine Substituents (P)</th>
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<tr>
<td><strong>Esters</strong></td>
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<td>Cocaine</td>
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<td>Procaine (Novocain)</td>
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<td>Tetracaine (Pontocaine)</td>
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<td>Benzocaine</td>
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<td><strong>Amides</strong></td>
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<td>Lidocaine (Xylocaine)</td>
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<td>Mepivacaine (Carbocaine, Isocaine)</td>
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<td>Bupivacaine (Marcaine), levobupivacaine (Chirocaine)</td>
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<td>Etidocaine (Duranest)</td>
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<td>Prilocaine (Citanest)</td>
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Local anesthetics can provide highly effective analgesia in well-defined regions of the body. The usual routes of administration include topical application (e.g., nasal mucosa, wound margins), injection in the vicinity of peripheral nerve endings and major nerve trunks (infiltration), and injection into the epidural or subarachnoid spaces surrounding the spinal cord (Figure 26–2). Intravenous regional anesthesia of the arm or leg (Bier block) is used for short surgical procedures (< 45 minutes). This is accomplished by intravenous injection of the anesthetic agent into a distal vein while the circulation of the limb is isolated with a proximally placed tourniquet. Finally, an infiltration block of autonomic sympathetic fibers can be used to evaluate the role of sympathetic tone in patients with peripheral vasospasm.
The choice of local anesthetic for a specific procedure is usually based on the duration of action.
an intermediate duration of action; and tetracaine, bupivacaine, levobupivacaine, etidocaine, and ropivacaine are long-acting drugs (Table 26–1).

The anesthetic effect of the agents with short and intermediate durations of action can be prolonged by increasing the dose or by adding a vasoconstrictor agent (eg, epinephrine or phenylephrine). The vasoconstrictor retards the removal of drug from the injection site. In addition, it decreases the blood level and hence the probability of central nervous system toxicity.

The onset of local anesthesia can be accelerated by the use of solutions saturated with carbon dioxide ("carbonated"). The high tissue level of CO₂ results in intracellular acidosis (CO₂ crosses membranes readily), which in turn results in intracellular accumulation of the cationic form of the local anesthetic.

Repeated injection of local anesthetics can result in loss of effectiveness (ie, tachyphylaxis) due to extracellular acidosis. Local anesthetics are commonly marketed as hydrochloride salts (pH 4.0–6.0). After injection, the salts are buffered in the tissue to physiologic pH, thereby providing sufficient free base for diffusion through axonal membranes. However, repeated injections deplete the buffering capacity of the local tissues. The ensuing acidosis increases the extracellular cationic form, which diffuses poorly into axons. The clinical result is apparent tachyphylaxis, especially in areas of limited buffer reserve, such as the cerebrospinal fluid.

Pregnancy appears to increase susceptibility to local anesthetic toxicity in that median doses required for nerve block or to induce toxicity are reduced. Cardiac arrest leading to death following the epidural administration of 0.75% bupivacaine to women in labor resulted in the temporary withdrawal from the market of the high concentration of this long-acting local anesthetic and subsequent introduction of potentially less cardiotoxic alternatives (ie, ropivacaine and levobupivacaine) for this high-risk population. It is not clear whether the increased sensitivity during pregnancy is due to elevated estrogen, elevated progesterone, or some other factor.

Topical local anesthesia is often used for eye, ear, nose, and throat procedures and for cosmetic surgery. Satisfactory local anesthesia requires an agent capable of rapid penetration of the skin or mucosa and with limited tendency to diffuse away from the site of application. Cocaine, because of its excellent penetration and vasoconstrictor effects, has been used extensively for nose and throat procedures. It is somewhat irritating, however, and is thus much less popular for ophthalmic procedures. Recent concerns about its potential cardiotoxicity when combined with epinephrine has led most otolaryngologists and plastic surgeons to switch to a combination containing lidocaine and epinephrine. Other drugs used for topical anesthesia include lidocaine, tetracaine, pramoxine, dibucaine, benzocaine, and dyclonine.

Since local anesthetics are membrane-stabilizing drugs, both parenteral (eg, intravenous lidocaine) and oral (eg, mexiletine, tocainide) formulations of these drugs have been used to treat patients with neuropathic pain syndromes. Systemic local anesthetic drugs are commonly used as adjuvants to the combination of a tricyclic antidepressant (eg, amitriptyline) and an anticonvulsant (eg, carbamazepine) in patients who fail to respond to the standard tricyclic plus anticonvulsant combination. One to 3 weeks are required to observe a therapeutic effect after introduction of the local anesthetic in patients with neuropathic pain.

Toxicity

Two major forms of local anesthetic toxicity are recognized: direct neurotoxicity from the local effects of certain agents administered around the cord or other major nerve trunks, and systemic toxicity.
effects, since ultimately, local anesthetic agents are absorbed from the site of administration. If blood levels rise too high, effects on several organ systems may be observed.

Central Nervous System

All Local Anesthetics

Central nervous system effects at low doses include sleepiness, light-headedness, visual and auditory disturbances, and restlessness. An early symptom of local anesthetic toxicity is circumoral and tongue numbness and a metallic taste. At higher concentrations, nystagmus and muscular twitching occur. Finally, overt tonic-clonic convulsions followed by central nervous system depression and death may occur. Local anesthetics apparently cause depression of cortical inhibitory pathways, thereby allowing unopposed activity of excitatory components. This transitional stage of unbalanced excitation is then followed by generalized central nervous system depression at higher blood levels of local anesthetic.

Convulsions due to excessive blood levels can usually be prevented by administering the smallest dose of local anesthetic required for adequate anesthesia and by avoiding inadvertent intravascular injection or injection into highly perfused tissues. When large doses must be administered, premedication with a benzodiazepine, eg, oral diazepam or midazolam parenterally, appears to provide significant prophylaxis against local anesthetic seizures by raising the seizure threshold. If seizures do occur, it is important to prevent hypoxemia and acidosis. Although administration of oxygen does not prevent seizure activity, hyperoxemia may be beneficial after onset of seizures. Since hypercapnia and acidosis may lower the seizure threshold, hyperventilation is recommended during treatment of seizures. In addition, hyperventilation increases blood pH, which in turn lowers extracellular potassium. This action hyperpolarizes the transmembrane potential of axons, which favors the rested or low-affinity state of the sodium channels, resulting in decreased local anesthetic toxicity.

Seizures induced by local anesthetics can also be treated with small doses (given intravenously) of thiopental 1–2 mg/kg, propofol 0.5–1 mg/kg, midazolam 2–4 mg total dose, or diazepam 0.1 mg/kg. The muscular manifestations of seizures can be suppressed by a short-acting neuromuscular blocking agent (eg, succinylcholine, 0.5–1 mg/kg IV). It should be emphasized that succinylcholine does not obliterate central nervous system manifestations of seizure activity. Rapid tracheal intubation and mechanical ventilation can prevent pulmonary aspiration of gastric contents and facilitate hyperventilation therapy.

Cocaine

Since prehistoric times, the natives of Peru have chewed the leaves of the indigenous plant *Erythroxylon coca*, the source of cocaine, to obtain a feeling of well-being and reduce fatigue. Intense central nervous system effects can be achieved by sniffing cocaine powder and smoking cocaine base. Cocaine has become one of the most widely abused drugs (see Chapter 32: Drugs of Abuse). High doses of inhaled cocaine as well as injected cocaine have all of the toxicities described for other local anesthetics in general. In addition, cocaine can produce severe cardiovascular toxicity, including hypertension and arrhythmias.

Neurotoxicity

When applied at excessively high concentrations, all local anesthetics can be toxic to nerve tissue. Chloroprocaine and lidocaine appear to be more neurotoxic than other local anesthetics when used
for spinal anesthesia, producing so-called transient radicular irritation. It has been suggested that this toxicity results from pooling of high concentrations of the local anesthetic in the cauda equina. Although the mechanism of this neurotoxic action has not been established, both interference with axonal transport and disruption of calcium homeostasis have been shown to occur and could be responsible. Spinal neurotoxicity does not result from excessive sodium channel blockade.

Cardiovascular System

The cardiovascular effects of local anesthetics result partly from direct effects upon the cardiac and smooth muscle membranes and partly from indirect effects upon the autonomic nerves. As described in Chapter 14: Agents Used in Cardiac Arrhythmias, local anesthetics block cardiac sodium channels and thus depress abnormal cardiac pacemaker activity, excitability, and conduction. At very high concentrations, they may also block calcium channels. With the notable exception of cocaine, local anesthetics also depress the strength of cardiac contraction and cause arteriolar dilation, both effects leading to severe hypotension. Cardiovascular collapse and death are rare and usually occur only after large doses of 0.75% bupivacaine.

As noted above, cocaine differs from the other local anesthetics in its cardiovascular effects. Cocaine's blockade of norepinephrine reuptake results in vasoconstriction and hypertension. It may also precipitate cardiac arrhythmias. The vasoconstriction produced by cocaine can lead to ischemia and, in chronic abusers, to ulceration of the mucous membrane and even damage to the nasal septum when "snorted." This vasoconstrictor property of cocaine can be used clinically to decrease bleeding from mucosal damage in the nasopharynx.

Bupivacaine is more cardiotoxic than other local anesthetics. This reflects the fact that bupivacaine block of sodium channels is potentiated by the long action potential duration of cardiac cells (as compared to nerve fibers). Studies have shown that the most common electrocardiographic finding in patients with bupivacaine intoxication is slow idioventricular rhythm with broad QRS complexes and eventually, electromechanical dissociation.

Resuscitation from bupivacaine cardiovascular toxicity is extremely difficult. However, prompt resuscitation has been successful with standard cardiopulmonary support, including the prompt correction of acidosis by hyperventilation and administration of bicarbonate as well as epinephrine, atropine, and bretylium. Local anesthetics, especially bupivacaine, also inhibit basal and epinephrine-stimulated cAMP production. This finding places greater emphasis on aggressive epinephrine therapy during bupivacaine-induced cardiotoxicity. The (S)-isomer, levobupivacaine, appears to have a lower propensity for cardiovascular toxicity than the racemic mixture or the (R)-isomer and has recently been approved for clinical use. Ropivacaine, another newer local anesthetic, has clinical effects similar to those of bupivacaine but may be associated with a lower potential for cardiovascular toxicity. Ropivacaine is available only as the (S)-stereoisomer, which has inherently less affinity for the cardiac sodium channel.

Hematologic Effects

The administration of large doses (> 10 mg/kg) of prilocaine during regional anesthesia may lead to accumulation of the metabolite o-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin. When sufficient methemoglobin is present (3–5 mg/dL), the patient may appear cyanotic and the blood chocolate-colored. Although moderate levels of methemoglobinemia are well-tolerated by healthy individuals, they may cause decompensation in patients with cardiac or pulmonary disease. The treatment of methemoglobinemia involves the intravenous administration of reducing agents (eg, methylene blue or ascorbic acid), which rapidly convert methemoglobin to
hemoglobin.

Allergic Reactions

The ester type local anesthetics are metabolized to \( p \)-aminobenzoic acid derivatives. These metabolites are responsible for allergic reactions in a small percentage of the population. Amides are not metabolized to \( p \)-aminobenzoic acid, and allergic reactions to agents of the amide group are extremely rare.

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Preparations Available

**Articaine** (Septocaine)

Parenteral: 4% with 1:100,000 epinephrine

**Benzocaine** (generic, others)

Topical: 5, 6% creams; 15, 20% gels; 5, 20% ointments; 0.8% lotion; 20% liquid; 20% spray

**Bupivacaine** (generic, Marcaine, Sensorcaine)

Parenteral: 0.25, 0.5, 0.75% for injection; 0.25, 0.5, 0.75% with 1:200,000 epinephrine

**Butamben picrate** (Butesin Picrate)

Topical: 1% ointment

**Chloroprocaine** (generic, Nesacaine)

Parenteral: 1, 2, 3% for injection

**Cocaine** (generic)

Topical: 40, 100 mg/mL solutions; 5, 25 g powder

**Dibucaine** (generic, Nupercainal)

Topical: 0.5% cream; 1% ointment

**Dyclonine** (Dyclone)

Topical: 0.5, 1% solution

**Levo-bupivacaine** (Chirocaine)

Parenteral: 2.5, 5, 7.5 mg/mL

**Lidocaine** (generic, Xylocaine, others)
Parenteral: 0.5, 1, 1.5, 2, 4% for injection; 0.5, 1, 1.5, 2% with 1:200,000 epinephrine; 1, 2% with 1:100,000 epinephrine, 2% with 1:50,000 epinephrine

Topical: 2.5, 5% ointments; 0.5, 4% cream; 0.5, 2.5% gel; 2, 2.5, 4% solutions; 23, 46 mg/2 cm² patch

**Lidocaine and etidocaine eutectic mixture** (EMLA cream)

Topical: lidocaine 2.5% plus etidocaine 2.5%

**Mepivacaine** (generic, Carbocaine, others)

Parenteral: 1, 1.5, 2, 3% for injection; 2% with 1:20,000 levonordefrin

**Pramoxine** (Tronothane, others)

Topical: 1% cream, lotion, spray, and gel

**Praloxine** (Citane, others)

Parenteral: 4% for injection; 4% with 1:200,000 epinephrine

**Procaïne** (generic, Novocain)

Parenteral: 1, 2, 10% for injection

**Proparacaine** (generic, Alcain, others)

0.5% solution for ophthalmic use

**Ropivacaine** (Naropin)

Parenteral: 0.2, 0.5, 0.75, 1.0% solution for injection

**Tetracaine** (Pontocaine)

Parenteral: 1% for injection; 0.2, 0.3% with 6% dextrose for spinal anesthesia

Topical: 1% ointment; 0.5% solution (ophthalmic); 1, 2% cream; 2% solution for nose and throat; 2% gel

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**Chapter 27. Skeletal Muscle Relaxants**

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Skeletal Muscle Relaxants: Introduction

Drugs that affect skeletal muscles fall into two major therapeutic groups: those used during surgical procedures and in intensive care units to cause paralysis (ie, neuromuscular blockers), and those used to reduce spasticity in a variety of neurologic conditions (ie, spasmolytics). Neuromuscular blocking drugs interfere with transmission at the neuromuscular end plate and lack central nervous system activity. These compounds are used primarily as adjuncts to general anesthesia. Drugs in the spasmolytic group have traditionally been called "centrally acting" muscle relaxants. However, at least one of these latter agents (dantrolene) has no significant central effects.

Neuromuscular Blocking Drugs

History

During the 16th century, European explorers found that natives of the Amazon Basin of South America were using an arrow poison (curare) that produced death by skeletal muscle paralysis. The active compound from curare, d-tubocurarine, and its synthetic derivatives have had an enormous influence on the practice of anesthesia and surgery and have been very useful in defining normal neuromuscular physiologic mechanisms.

Normal Neuromuscular Function

The mechanism of neuromuscular transmission at the end plate is similar to that described for preganglionic cholinergic nerves in Chapter 6: Introduction to Autonomic Pharmacology, with arrival of an impulse at the motor nerve terminal, influx of calcium, and release of acetylcholine. Acetylcholine then diffuses across the synaptic cleft to the nicotinic receptor located on the motor end plate. As noted in Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs, this receptor is composed of five peptides: two alpha peptides, one beta, one gamma, and one delta peptide. Combination of two acetylcholine molecules with receptors on the two subunits causes opening of the channel. The resulting movements of sodium and potassium are associated with a graded depolarization of the end plate membrane. This change in voltage is termed the motor end plate potential. The magnitude of the end plate potential is directly related to the amount of acetylcholine released. If the potential is small, the permeability and the end plate potential return to normal without an impulse being propagated from the end plate region to the rest of the muscle membrane. However, if the end plate potential is large, the adjacent muscle membrane is depolarized, and an action potential will be propagated along the entire muscle fiber. Muscle contraction is then initiated by excitation-contraction coupling. The released acetylcholine is quickly removed from the end plate region by diffusion and enzymatic destruction by the local acetylcholinesterase enzyme.

At least two additional types of acetylcholine receptors are associated with the neuromuscular apparatus. One is located on the presynaptic motor axon terminal; activation of these receptors mobilizes additional transmitter for subsequent release, perhaps by mobilizing more acetylcholine vesicles within the ending. The second type of receptor is found on perijunctional cells and is not normally involved in neuromuscular transmission. However, under certain conditions (eg, prolonged immobilization, burns), these receptors may proliferate sufficiently to affect subsequent neuromuscular transmission.

Skeletal muscle relaxation and paralysis can occur from interruption of function at several different sites, including the central nervous system, myelinated somatic nerves, unmyelinated motor nerve terminals, nicotinic acetylcholine receptors, the motor end plate, and the muscle membrane or
In practice, blockade of end plate function is accomplished by two basic mechanisms. Pharmacologic blockade of the physiologic agonist acetylcholine is characteristic of the antagonist neuromuscular blocking drugs. These drugs prevent access of the transmitter to its receptor and prevent depolarization. The prototype of this nondepolarizing subgroup is \textit{d-tubocurarine}. Block of transmission can also be produced by an excess of the depolarizing agonist, namely acetylcholine. This paradoxical effect of acetylcholine also occurs at the ganglionic nicotinic acetylcholine receptor. The clinically useful prototypical depolarizing blocking drug is \textit{succinylcholine}. A similar depolarizing block can be produced by acetylcholine itself if very high local concentrations are achieved in the synaptic cleft (eg, in cholinesterase inhibitor intoxication), by nicotine, and by other nicotinic agonists. However, because the block produced by these drugs cannot be controlled adequately, they are of no clinical value in this application.

\textbf{Katzung PHARMACOLOGY, 9e > Section V. Drugs That Act in the Central Nervous System > Chapter 27. Skeletal Muscle Relaxants >}

\textbf{Basic Pharmacology of Neuromuscular Blocking Drugs}

\textbf{Chemistry}

All of the available neuromuscular blocking drugs bear a structural resemblance to acetylcholine. In fact, succinylcholine is two acetylcholine molecules linked end-to-end (Figure 27–2). In contrast to the single linear structure of succinylcholine and other depolarizing drugs, the nondepolarizing
agents (eg, pancuronium) conceal the "double-acetylcholine" structure in one of two types of bulky, semi-rigid ring systems (Figure 27–2). The two major families of nondepolarizing blocking drugs—the isoquinoline and steroid derivatives—are shown in Figures 27–3 and 27–4. Another feature common to all currently used neuromuscular blockers is the presence of one or two quaternary nitrogens, which makes them poorly lipid-soluble and limits entry into the central nervous system.

Figure 27–2.

Structural relationship of succinylcholine, a depolarizing agent, and pancuronium, a nondepolarizing agent, to acetylcholine, the neuromuscular transmitter. Succinylcholine, originally called diacetylcholine, is simply two molecules of acetylcholine linked through the acetate methyl groups. Pancuronium may be viewed as two acetylcholine-like fragments (outlined in color) oriented on a steroid nucleus.

Figure 27–3.
Clinical Pharmacology of Neuromuscular Blocking Drugs

Skeletal Muscle Paralysis

Before the introduction of neuromuscular blocking drugs, profound skeletal muscle relaxation for intracavitary operations could be achieved only by producing deep levels of anesthesia that was often associated with profound depressant effects on the cardiovascular and respiratory systems. The adjunctive use of neuromuscular blocking drugs makes it possible to achieve adequate muscle relaxation for all types of surgical procedures without the cardiorespiratory depressant effects of deep anesthesia.

Assessment of Neuromuscular Transmission

Monitoring the effect of muscle relaxants during surgery (and recovery following the use of cholinesterase inhibitors) typically involves the use of a device that produces transdermal electrical stimulation of one of the peripheral nerves to the hand and recording of the evoked contractions (twitches; Figure 27–6). The motor responses to different patterns of peripheral nerve stimulation are measured. The three most commonly used patterns of include (1) single-twitch stimulation, (2) train-of-four (TOF) stimulation, and (3) tetanic stimulation. Two newer modalities are also available to monitor neuromuscular transmission: double-burst stimulation and posttetanic count.

With single-twitch stimulation, a single supramaximal electrical stimulus is applied to a peripheral nerve at frequencies from 0.1 Hz to 1.0 Hz. The higher frequency is often used during induction and reversal to more accurately determine the peak (maximal) drug effect. TOF stimulation involves four successive supramaximal stimuli given at intervals of 0.5 second (2 Hz). Each stimulus in the TOF causes the muscle to contract, and the relative magnitude of the response of the fourth twitch compared to the first twitch is the TOF ratio. With a depolarizing block, all four twitches are reduced in a dose-related fashion. With a nondepolarizing block, the TOF ratio decreases (“fades”) and is inversely proportionate to the degree of blockade. During recovery from nondepolarizing block, the amount of fade decreases as the TOF ratio approaches 1.0. Fade in the TOF response after administration of succinylcholine signifies the development of a phase II block.

Finally, tetanic stimulation consists of very rapid (30–100 Hz) delivery of electrical stimuli for several seconds. During a nondepolarizing block and a phase II block after succinylcholine, the response will not be sustained and fade is observed. Fade in response to tetanic stimulation is normally considered a presynaptic event. However, the degree of fade depends primarily on the degree of neuromuscular blockade. During a partial nondepolarizing blockade, tetanic nerve stimulation is followed by a posttetanic increase in the twitch response, a manifestation of so-called posttetanic facilitation of neuromuscular transmission. During very intense neuromuscular blockade, there is no response to either tetanic or posttetanic stimulation. As the intensity of the block diminishes, the response to posttetanic twitch stimulation reappears. The time to reappearance of the first response to TOF stimulation is related to the posttetanic count.

The double-burst stimulation pattern is a newer mode of electrical nerve stimulation developed with the goal of allowing for manual detection of residual neuromuscular blockade when it is not possible to record the responses to single-twitch, TOF, or tetanic stimulation. In this pattern, three nerve stimuli are delivered at 50 Hz followed by a 700 ms rest period and then by two or three additional stimuli at 50 Hz. It is easier to detect fade in the responses to double-burst stimulation
than in the responses to TOF stimulation. Note that the absence of fade in the responses to double-burst stimulation implies that clinically significant residual neuromuscular blockade does not exist.

Nondepolarizing Drugs

During anesthesia, the intravenous administration of tubocurarine, 0.1–0.4 mg/kg, will initially cause motor weakness, followed by the skeletal muscles becoming totally flaccid and inexcitable to electrical stimulation (Figure 27–8). In general, larger muscles (eg, abdominal, trunk, paraspinal, diaphragm) are more resistant to blockade and recover more rapidly than smaller muscles (eg, facial, foot, hand). The diaphragm is usually the last muscle to be paralyzed. Assuming that ventilation is adequately maintained, no adverse effects occur. When administration of muscle relaxants is discontinued, recovery of muscles usually occurs in reverse order, with the diaphragm regaining function first, depending on the relaxant's elimination half-life. The pharmacologic effect of tubocurarine, 0.3 mg/kg IV, usually lasts 45–60 minutes. However, subtle evidence of residual muscle paralysis detected using a neuromuscular monitor may last for another hour. Potency and duration of action of the other nondepolarizing drugs are shown in Table 27–1. In addition to the duration of action, the most important property distinguishing the nondepolarizing relaxants is the time to onset of effect, which determines how rapidly the patient's trachea can be intubated with a tracheal tube. Of the nondepolarizing drugs, rapacuronium has the fastest onset of effect (45–90 seconds) followed by rocuronium (60–120 seconds). As earlier noted, rapacuronium is no longer available.

Figure 27–8.

<table>
<thead>
<tr>
<th>Isoflurane (1.25 MAC)</th>
<th>1 min</th>
<th>Tubocurarine (3 mg/m²)</th>
<th>23 min</th>
</tr>
</thead>
</table>

| Halothane (1.25 MAC) | 1 min | Tubocurarine (6 mg/m²) | 11 min |

Neuromuscular blockade from tubocurarine during isoflurane and halothane anesthesia in patients. Note that at equivalent levels of anesthesia, isoflurane augments the block far more than does halothane.

Depolarizing Drugs

Following the intravenous administration of succinylcholine, 0.75–1.5 mg/kg, transient muscle
fasciculations occur, especially over the chest and abdomen, though general anesthesia tends to attenuate them. As complete paralysis develops, the arm, neck, and leg muscles are involved at a time when there is only slight weakness of the facial and pharyngeal muscles. However, respiratory muscle weakness follows rapidly, usually within 60 seconds (Figure 27–9). As a result of succinylcholine's rapid hydrolysis by cholinesterase in the plasma and liver, the duration of neuromuscular block typically lasts 5–10 minutes (Table 27–1).

Cardiovascular Effects

Vecuronium, pipecuronium, doxacurium, cisatracurium, and rocuronium have minimal cardiovascular effects. The other currently used nondepolarizing muscle relaxants (pancuronium, atracurium, mivacurium) produce some cardiovascular effects that are mediated by autonomic or histamine receptors or both (Table 27–3). Tubocurarine and, to a lesser extent, metocurine, mivacurium, and atracurium, can produce hypotension as a result of systemic histamine release, and with larger doses ganglionic blockade may occur with tubocurarine and metocurine. Premedication with an antihistamine drug will attenuate tubocurarine- and mivacurium-induced hypotension. Pancuronium causes a moderate increase in heart rate and a smaller increase in cardiac output, with little or no change in systemic vascular resistance. Although pancuronium-induced tachycardia is primarily due to a vagolytic action, release of norepinephrine from adrenergic nerve endings and blockade of neuronal uptake of norepinephrine have been suggested as secondary mechanisms. Effects of nondepolarizing blockers on the airways are discussed in Bronchospasm Induced by Neuromuscular Blockers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Autonomic Ganglia</th>
<th>Effect on Cardiac Muscarinic Receptors</th>
<th>Tendency to Cause Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoquinoline derivatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>Metocurine</td>
<td>Weak block</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>None</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Weak block</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Steroid derivatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>None</td>
<td>Moderate block</td>
<td>None</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rapacuronium(^1)</td>
<td>None</td>
<td>Very slight block</td>
<td>None</td>
</tr>
<tr>
<td>Rocuronium(^2)</td>
<td>None</td>
<td>Slight</td>
<td>None</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallamine</td>
<td>None</td>
<td>Strong block</td>
<td>None</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Stimulation</td>
<td>Stimulation</td>
<td>Slight</td>
</tr>
</tbody>
</table>

\(^1\) Withdrawn from clinical use.

\(^2\) Allergic reactions have been reported.

Succinylcholine can cause cardiac arrhythmias when administered during halothane anesthesia. The drug stimulates all autonomic cholinoreceptors, including the nicotinic receptors in both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart (e.g., sinus node). The negative inotropic and chronotropic responses to succinylcholine can be attenuated by administration of an anticholinergic drug (e.g., glycopyrrolate, atropine). With large doses of succinylcholine, positive inotropic and chronotropic effects may result. On the other hand, bradycardia has been repeatedly observed when a second dose of succinylcholine is given less than 5 minutes after the first dose. This transient bradycardia can be prevented by thiopental, atropine, ganglionic-blocking drugs, and even nondepolarizing muscle relaxants. Direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in this bradycardic response.

Other Adverse Effects of Depolarizing Blockade

Hyperkalemia

Patients with burns, nerve damage or neuromuscular disease, closed head injury, and other trauma can respond to succinylcholine by an exaggerated release of potassium into the blood, occasionally resulting in cardiac arrest. As a result of the cardiac arrests (presumably caused by hyperkalemia), the Food and Drug Administration recommended in 1993 that succinylcholine no longer be used in children. However, this highly controversial contraindication was subsequently modified to a simple warning because no acceptable alternative to succinylcholine was available for rapid-sequence inductions.

Increased Intraocular Pressure

Administration of succinylcholine is followed by a transient increase in intraocular pressure that is manifested less than 60 seconds after intravenous injection, peaks at 2–4 minutes, and declines after
5 minutes. The mechanism for this effect has not been clearly defined, but it may involve contraction of tonic myofibrils or transient dilation of choroidal blood vessels. Despite the increase in intraocular pressure, the use of succinylcholine for ophthalmologic operations is not contraindicated unless the anterior chamber is to be opened.

Increased Intragastric Pressure

In heavily muscled patients, the fasciculations associated with succinylcholine will cause an increase in intragastric pressure ranging from 5 cm to 40 cm H₂O. This may make emesis more likely, with the potential hazard of aspiration of gastric contents. This complication is more likely to occur in patients with delayed gastric emptying (eg, diabetes, esophageal dysfunction, obesity).

Muscle Pain

This is a common postoperative complaint of heavily muscled patients and those who have received large doses of succinylcholine. The true incidence of this symptom is difficult to establish because of subjective factors and differences in study design, but it has been reported in 0.2–20% of patients in different studies. It occurs more frequently in ambulatory than in bedridden patients. The pain is thought to be secondary to the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis. However, there is controversy over whether the incidence of muscle pain following succinylcholine is really higher than that following nondepolarizing muscle relaxants when other potentially confounding factors are considered.

Interactions with Other Drugs

Anesthetics

Inhaled anesthetics augment the neuromuscular blockade produced by nondepolarizing muscle relaxants in a dose-dependent fashion. Of the anesthetics that have been studied, inhaled anesthetics augment the effects of muscle relaxants in the following order: isoflurane (most); then sevoflurane, desflurane, enflurane, and halothane (Figure 27–8); and finally nitrous oxide (least). The most important factors involved in this interaction are the following: (1) nervous system depression at sites proximal to the neuromuscular junction (ie, central nervous system); (2) increased muscle blood flow (ie, due to peripheral vasodilation), which allows a larger fraction of the injected muscle relaxant to reach the neuromuscular junction; and (3) decreased sensitivity of the postjunctional membrane to depolarization.

Antibiotics

Numerous reports have appeared describing enhancement of neuromuscular blockade by antibiotics, especially the aminoglycosides. Many of the antibiotics have been shown to cause a depression of evoked release of acetylcholine similar to that caused by magnesium. The mechanism of this prejunctional effect appears to be blockade of specific P-type calcium channels. These antibiotics also have postjunctional activity.

Local Anesthetics and Antiarrhythmic Drugs

In large doses, most local anesthetics block neuromuscular transmission. However, in smaller doses, they enhance the neuromuscular block produced by both nondepolarizing and depolarizing muscle relaxants. In small doses, local anesthetics depress posttetanic potentiation, and this is thought to be a prejunctional neural effect. With higher doses, local anesthetics block acetylcholine-induced
muscle contractions. This stabilizing effect is the result of blockade of the nicotinic receptor ion channels. Experimentally, similar effects can be demonstrated with sodium channel-blocking antiarrhythmic drugs such as quinidine. However, at the doses used for cardiac arrhythmias, this interaction is of little or no clinical significance. Higher concentrations of bupivacaine (0.75%) have been associated with cardiac arrhythmias independent of the muscle relaxant used.

Other Neuromuscular Blocking Drugs

The end plate-depolarizing effect of succinylcholine can be antagonized by administering a small dose of a nondepolarizing blocker. To prevent the fasciculations associated with succinylcholine administration, a small nonparalyzing dose of a nondepolarizer can be given before succinylcholine (eg, d-tubocurarine 2 mg intravenously or pancuronium 0.5 mg intravenously). While this dose usually reduces fasciculations and postoperative pain, it can increase the amount of succinylcholine required for relaxation by 50–90% and may produce a feeling of weakness in awake patients. Therefore, preventive curarization prior to succinylcholine is no longer widely practiced.

Effects of Diseases & Aging on the Neuromuscular Response

Several diseases can diminish or augment the neuromuscular blockade produced by nondepolarizing muscle relaxants. Myasthenia gravis strongly enhances the neuromuscular blockade produced by these drugs. Advanced age (> 70 years) is associated with a prolonged duration of action from nondepolarizing relaxants as a result of decreased clearance of the drugs by the liver and kidneys. As a result, the dose of neuromuscular blocking drugs should be reduced in elderly patients.

Conversely, patients with severe burns and those with upper motor neuron disease are resistant to nondepolarizing muscle relaxants. This "desensitization" is probably caused by proliferation of extrajunctional receptors, which results in an increased dose requirement for the nondepolarizing relaxant to block a sufficient number of receptors.

Reversal of Nondepolarizing Neuromuscular Blockade

The cholinesterase inhibitors effectively antagonize the neuromuscular blockade caused by nondepolarizing drugs. Their general pharmacology is discussed in Chapter 7: Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs. Neostigmine and pyridostigmine antagonize nondepolarizing neuromuscular blockade by increasing the availability of acetylcholine at the motor end plate, mainly by inhibition of acetylcholinesterase. To a lesser extent, these cholinesterase inhibitors also increase release of transmitter from the motor nerve terminal. In contrast, edrophonium antagonizes neuromuscular blockade purely by inhibiting acetylcholinesterase. Edrophonium may be less effective than neostigmine in reversing the effects of most nondepolarizing blockers in the presence of a more profound degree of neuromuscular blockade. These differences are important in determining recovery from "residual block," the neuromuscular blockade remaining after completion of surgery and movement of the patient to the recovery room. Unsuspected residual block may result in hypoxia and even apnea, especially if patients receive other depressant medications during the recovery period.

Since mivacurium is metabolized by plasma cholinesterase, the interaction with the reversal drugs is unpredictable. On one hand, the neuromuscular blockade is antagonized because of increased acetylcholine concentrations in the synapse. On the other hand, mivacurium concentration may be higher because of decreased plasma cholinesterase breakdown of the muscle relaxant. The former effect usually dominates clinically, and mivacurium block is reversed by neostigmine.
Uses of Neuromuscular Blocking Drugs

Surgical Relaxation

By far the most important application of the neuromuscular blockers is in facilitating surgery. This is especially important in intra-abdominal and intrathoracic procedures.

Control of Ventilation

In critically ill patients who have ventilatory failure from various causes (eg, severe bronchospasm, pneumonia, chronic obstructive airway disease), it may be necessary to control ventilation to provide adequate gas exchange and to prevent atelectasis. Muscle paralysis is produced by administration of neuromuscular blocking drugs to eliminate chest wall resistance and ineffective spontaneous ventilation.

Treatment of Convulsions

Neuromuscular blocking drugs are sometimes used to attenuate or eliminate the peripheral manifestations of convulsions associated with epilepsy or local anesthetic toxicity. Although this approach is effective in eliminating the muscular manifestations of the seizures, it has no effect on the central processes involved since neuromuscular blocking drugs do not cross the blood-brain barrier.

Spasmyloytic Drugs

Spasticity is characterized by an increase in tonic stretch reflexes and flexor muscle spasms (ie, increased basal muscle tone), together with muscle weakness. It is often associated with cerebral palsy, multiple sclerosis, and stroke. These conditions often involve abnormal function of the bowel and bladder as well as skeletal muscle. The mechanisms underlying clinical spasticity appear to involve not only the stretch reflex arc itself but also higher centers in the central nervous system (upper motor neuron lesion), with damage to descending pathways in the spinal cord, resulting in hyperexcitability of the alpha motoneurons in the cord. Nevertheless, pharmacologic therapy may ameliorate some of the symptoms of spasticity by modifying the stretch reflex arc or by interfering directly with skeletal muscle (ie, excitation-contraction coupling). The important components involved in these processes are shown in Figure 27–10.
Diagram of the structures involved in the stretch reflex arc. I is an inhibitory interneuron; E indicates an excitatory presynaptic terminal; la is a primary intrafusal afferent fiber; Ca\(^{2+}\) denotes activator calcium stored in the sarcoplasmic reticulum of skeletal muscle. (Reproduced, with permission, from Young RR, Delwaide PJ: Drug therapy: Spasticity. N Engl J Med 1981;304:28.)

Drugs that modify this reflex arc may modulate excitatory or inhibitory synapses (Chapter 21: Introduction to the Pharmacology of CNS Drugs). Thus, to reduce the hyperactive stretch reflex, it is desirable to reduce the activity of the la fibers that excite the primary motoneuron or to enhance the activity of the inhibitory internuncial neurons. These structures are shown in greater detail in Figure 27–11.
A variety of pharmacologic agents described as depressants of the spinal "polysynaptic" reflex arc (eg, barbiturates [phenobarbital] and glycerol ethers [mephenesin]) have been used to treat these conditions of excess skeletal tone. However, as illustrated in Figure 27–11, nonspecific depression of synapses involved in the stretch reflex could reduce the desired inhibitory activity as well as the excitatory transmission. During the past several decades, more specific therapies have become available. Unfortunately, the lack of convenient and quantifiable measures of clinical response and of appropriate experimental models has hampered development of better agents for this heterogeneous group of medical conditions. Furthermore, while currently available drugs do provide significant relief from painful muscle spasms, they are all less effective in improving meaningful function (eg, mobility and return to work).

**Diazepam**

As described in Chapter 22: Sedative-Hypnotic Drugs, benzodiazepines facilitate the action of y-aminobutyric acid (GABA) in the central nervous system. Diazepam acts at all GABA_A synapses, but its action in reducing spasticity is at least partly mediated in the spinal cord because it is somewhat effective in patients with cord transection. It can be used in patients with muscle spasm of almost any origin, including local muscle trauma. However, it produces sedation in most patients at the doses required to significantly reduce muscle tone. Dosage is usually begun at 4 mg/d and gradually increased to a maximum of 60 mg/d. Other benzodiazepines have been used as
spasmolytics, but experience with them is much more limited.

Baclofen

Baclofen ($p$-chlorophenyl-GABA) was designed to be an orally active GABA-mimetic agent. The structure is shown below.

![Baclofen Structure]

Baclofen exerts its spasmolytic activity at GABA$_B$ receptors. Activation of these receptors in the brain by baclofen results in hyperpolarization, probably by increased K$^+$ conductance. It has been suggested that hyperpolarization (in the spinal cord as well as in the brain) causes presynaptic inhibition by reducing calcium influx (Figure 27–11) and reduces the release of excitatory transmitters in both the brain and the spinal cord. Baclofen may also reduce pain in patients with spasticity, perhaps by inhibiting the release of substance P in the spinal cord.

Baclofen is at least as effective as diazepam in reducing spasticity and produces much less sedation. In addition, baclofen does not reduce overall muscle strength as much as dantrolene. It is rapidly and completely absorbed after oral administration and has a plasma half-life of 3–4 hours. Dosage is started at 15 mg twice daily, increasing as tolerated to 100 mg daily. Adverse effects of this drug include drowsiness, to which the patient may become tolerant with chronic administration. Increased seizure activity has been reported in epileptic patients. Therefore, withdrawal of baclofen must be done very slowly.

Studies have confirmed that intrathecal administration of baclofen can control severe spasticity and muscle pain that is not responsive to medication by other routes of administration. Owing to the poor egress of baclofen from the spinal cord, peripheral symptoms are rare. Therefore, higher central concentrations of the drug may be tolerated. Partial tolerance to the effect of the drug may occur after several months of therapy but can be overcome by upward dosage adjustments to maintain the beneficial effect. Several cases of excessive somnolence, respiratory depression, and even coma have been reported. Although a major disadvantage of this therapeutic approach is the difficulty of maintaining the drug delivery catheter in the subarachnoid space, long-term intrathecal baclofen therapy can improve the quality of life for patients with severe spastic disorders.

Oral baclofen has been studied in several other medical conditions. Preliminary studies suggest that it may be effective in reducing craving in recovering alcoholics. It has also been found effective in preventing migraine attacks in some patients.

Tizanidine

As noted in Chapter 11: Antihypertensive Agents, $\alpha$-agonists such as clonidine and other imidazoline compounds have a variety of effects on the central nervous system that are not fully understood. Among these effects is the ability to reduce muscle spasm. Tizanidine is a congener of clonidine that has been studied for its spasmytic actions. Tizanidine has significant $\alpha_2$-adrenoceptor agonist effects, but it reduces spasticity in experimental models at doses that cause less cardiovascular effect than clonidine. Neurophysiologic studies in animals and humans suggest that tizanidine reinforces both presynaptic and postsynaptic inhibition in the cord. It also inhibits
nociceptive transmission in the spinal dorsal horn.

Clinical trials suggest that tizanidine may produce a significant benefit in patients with spasticity. These trials report comparable efficacy in relieving muscle spasm to diazepam, baclofen, and dantrolene. However, tizanidine produces a different spectrum of adverse effects, including drowsiness, hypotension, dry mouth, and asthenia. The dosage requirements vary markedly among patients, suggesting that individual dosage titration is necessary to achieve an optimal effect.

Other Centrally Active Spasmolytic Drugs

**Gabapentin** is an antiepileptic drug (see Chapter 24: Antiseizure Drugs) that has shown considerable promise as a spasmylytic agent in several studies involving patients with multiple sclerosis. **Progabide** and **glycine** have also been found in preliminary studies to reduce spasticity. Progabide is a GABA<sub>A</sub> and GABA<sub>B</sub> agonist and has active metabolites, including GABA itself. **Glycine** is another inhibitory amino acid neurotransmitter (see Chapter 21: Introduction to the Pharmacology of CNS Drugs). It appears to possess pharmacologic activity when given orally and readily passes the blood-brain barrier. **Idrocilamide** and **riluzole** are newer drugs for the treatment of amyotrophic lateral sclerosis that appear to have spasm-reducing effects, possibly through inhibition of glutamatergic transmission in the central nervous system.

Dantrolene

Dantrolene is a hydantoin derivative related to phenytoin that has a unique mechanism of spasmylytic activity. In contrast to the centrally active drugs, dantrolene reduces skeletal muscle strength by interfering with excitation-contraction coupling in the muscle fibers. The normal contractile response involves release of calcium from its stores in the sarcoplasmic reticulum (see Figures 13–1 and 27–10). This activator calcium brings about the tension-generating interaction of actin with myosin. Calcium is released from the sarcoplasmic reticulum via a calcium channel, sometimes called the ryanodine receptor channel because the plant alkaloid **ryanodine** combines with a receptor on the channel protein and, in the case of the skeletal muscle channel, locks it in the open position.

![Dantrolene](image)

Dantrolene interferes with the release of activator calcium through this sarcoplasmic reticulum calcium channel by binding to the ryanodine receptor. Motor units that contract rapidly are more sensitive to the drug's effects than are slower-responding units. Cardiac muscle and smooth muscle are depressed only slightly, perhaps because the release of calcium from their sarcoplasmic reticulum involves a somewhat different process.

Treatment with dantrolene is usually initiated with 25 mg daily as a single dose, increasing to a maximum of 100 mg four times daily as tolerated. Only about one third of an oral dose of dantrolene is absorbed, and the elimination half-life of the drug is about 8 hours. Major adverse effects are generalized muscle weakness, sedation, and occasionally hepatitis.

A special application of dantrolene is in the treatment of **malignant hyperthermia**, a rare heritable
disorder that can be triggered by a variety of stimuli, including general anesthetics (eg, volatile anesthetics) and neuromuscular blocking drugs (eg, succinylcholine). Patients at risk for this condition have a hereditary impairment in the ability of the sarcoplasmic reticulum to sequester calcium. Following administration of one of the triggering agents, there is a sudden and prolonged release of calcium, with massive muscle contraction, lactic acid production, and increased body temperature. Prompt treatment is essential to control acidosis and body temperature and to reduce calcium release. The latter is accomplished with intravenous dantrolene, starting with a dose of 1 mg/kg intravenously and repeating as necessary to a maximum dose of 10 mg/kg.

Botulinum Toxin

The therapeutic use of botulinum toxin for ophthalmic purposes and for local muscle spasm was mentioned in Chapter 6: Introduction to Autonomic Pharmacology. Local injection of botulinum toxin has become popular for the treatment of generalized spastic disorders (eg, cerebral palsy). Most clinical studies to date have involved administration in one or two limbs, and the benefits appear to persist for weeks to several months after a single treatment. Most studies to date have utilized type A botulinum toxin, but type B is also available.

Drugs Used to Treat Acute Local Muscle Spasm

A large number of drugs (eg, carisoprodol, chlorphenesin, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine) are promoted for the relief of acute muscle spasm caused by local tissue trauma or muscular strains. It has been suggested that these drugs act primarily at the level of the brain stem. Cyclobenzaprine may be regarded as the prototype of the group. Cyclobenzaprine is structurally related to the tricyclic antidepressants and possesses antimuscarinic effects. It is ineffective in treating muscle spasm due to cerebral palsy or spinal cord injury. The drug has strong antimuscarinic actions and may cause significant sedation as well as confusion and transient visual hallucinations. The dosage of cyclobenzaprine for acute injury-related muscle spasm is 20–40 mg/d in divided doses.

Bronchospasm Induced by Neuromuscular Blockers

Skeletal muscle relaxants have no direct effect on bronchial smooth muscle, but tubocurarine and mivacurium have been known to cause bronchoconstriction through the release of histamine. It was therefore unexpected that rapacuronium, which does not release histamine, caused severe bronchospasm in a significant number of patients during rapid-sequence induction for intubation. This dangerous (and in several cases fatal) effect was associated with young age (especially infants and children) and a history of reactive airway disease. Research indicates that rapacuronium blocks presynaptic M2 muscarinic receptors (which modulate acetylcholine release) more effectively than postsynaptic M3 receptors (which evoke bronchial smooth muscle contraction). This suggests that in reactive airways, rapacuronium might greatly enhance the release of acetylcholine onto inadequately blocked postsynaptic muscarinic receptors.

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Preparations Available

Neuromuscular Blocking Drugs

**Atracurium** (Tracrium)
Parenteral: 10 mg/mL for injection

**Cisatracurium** (Nimbex)
Parenteral: 2, 10 mg/mL for IV injection

**Doxacurium** (Nuromax)
Parenteral: 1 mg/mL for IV injection

**Metocurine** (generic, Metubine Iodide)
Parenteral: 2 mg/mL for injection

**Mivacurium** (Mivacron)
Parenteral: 0.5, 2 mg/mL for injection

**Pancuronium** (generic, Pavulon)
Parenteral: 1, 2 mg/mL for injection

**Pipecuronium** (Arduan)
Parenteral: 1 mg/mL for IV injection

**Rocuronium** (Zemuron)
Parenteral: 10 mg/mL for IV injection

**Succinylcholine** (generic, Anectine)
Parenteral: 20, 50, 100 mg/mL for injection; 100, 500 mg per vial powders to reconstitute for injection

**Tubocurarine** (generic)
Parenteral: 3 mg (20 units)/mL for injection

**Vecuronium** (generic, Norcuron)
Parenteral: 10, 20 mg powder to reconstitute for injection

Muscle Relaxants (Spasmolytics)
**Baclofen** (generic, Lioresal)
Oral: 10, 20 mg tablets
Intrathecal: 0.05, 0.5, 2 mg/mL

**Botulinum toxin type A** (Botox)
Parenteral: Powder for solution, 100 units/vial

**Botulinum toxin type B** (Myobloc)
Parenteral: 5000 units/mL for injection

**Carisoprodol** (generic, Soma)
Oral: 350 mg tablets

**Chlorphenesin** (Maolate)
Oral: 400 mg tablets

**Chlorzoxazone** (generic, Paraflex)
Oral: 250, 500 mg tablets, caplets

**Cyclobenzaprine** (generic, Flexeril)
Oral: 10 mg tablets

**Dantrolene** (Dantrium)
Oral: 25, 50, 100 mg capsules
Parenteral: 20 mg per vial powder to reconstitute for injection

**Diazepam** (generic, Valium)
Oral: 2, 5, 10 mg tablets; 5 mg/5 mL, 5 mg/mL solutions
Parenteral: 5 mg/mL for injection

**Gabapentin** (Neurontin)
Oral: 100, 300, 400 mg capsules; 600, 800 mg tablets

*Note:* This drug is labeled for use only in epilepsy.

**Metaxalone** (Skelaxin)
Methocarbamol (generic, Robaxin)
Oral: 400 mg tablets
Methocarbamol (generic, Robaxin)
Oral: 500, 750 mg tablets
Parenteral: 100 mg/mL for IM, IV injection
Orphenadrine (generic, Norflex)
Oral: 100 mg tablets; 100 mg sustained-release tablets
Parenteral: 30 mg/mL for IM, IV injection
Riluzole (Rilutek)
Oral: 50 mg tablets
Note: This drug is labeled only for use in amyotrophic lateral sclerosis.
Tizanidine (Zanaflex)
Oral: 4 mg tablets

Chapter 28. Pharmacologic Management of Parkinsonism & Other Movement Disorders

Several different types of abnormal movement are recognized. Tremor consists of a rhythmic oscillatory movement around a joint and is best characterized by its relation to activity. Tremor present at rest is characteristic of parkinsonism, when it is often associated with rigidity and an impairment of voluntary activity. Tremor may occur during maintenance of sustained posture (postural tremor) or during movement (intention tremor). A conspicuous postural tremor is the cardinal feature of benign essential or familial tremor. Intention tremor occurs in patients with a lesion of the brainstem or cerebellum, especially when the superior cerebellar peduncle is involved, and may also occur as a manifestation of toxicity from alcohol or certain other drugs.

Chorea consists of irregular, unpredictable, involuntary muscle jerks that occur in different parts of the body and impair voluntary activity. In some instances, the proximal muscles of the limbs are most severely affected, and because the abnormal movements are then particularly violent, the term ballismus has been used to describe them. Chorea may be hereditary or may occur as a complication
of a number of general medical disorders and of therapy with certain drugs.

Abnormal movements may be slow and writhing in character (athetosis) and in some instances are so sustained that they are more properly regarded as abnormal postures (dystonia). Athetosis or dystonia may occur with perinatal brain damage, with focal or generalized cerebral lesions, as an acute complication of certain drugs, as an accompaniment of diverse neurologic disorders, or as an isolated inherited phenomenon of uncertain cause known as idiopathic torsion dystonia or dystonia musculorum deformans. Its physiologic basis is uncertain, and treatment is unsatisfactory.

**Tics** are sudden coordinated abnormal movements that tend to occur repetitively, particularly about the face and head, especially in children, and can be suppressed voluntarily for short periods of time. Common tics include, for example, repetitive sniffing or shoulder shrugging. Tics may be single or multiple and transient or chronic. Gilles de la Tourette's syndrome is characterized by chronic multiple tics; its pharmacologic management is discussed at the end of this chapter.

Many of the movement disorders have been attributed to disturbances of the basal ganglia, but the precise function of these anatomic structures is not yet fully understood, and it is not possible to relate individual symptoms to involvement at specific sites.

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**Parkinsonism (Paralysis Agitans)**

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a wide variety of reasons but is usually idiopathic. The pathophysiologic basis of the idiopathic disorder may relate to exposure to some unrecognized neurotoxin or to the occurrence of oxidation reactions with the generation of free radicals. Studies in twins suggest that genetic factors may also be important, especially when the disease occurs in patients under age 50. Parkinson's disease is generally progressive, leading to increasing disability unless effective treatment is provided.

The normally high concentration of dopamine in the basal ganglia of the brain is reduced in parkinsonism, and pharmacologic attempts to restore dopaminergic activity with levodopa and dopamine agonists have been successful in alleviating many of the clinical features of the disorder. An alternative but complementary approach has been to restore the normal balance of cholinergic and dopaminergic influences on the basal ganglia with antimuscarinic drugs. The pathophysiologic basis for these therapies is that in idiopathic parkinsonism, dopaminergic neurons in the substantia nigra that normally inhibit the output of GABAergic cells in the corpus striatum are lost (Figure 28–1). (In contrast, Huntington's chorea involves the loss of some cholinergic neurons and an even greater loss of the GABAergic cells that exit the corpus striatum.) Drugs that induce parkinsonian syndromes either are dopamine receptor antagonists (eg, antipsychotic agents; see Chapter 29: Antipsychotic Agents & Lithium) or lead to the destruction of the dopaminergic nigrostriatal neurons (eg, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]; see below).

Figure 28–1.
Levodopa

Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism. However, (–)-3-(3,4-dihydroxyphenyl)-L-alanine (levodopa), the immediate metabolic precursor of dopamine, does penetrate the brain, where it is decarboxylated to dopamine (see Figure 6–5). Several dopamine agonists have also been developed and may lead to clinical benefit, as discussed below.

Dopamine receptors are discussed in detail in Chapter 21: Introduction to the Pharmacology of CNS Drugs and Chapter 29: Antipsychotic Agents & Lithium. Dopamine receptors of the D₁ type are located in the zona compacta of the substantia nigra and presynaptically on striatal axons coming from cortical neurons and from dopaminergic cells in the substantia nigra. The D₂ receptors are located postsynaptically on striatal neurons and presynaptically on axons in the substantia nigra belonging to neurons in the basal ganglia. The benefits of dopaminergic antiparkinsonism drugs appear to depend mostly on stimulation of the D₂ receptors, but D₁-receptor stimulation may also be required for maximal benefit. Dopamine agonist or partial agonist ergot derivatives such as lergotrile and bromocriptine that are powerful stimulators of the D₂ receptors have antiparkinsonism properties, whereas certain dopamine blockers that are selective D₂ antagonists can induce parkinsonism.

Chemistry
As discussed in Chapter 6: Introduction to Autonomic Pharmacology, dopa is the precursor of dopamine and norepinephrine. Its structure is shown in Figure 28–2. Levodopa is the levorotatory stereoisomer of dopa.

Figure 28–2.

![Chemical structures](image)

Some drugs used in the treatment of parkinsonism.

Pharmacokinetics

Levodopa is rapidly absorbed from the small intestine, but its absorption depends on the rate of gastric emptying and the pH of the gastric contents. Food will delay the appearance of levodopa in the plasma. Moreover, certain amino acids from ingested food can compete with the drug for absorption from the gut and for transport from the blood to the brain. Plasma concentrations usually peak between 1 and 2 hours after an oral dose, and the plasma half-life is usually between 1 and 3 hours, although it varies considerably between individuals. About two thirds of the dose appears in the urine as metabolites within 8 hours of an oral dose, the main metabolic products being 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) and dihydroxy-phenylacetic acid (DOPAC). Unfortunately, only about 1–3% of administered levodopa actually enters the brain unaltered, the remainder being metabolized extracerebrally, predominantly by decarboxylation to dopamine, which does not penetrate the blood-brain barrier. This means that levodopa must be given in large amounts when it is used alone. However, when it is given in combination with a dopa decarboxylase inhibitor that does not penetrate the blood-brain barrier, the peripheral metabolism of levodopa is reduced, plasma levels of levodopa are higher, plasma half-life is longer, and more dopa is available for entry into the brain (Figure 28–3). Indeed, concomitant administration of a peripheral dopa decarboxylase inhibitor may reduce the daily requirements of levodopa by
approximately 75%.

Figure 28–3.

Fate of orally administered levodopa and the effect of carbidopa, estimated from animal data. The width of each pathway indicates the absolute amount of the drug present at each site, while the percentages shown denote the relative proportion of the administered dose. The benefits of coadministration of carbidopa include reduction of the amount of levodopa diverted to peripheral tissues and an increase in the fraction of the dose that reaches the brain. (GI, gastrointestinal.) (Data from Nutt JG, Fellman JH: Pharmacokinetics of levodopa. Clin Neuropharmacol 1984;7:35.)

Clinical Use
The best results of levodopa treatment are obtained in the first few years of treatment. This is sometimes because the daily dose of levodopa must be reduced with time in order to avoid side effects at doses that were well tolerated at the outset. The reason that adverse effects develop in this way is unclear, but selective denervation or drug-induced supersensitivity may be responsible. Some patients also become less responsive to levodopa, so that previously effective doses eventually fail to produce any therapeutic benefit. Responsiveness to levodopa may ultimately be lost completely, perhaps because of the disappearance of dopaminergic nigrostriatal nerve terminals or some pathologic process directly involving the striatal dopamine receptors. For such reasons, the benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy irrespective of the initial therapeutic response. Although levodopa therapy does not stop the progression of parkinsonism, its early initiation lowers the mortality rate. However, long-term therapy may lead to a number of problems in management such as development of the on-off phenomenon discussed below. The most appropriate time to introduce levodopa therapy must therefore be determined individually.

When levodopa is used, it is generally given in combination with carbidopa (Figure 28–2), a peripheral dopa decarboxylase inhibitor, for the reasons set forth above. Sinemet is a dopa preparation containing carbidopa and levodopa in fixed proportion (1:10 or 1:4). Treatment is started with a small dose, eg, Sinemet-25/100 (carbidopa 25 mg, levodopa 100 mg) three times daily, and gradually increased depending on the therapeutic response and development of adverse effects. It should be taken 30–60 minutes before meals. Most patients ultimately require Sinemet-25/250 (carbidopa 25 mg, levodopa 250 mg) three or four times daily. It is generally preferable to keep treatment with this agent at a low level (eg, Sinemet-25/100 three times daily) and to increase dopaminergic therapy by the addition of a dopamine agonist if necessary, in order to reduce the risk of development of response fluctuations, as discussed below. A controlled-release formulation of Sinemet is available and may be helpful in patients with established response fluctuations or as a means of reducing dosing frequency.

Levodopa can ameliorate all of the clinical features of parkinsonism, but it is particularly effective in relieving bradykinesia and any disabilities resulting from it. When it is first introduced, about one third of patients respond very well and one third less well. Most of the remainder either are unable to tolerate the medication or simply do not respond at all.

Adverse Effects

Gastrointestinal Effects

When levodopa is given without a peripheral decarboxylase inhibitor, anorexia and nausea and vomiting occur in about 80% of patients. These adverse effects can be minimized by taking the drug in divided doses, with or immediately after meals, and by increasing the total daily dose very slowly; antacids taken 30–60 minutes before levodopa may also be beneficial. The vomiting has been attributed to stimulation of an emetic center located in the brainstem but outside the blood-brain barrier to dopamine and to peripheral decarboxylase inhibitors. Fortunately, tolerance to this emetic effect develops in many patients after several months. Antiemetics such as phenothiazines should be avoided because they reduce the antiparkinsonism effects of levodopa and may exacerbate the disease.

When levodopa is given in combination with carbidopa to reduce its extracerebral metabolism, adverse gastrointestinal effects are much less frequent and troublesome, occurring in fewer than 20% of cases, so that patients can tolerate proportionately higher doses.
Cardiovascular Effects

A variety of cardiac arrhythmias have been described in patients receiving levodopa, including tachycardia, ventricular extrasystoles and, rarely, atrial fibrillation. This effect has been attributed to increased catecholamine formation peripherally. The incidence of such arrhythmias is low, even in the presence of established cardiac disease, and may be reduced still further if the levodopa is taken in combination with a peripheral decarboxylase inhibitor. In parkinsonism patients who also have heart disease, the anticipated benefits of levodopa, especially when combined with carbidopa, generally outweigh the slight risk of inducing a cardiac arrhythmia.

Postural hypotension is common and often asymptomatic, and tends to diminish with continuing treatment. Hypertension may also occur, especially in the presence of nonselective monoamine oxidase inhibitors or sympathomimetics or when massive doses of levodopa are being taken.

Dyskinesias

Dyskinesias occur in up to 80% of patients receiving levodopa therapy for long periods. The form and nature of dopa dyskinesias vary widely in different patients but tend to remain constant in character in individual patients. Chorea, ballismus, athetosis, dystonia, myoclonus, tics, and tremor may occur individually or in any combination in the face, trunk, or limbs. Choreoathetosis of the face and distal extremities is the most common presentation. The development of dyskinesias is dose-related, but there is considerable individual variation in the dose required to produce them.

Behavioral Effects

A wide variety of adverse mental effects have been reported including depression, anxiety, agitation, insomnia, somnolence, confusion, delusions, hallucinations, nightmares, euphoria, and other changes in mood or personality. Such adverse effects are more common in patients taking levodopa in combination with a decarboxylase inhibitor rather than levodopa alone, presumably because higher levels are reached in the brain. They may be precipitated by intercurrent illness or operation. It may be necessary to reduce or withdraw the medication. Several atypical antipsychotic agents are now available and may be particularly helpful in counteracting the behavioral complications of levodopa. Clozapine requires weekly blood counts because it leads to marrow suppression in rare instances. The starting dose is 6.25 mg at bedtime, with subsequent increments depending on response and tolerance; doses of 25–100 mg/d are typical. Olanzapine, quetiapine, and risperidone have also been used; they are less expensive than clozapine and do not cause marrow suppression but sometimes seem less effective.

Fluctuations in Response

Certain fluctuations in clinical response to levodopa occur with increasing frequency as treatment continues. In some patients, these fluctuations relate to the timing of levodopa intake, and they are then referred to as wearing-off reactions or end-of-dose akinesia. In other instances, fluctuations in clinical state are unrelated to the timing of doses (on-off phenomenon). In the on-off phenomenon, off-periods of marked akinesia alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia. The phenomenon is most likely to occur in patients who responded well to treatment initially. The exact mechanism is unknown.

Miscellaneous Adverse Effects

Mydriasis may occur and may precipitate an attack of acute glaucoma in some patients. Other
reported but rare adverse effects include various blood dyscrasias; a positive Coombs test with evidence of hemolysis; hot flushes; aggravation or precipitation of gout; abnormalities of smell or taste; brownish discoloration of saliva, urine, or vaginal secretions; priapism; and mild—usually transient—elevations of blood urea nitrogen and of serum transaminases, alkaline phosphatase, and bilirubin.

Drug Holidays

A drug holiday (for 3–21 days) may alleviate some of the neurologic and behavioral adverse effects of levodopa but is usually of little help in the management of the on-off phenomenon. Up to two thirds of patients show temporary improved responsiveness to levodopa when the drug is reinstituted, and—because they can be managed on lower doses than before—adverse mental effects and dyskinesias are less troublesome. Fluctuations in response (on-off phenomenon) are reduced in many instances, but any benefit in this regard is usually short-lived. Furthermore, a drug holiday carries the risks of aspiration pneumonia, venous thrombosis, pulmonary embolism, and depression resulting from the immobility accompanying severe parkinsonism. For these reasons and because of the temporary nature of any benefit, drug holidays are no longer recommended.

Drug Interactions

Pharmacologic doses of pyridoxine (vitamin B6) enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken. Levodopa should not be given to patients taking monoamine oxidase A inhibitors or within 2 weeks of their discontinuance, because such a combination can lead to hypertensive crises.

Contraindications

Levodopa should not be given to psychotic patients, as it may exacerbate the mental disturbance. It is also contraindicated in patients with angle-closure glaucoma, but those with chronic open-angle glaucoma may be given levodopa if intraocular pressure is well controlled and can be monitored. It is best given combined with carbidopa to patients with cardiac disease, but even so the risk of cardiac dysrhythmia is slight. Patients with active peptic ulcer must also be managed carefully, since gastrointestinal bleeding has occasionally occurred with levodopa. Because levodopa is a precursor of skin melanin and conceivably may activate malignant melanoma, its use should be avoided in patients with a history of melanoma or with suspicious undiagnosed skin lesions.

Dopamine Agonists

Drugs acting directly on dopamine receptors may have a beneficial effect additional to that of levodopa. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, have no potentially toxic metabolites, and do not compete with other substances for active transport into the blood and across the blood-brain barrier. Moreover, drugs selectively affecting certain (but not all) dopamine receptors may have more limited adverse effects than levodopa. There are a number of dopamine agonists with antiparkinsonism activity. The older dopamine agonists (bromocriptine and pergolide) are ergot derivatives (see Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids), unlike the newer agents (pramipexole and ropinirole). There is no evidence that one agonist is superior to another; individual patients, however, may respond to one but not another of these agents.

Dopamine agonists have an important role as first-line therapy for Parkinson's disease, and their use is associated with a lower incidence of the response fluctuations and dyskinesias occurring with
long-term levodopa therapy. In consequence, dopaminergic therapy may best be initiated with a dopamine agonist. Alternatively, a low dose of carbidopa plus levodopa (eg, Sinemet-25/100 three times daily) is introduced and a dopamine agonist is then added. In either case, the dose of the dopamine agonist is built up gradually depending on response and tolerance. Dopamine agonists may also be given to parkinsonian patients taking levodopa who have end-of-dose akinesia or on-off phenomenon or who are becoming resistant to treatment with levodopa. In such circumstances, it is generally necessary to lower the dose of levodopa to prevent intolerable adverse effects. The response to a dopamine agonist is generally disappointing in patients who have never responded to levodopa.

Bromocriptine

Bromocriptine is a D₂ agonist; its structure is shown in Table 16–4. This drug has been widely used to treat Parkinson's disease and has also been used to treat certain endocrinologic disorders, especially hyperprolactinemia (see Chapter 37: Hypothalamic & Pituitary Hormones), but in lower doses than for parkinsonism. Bromocriptine is absorbed to a variable extent from the gastrointestinal tract; peak plasma levels are reached within 1–2 hours after an oral dose. It is excreted in the bile and feces. The usual daily dose of bromocriptine in the treatment of parkinsonism is between 7.5 and 30 mg, depending on response and tolerance. In order to minimize adverse effects, the dose is built up slowly over 2 or 3 months from a starting level of 1.25 mg twice daily after meals; the daily dose is then increased by 2.5 mg every 2 weeks depending on the response or the development of adverse reactions.

Pergolide

Pergolide, another ergot derivative, directly stimulates both D₁ and D₂ receptors. It too has been widely used for parkinsonism, and comparative studies suggest that it is more effective than bromocriptine in relieving the symptoms and signs of parkinsonism, increasing "on-time" among response fluctuators, and permitting the levodopa dose to be reduced. The average therapeutic dose is 3 mg daily. Patients are generally started on 0.05 mg daily and the dose is built up over about 4 weeks by increments until benefit occurs or side effects limit further increments.

Pramipexole

Pramipexole, which is not an ergot derivative, has preferential affinity for the D₃ family of receptors. It is effective when used as monotherapy for mild parkinsonism. It is also helpful in patients with advanced disease, permitting the dose of levodopa to be reduced and smoothing out response fluctuations. It may ameliorate affective symptoms. A possible neuroprotective effect has been suggested by its ability to scavenge hydrogen peroxide and enhance neurotrophic activity in mesencephalic dopaminergic cell cultures. Pramipexole is rapidly absorbed, reaching peak plasma concentrations in approximately 2 hours, and is excreted largely unchanged in the urine. It is started at a dose of 0.125 mg three times daily; the dose is doubled after 1 week and again after another week. Further increments in the daily dose are by 0.75 mg at weekly intervals depending on response and tolerance. Most patients require between 0.5 and 1.5 mg three times daily. Renal insufficiency may necessitate dosage adjustment.
Ropinirole

Ropinirole, another nonergoline derivative, is a relatively pure D2 receptor agonist that is effective as monotherapy in patients with mild disease and as a means of smoothing the response to levodopa in patients with more advanced disease and response fluctuations. It is introduced in a dose of 0.25 mg three times daily, and the total daily dose is then increased by 0.75 mg at weekly intervals until the fourth week and by 1.5 mg thereafter. In most instances, a dose of between 2 and 8 mg three times daily is necessary. Ropinirole is metabolized by CYP1A2; drugs metabolized by the liver may significantly reduce its clearance.

Adverse Effects of Dopamine Agonists

Gastrointestinal Effects

Anorexia and nausea and vomiting may occur when a dopamine agonist is introduced and can be minimized by taking the medication with meals. Constipation, dyspepsia, and symptoms of reflux esophagitis may also occur. Bleeding from peptic ulceration has been reported.

Cardiovascular Effects

Postural hypotension may occur, particularly at the initiation of therapy. Painless digital vasospasm is a dose-related complication of long-term treatment with the ergot derivatives (bromocriptine or pergolide). When cardiac arrhythmias occur, they are an indication for discontinuing treatment. Peripheral edema is sometimes problematic.

Dyskinesias

Abnormal movements similar to those introduced by levodopa may occur and are reversed by reducing the total dose of dopaminergic drugs being taken.

Mental Disturbances
Confusion, hallucinations, delusions, and other psychiatric reactions are other complications of dopaminergic treatment and are more common and severe with dopamine agonists than levodopa. They clear on withdrawal of the offending medication.

Miscellaneous

Headache, nasal congestion, increased arousal, pulmonary infiltrates, pleural and retroperitoneal fibrosis, and erythromelalgia are other reported side effects of the ergot-derived dopamine agonists. Erythromelalgia consists of red, tender, painful, swollen feet and, occasionally, hands, at times associated with arthralgia; symptoms and signs clear within a few days of withdrawal of the causal drug. In rare instances, an uncontrollable tendency to fall asleep at inappropriate times has occurred, particularly in patients receiving pramipexole or ropinirole, requiring the discontinuation of medication.

Contraindications

Dopamine agonists are contraindicated in patients with a history of psychotic illness or recent myocardial infarction, or with active peptic ulceration. The ergot-derived agonists are best avoided in patients with peripheral vascular disease.

Monoamine Oxidase Inhibitors

Two types of monoamine oxidase have been distinguished. Monoamine oxidase A metabolizes norepinephrine and serotonin; monoamine oxidase B metabolizes dopamine. Selegiline (deprenyl) (Figure 28–2), a selective inhibitor of monoamine oxidase B, retards the breakdown of dopamine; in consequence, it enhances and prolongs the antiparkinsonism effect of levodopa (thereby allowing the dose of levodopa to be reduced) and may reduce mild on-off or wearing-off phenomena. It is therefore used as adjunctive therapy for patients with a declining or fluctuating response to levodopa. The standard dose is 5 mg with breakfast and 5 mg with lunch. Selegiline may cause insomnia when taken later during the day. It should not be taken by patients receiving meperidine, tricyclic antidepressants, or serotonin reuptake inhibitors because of the risk of acute toxic interactions. The adverse effects of levodopa may be increased by selegiline. Selegiline has only a minor therapeutic effect on parkinsonism when given alone, but studies in animals suggest that it may reduce disease progression. Such an effect of antioxidative therapy on disease progression may be expected if Parkinson's disease is associated with the oxidative generation of free radicals. However, any neuroprotective effect of selegiline may relate to its metabolite, desmethylselegiline, and involve antiapoptotic mechanisms. Studies to test the effect of selegiline on the progression of parkinsonism in humans have yielded ambiguous results. The findings in a large multicenter study have been taken to suggest a beneficial effect in slowing disease progression but may simply have reflected a symptomatic response.

Rasagiline, another monoamine oxidase B inhibitor, is more potent than selegiline in preventing MPTP-induced parkinsonism and is currently under study as a neuroprotective agent.

The combined administration of levodopa and an inhibitor of both forms of monoamine oxidase must be avoided, since it may lead to hypertensive crises, probably because of the peripheral accumulation of norepinephrine.

Catechol-O-Methyltransferase Inhibitors

Inhibition of dopa decarboxylase is associated with compensatory activation of other pathways of
levodopa metabolism, especially catechol-O-methyltransferase (COMT), and this increases plasma levels of 3-O-methyldopa (3OMD). Elevated levels of 3OMD have been associated with a poor therapeutic response to levodopa, perhaps in part because 3OMD competes with levodopa for an active carrier mechanism that governs its transport across the intestinal mucosa and the blood-brain barrier. Selective COMT inhibitors such as tolcapone and entacapone also prolong the action of levodopa by diminishing its peripheral metabolism. Levodopa clearance is decreased, and relative bioavailability of levodopa is thus increased. Neither the time to reach peak concentration nor the maximal concentration of levodopa is increased. These agents may be helpful in patients receiving levodopa who have developed response fluctuations—leading to a smoother response, more prolonged "on-time," and the option of reducing total daily levodopa dose. Tolcapone and entacapone are both widely available, but entacapone is generally preferred because it has not been associated with hepatotoxicity.

The pharmacologic effects of tolcapone and entacapone are similar, and both are rapidly absorbed, bound to plasma proteins, and metabolized prior to excretion. However, tolcapone has both central and peripheral effects, whereas the effect of entacapone is peripheral. The half-life of both drugs is approximately 2 hours, but tolcapone is slightly more potent and has a longer duration of action. Tolcapone is taken in a standard dose of 100 mg three times daily; some patients require a daily dose of twice that amount. By contrast, entacapone (200 mg) needs to be taken with each dose of levodopa, up to five times daily.

Adverse effects of the COMT inhibitors relate in part to increased levodopa exposure and include dyskinesias, nausea, and confusion. It is often necessary to lower the daily dose of levodopa by about 30% in the first 48 hours to avoid or reverse such complications. Other side effects include diarrhea, abdominal pain, orthostatic hypotension, sleep disturbances, and an orange discoloration of the urine. Tolcapone may cause an increase in liver enzyme levels and has been rarely associated with death from acute hepatic failure; accordingly, its use in the USA requires signed patient consent (as provided in the product labeling) plus monitoring of liver function tests every 2 weeks during the first year and less frequently thereafter. No such toxicity has been reported with entacapone.

**Amantadine**

Amantadine, an antiviral agent, was by chance found to have antiparkinsonism properties. Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine. Release of catecholamines from peripheral stores has been documented.

**Pharmacokinetics**

Peak plasma concentrations of amantadine are reached 1–4 hours after an oral dose. The plasma half-life is between 2 and 4 hours, most of the drug being excreted unchanged in the urine.

**Clinical Use**

Amantadine is less potent than levodopa and its benefits may be short-lived, often disappearing after only a few weeks of treatment. Nevertheless, during that time it may favorably influence the bradykinesia, rigidity, and tremor of parkinsonism. The standard dose is 100 mg orally twice or three times daily.

**Adverse Effects**
Amantadine has a number of undesirable central nervous system effects, all of which can be reversed by stopping the drug. These include restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, and confusion. Overdosage may produce an acute toxic psychosis. With doses several times higher than recommended, convulsions have occurred.

Livedo reticularis sometimes occurs in patients taking amantadine and usually clears within a month after the drug is withdrawn. Other dermatologic reactions have also been described. Peripheral edema, another well-recognized complication, is not accompanied by signs of cardiac, hepatic, or renal disease and responds to diuretics. Other adverse reactions include headache, heart failure, postural hypotension, urinary retention, and gastrointestinal disturbances (e.g., anorexia, nausea, constipation, and dry mouth).

Contraindications

Amantadine should be used with caution in patients with a history of seizures or heart failure.

Acetylcholine-Blocking Drugs

A number of centrally acting antimuscarinic preparations are available that differ in their potency and in their efficacy in different patients.

Clinical Use

Treatment is started with a low dose of one of the drugs in this category, the level of medication gradually being increased until benefit occurs or adverse effects limit further increments. Antimuscarinic drugs may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia. If patients do not respond to one drug, a trial with another is warranted and may be successful. Some of the more commonly used drugs are listed in Table 28–1.

<table>
<thead>
<tr>
<th>Table 28–1. Some Drugs with Antimuscarinic Properties Used in Parkinsonism.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Benztropine mesylate</td>
</tr>
<tr>
<td>Biperiden</td>
</tr>
<tr>
<td>Orphenadrine</td>
</tr>
<tr>
<td>Procyclidine</td>
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<tr>
<td>Trihexyphenidyl</td>
</tr>
</tbody>
</table>

Adverse Effects

Antimuscarinic drugs have a number of central nervous system effects, including drowsiness, mental slowness, inattention, restlessness, confusion, agitation, delusions, hallucinations, and mood changes. Other common effects include dryness of the mouth, blurring of vision, mydriasis, urinary retention, nausea and vomiting, constipation, tachycardia, tachypnea, increased intraocular pressure, palpitations, and cardiac arrhythmias. Dyskinesias occur in rare cases. Acute suppurative parotitis sometimes occurs as a complication of dryness of the mouth.
If medication is to be withdrawn, this should be accomplished gradually rather than abruptly in order to prevent acute exacerbation of parkinsonism.

Contraindications

Acetylcholine-blocking drugs should be avoided in patients with prostatic hyperplasia, obstructive gastrointestinal disease (eg, pyloric stenosis or paralytic ileus), or angle-closure glaucoma. In parkinsonism patients receiving antimuscarinic medication, concomitant administration of other drugs with antimuscarinic properties (eg, tricyclic antidepressants or antihistamines) may precipitate some of the complications mentioned above.

Surgical Procedures

In patients with advanced disease that is poorly responsive to pharmacotherapy, worthwhile benefit may follow thalamotomy (for conspicuous tremor) or posteroverentral pallidotomy. Ablative surgical procedures, however, are being replaced by functional, reversible lesions induced by high-frequency deep-brain stimulation, which has a lower morbidity. Thalamic stimulation by an implanted electrode and stimulator is very effective for the relief of tremor, and stimulation of the subthalamic nucleus or globus pallidus internus has yielded good results for management of the clinical fluctuation occurring in advanced parkinsonism. The anatomic substrate for such therapy is indicated in Figure 28–4. Such procedures are contraindicated in patients with secondary or atypical parkinsonism. Transplantation of dopaminergic tissue (fetal substantia nigra tissue) has been reported to confer benefit in some parkinsonism patients, but the results are conflicting and uncontrollable dyskinesias have occurred in some patients. Such procedures are best regarded as investigational.

Figure 28–4.
Functional circuitry between the cortex, basal ganglia, and thalamus. The involved neurotransmitters are indicated. In Parkinson's disease, there is degeneration of the pars compacta of the substantia nigra, leading to overactivity in the indirect pathway (color) and increased glutamatergic activity by the subthalamic nucleus.

Neuroprotective Therapy

A number of different compounds are currently under investigation as potential neuroprotective agents that may slow disease progression. These include antioxidants, antiapoptotic agents, glutamate antagonists, intraparenchymally administered glial-derived neurotrophic factor, coenzyme Q10, and anti-inflammatory drugs. The role of these agents remains to be established, however, and their use for therapeutic purposes is not indicated at this time.

General Comments on Drug Management of Patients with Parkinsonism

Parkinson's disease generally follows a progressive course. Moreover, the benefits of levodopa therapy often seem to diminish with time and certain adverse effects may complicate long-term levodopa treatment. Nevertheless, evidence is accumulating that dopaminergic therapy at a relatively early stage may be most effective in alleviating symptoms of parkinsonism and may also favorably affect the mortality rate due to the disease. Symptomatic treatment of mild parkinsonism is probably best avoided until there is some degree of disability or until symptoms begin to have a significant impact on the patient's lifestyle. When treatment becomes necessary, a trial of
amantadine or an antimuscarinic drug (or both) may be worthwhile. With disease progression, dopaminergic therapy becomes necessary. This can conveniently be initiated with a dopamine agonist, either alone or in combination with low-dose Sinemet therapy. Physical therapy is helpful in improving mobility. In patients with severe parkinsonism and long-term complications of levodopa therapy, such as the on-off phenomena, a trial of treatment with a COMT inhibitor may be worthwhile. Regulation of dietary protein intake may also improve response fluctuations. Pallidotomy or deep-brain stimulation may be helpful in patients who fail to respond adequately to these measures. Treating patients who are young or have mild parkinsonism with selegiline may delay disease progression and merits consideration.

Drug-Induced Parkinsonism

Reserpine and the related drug tetrabenazine deplete biogenic monoamines from their storage sites, while haloperidol and the phenothiazines block dopamine receptors. These drugs may therefore produce a parkinsonian syndrome, usually within 3 months after introduction, which is related to high dosage and clears over a few weeks or months after withdrawal. If treatment is necessary, antimuscarinic agents are preferred. Levodopa is of no help if neuroleptic drugs are continued and may in fact aggravate the mental disorder for which antipsychotic drugs were prescribed originally.

In 1983, a drug-induced form of parkinsonism was discovered in individuals who attempted to synthesize and use a narcotic drug related to meperidine but actually synthesized and self-administered MPTP, as discussed in the MPTP & Parkinsonism.

MPTP & Parkinsonism

Reports in the early 1980s of a rapidly progressive form of parkinsonism in young persons opened a new area of research in the etiology and treatment of parkinsonism. The initial report described apparently healthy young people who attempted to support their opioid habit with a meperidine analog synthesized by an amateur chemist. They unwittingly self-administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and subsequently developed a very severe form of parkinsonism.

MPTP is a protoxin that is converted by monoamine oxidase B to N-methyl-4-phenylpyridinium (MPP⁺). MPP⁺ is selectively taken up by cells in the substantia nigra through an active mechanism normally responsible for dopamine reuptake. MPP⁺ inhibits mitochondrial complex I, thereby inhibiting oxidative phosphorylation. The interaction of MPP⁺ with complex I probably leads to cell death and thus to striatal dopamine depletion and parkinsonism.

Recognition of the effects of MPTP suggested that spontaneously occurring Parkinson's disease may result from exposure to an environmental toxin that is similarly selective in its target. However, no such toxin has yet been identified. It also suggested a successful means of producing an experimental model of Parkinson's disease in animals, especially nonhuman primates. This model is assisting in the development of new antiparkinsonism drugs. Pretreatment of exposed animals with a monoamine oxidase B inhibitor such as selegiline prevents the conversion of MPTP to MPP⁺ and thus protects against the occurrence of parkinsonism. This observation has provided one reason to believe that selegiline may retard the progression of Parkinson's disease in humans.
Other Movement Disorders

Tremor

Tremor consists of rhythmic oscillatory movements. Physiologic postural tremor, which is a normal phenomenon, is enhanced in amplitude by anxiety, fatigue, thyrotoxicosis, and intravenous epinephrine or isoproterenol. Propranolol reduces its amplitude and, if administered intra-arterially, prevents the response to isoproterenol in the perfused limb, presumably through some peripheral action. Certain drugs—especially the bronchodilators, valproate, tricyclic antidepressants, and lithium—may produce a dose-dependent exaggeration of the normal physiologic tremor that is reversed by discontinuing the drug. Although the tremor produced by sympathomimetics such as terbutaline (a bronchodilator) is blocked by propranolol, which antagonizes both $\beta_1$ and $\beta_2$ receptors, it is not blocked by metoprolol, a $\beta_1$-selective antagonist, suggesting that such tremor is mediated mainly by the $\beta_2$ receptors.

Essential tremor is a postural tremor, sometimes familial, that is clinically similar to physiologic tremor. Dysfunction of $\beta_1$ receptors has been implicated in some instances, since the tremor may respond dramatically to standard doses of metoprolol as well as to propranolol. The most useful approach is with propranolol, but whether the response depends on a central or peripheral action is unclear. The pharmacokinetics, pharmacologic effects, and adverse reactions of propranolol are discussed in Chapter 10: Adrenoceptor Antagonist Drugs. Daily doses of propranolol on the order of 120 mg (range, 60–240 mg) are usually required, and reported adverse effects have been few. Propranolol should be used with caution in patients with heart failure, heart block, asthma, and hypoglycemia. Patients can be instructed to take their own pulse and call the physician if significant bradycardia develops. Metoprolol is sometimes useful in treating tremor when patients have concomitant pulmonary disease that contraindicates use of propranolol. Primidone (an antiepileptic drug; see Chapter 24: Antiseizure Drugs), in gradually increasing doses up to 250 mg three times daily, is also effective in providing symptomatic control in some cases. Patients with tremor are very sensitive to primidone and often cannot tolerate the doses used to treat seizures; they should be started on 50 mg once daily and the daily dose increased by 50 mg every 2 weeks depending on response. Topiramate, another antiepileptic drug, may also be helpful in a dose of 400 mg daily, built up gradually. Small quantities of alcohol may suppress essential tremor but only for a short time and by an unknown mechanism. Diazepam, chlordiazepoxide, mephenesin, and antiparkinsonism agents have been advocated in the past but are generally worthless. Alprazolam (in doses up to 3 mg daily) is helpful in some patients. Thalamic stimulation (discussed earlier) is often worthwhile in advanced cases refractory to pharmacotherapy.

Intention tremor is present during movement but not at rest; sometimes it occurs as a toxic manifestation of alcohol or drugs such as phenytoin. Withdrawal or reduction in dosage provides dramatic relief. There is no satisfactory pharmacologic treatment for intention tremor due to other neurologic disorders.

Rest tremor is usually due to parkinsonism.

Huntington's Disease

This dominantly inherited disorder is characterized by progressive chorea and dementia that usually
begin in adulthood. The development of chorea seems to be related to an imbalance of dopamine, acetylcholine, GABA, and perhaps other neurotransmitters in the basal ganglia (Figure 28–1). Pharmacologic studies indicate that chorea results from functional overactivity in dopaminergic nigrostriatal pathways, perhaps because of increased responsiveness of postsynaptic dopamine receptors or deficiency of a neurotransmitter that normally antagonizes dopamine. Drugs that impair dopaminergic neurotransmission, either by depleting central monoamines (eg, reserpine, tetrabenazine) or by blocking dopamine receptors (eg, phenothiazines, butyrophenones), often alleviate chorea, whereas dopamine-like drugs such as levodopa tend to exacerbate it.

Both GABA and the enzyme (glutamic acid decarboxylase) concerned with its synthesis are markedly reduced in the basal ganglia of patients with Huntington's disease, and GABA receptors are usually implicated in inhibitory pathways. There is also a significant decline in concentration of choline acetyltransferase, the enzyme responsible for synthesizing acetylcholine, in the basal ganglia of these patients. These findings may be of pathophysiologic significance and have led to attempts to alleviate chorea by enhancing central GABA or acetylcholine activity. Unfortunately, such pharmacologic manipulations have been disappointing, yielding no consistently beneficial response, and as a consequence the most commonly used drugs for controlling dyskinesia in patients with Huntington's disease are still those that interfere with dopamine activity. With all of the latter drugs, however, reduction of abnormal movements may be associated with iatrogenic parkinsonism.

Reserpine depletes cerebral dopamine by preventing intraneuronal storage; it is introduced in low doses (eg, 0.25 mg daily), and the daily dose is then built up gradually (eg, by 0.25 mg every week) until benefit occurs or adverse effects become troublesome. A daily dose of 2–5 mg is often effective in suppressing abnormal movements, but adverse effects may include hypotension, depression, sedation, diarrhea, and nasal congestion. Tetrabenazine resembles reserpine in depleting cerebral dopamine and has less troublesome adverse effects, but it is not available in the USA. Treatment with postsynaptic dopamine receptor blockers such as phenothiazines and butyrophenones may also be helpful. Haloperidol is started in a small dose, eg, 1 mg twice daily, and increased every 4 days depending on the response. If haloperidol is not helpful, treatment with increasing doses of perphenazine up to a total of about 20 mg daily sometimes helps. Several recent reports suggest that olanzapine may also be helpful; the dose varies with the patient, but 10 mg daily is often sufficient although doses as high as 30 mg daily are sometimes required. The pharmacokinetics and clinical properties of these drugs are considered in greater detail elsewhere in this book.

Other Forms of Chorea

Treatment is directed at the underlying cause when chorea occurs as a complication of general medical disorders such as thyrotoxicosis, polycythemia vera rubra, systemic lupus erythematosus, hypocalcemia, and hepatic cirrhosis. Drug-induced chorea is managed by withdrawal of the offending substance, which may be levodopa, an antimuscarinic drug, amphetamine, lithium, phenytoin, or an oral contraceptive. Neuroleptic drugs may also produce an acute or tardive dyskinesia (discussed below). Sydenham's chorea is temporary and usually so mild that pharmacologic management of the dyskinesia is unnecessary, but dopamine-blocking drugs are effective in suppressing it.

Ballismus

The biochemical basis of ballismus is unknown, but the pharmacologic approach to management is the same as for chorea. Treatment with haloperidol, perphenazine, or other dopamine-blocking
drugs may be helpful.

Athetosis & Dystonia

The pharmacologic basis of these disorders is unknown, and there is no satisfactory medical treatment for them. Occasional patients with dystonia may respond to diazepam, amantadine, antimuscarinic drugs (in high dosage), levodopa, carbamazepine, baclofen, haloperidol, or phenothiazines. A trial of these pharmacologic approaches is worthwhile even though often not successful. Patients with focal dystonias such as blepharospasm or torticollis may benefit from injection of botulinum toxin into the overactive muscles.

Tics

The pathophysiologic basis of tics is unknown. Chronic multiple tics (Gilles de la Tourette's syndrome) may require treatment if the disorder is severe or is having a significant impact on the patient's life. The most effective pharmacologic approach is with haloperidol, and patients are better able to tolerate this drug if treatment is started with a small dosage (eg, 0.25 or 0.5 mg daily) and then increased very gradually over the following weeks. Most patients ultimately require a total daily dose of 3–8 mg. If haloperidol is not helpful, fluphenazine, clonazepam, clonidine, or carbamazepine should be tried. The pharmacologic properties of these drugs are discussed elsewhere in this book. Pimozide, an oral dopamine blocker, may help patients intolerant or unresponsive to haloperidol. The role of the newer atypical antipsychotic agents, such as risperidone, is unclear.

Drug-Induced Dyskinesias

The pharmacologic basis of the acute dyskinesia or dystonia sometimes precipitated by the first few doses of a phenothiazine is not clear. In most instances, parenteral administration of an antimuscarinic drug such as benztropine (2 mg intravenously), diphenhydramine (50 mg intravenously), or biperiden (2–5 mg intravenously or intramuscularly) is helpful, while in other instances diazepam (10 mg intravenously) alleviates the abnormal movements. 

Tardive dyskinesia, a disorder characterized by a variety of abnormal movements, is a common complication of long-term neuroleptic drug treatment (see Chapter 29: Antipsychotic Agents & Lithium). Unfortunately, its precise pharmacologic basis is unclear. A reduction in dose of the offending medication, a dopamine receptor blocker, commonly worsens the dyskinesia, while an increase in dose may suppress it. The drugs most likely to provide immediate symptomatic benefit are those interfering with dopaminergic function, either by depletion (eg, reserpine, tetrabenazine) or receptor blockade (eg, phenothiazines, butyrophenones). Paradoxically, the receptor-blocking drugs are the very ones that also cause the dyskinesia, and they are probably best avoided to prevent the development of a spiral phenomenon in which continuing aggravation of the dyskinesia by the drugs used to control it necessitates increasingly higher doses for its temporary suppression. 

Because tardive dyskinesia developing in adults is usually irreversible and has no satisfactory treatment, care must be taken to reduce the likelihood of its occurrence. Antipsychotic medication should be prescribed only when necessary and should be withheld periodically to assess the need for continued treatment and to unmask incipient dyskinesia. Thioridazine, a phenothiazine with a piperidine side chain, is an effective antipsychotic that seems less likely than most to cause extrapyramidal reactions, perhaps because it has little effect on dopamine receptors in the striatal system. Finally, antimuscarinic drugs should not be prescribed routinely in patients receiving
neuroleptics, since the combination may increase the likelihood of dyskinesia.

Wilson's Disease

Wilson's disease, a recessively inherited disorder of copper metabolism, is characterized biochemically by reduced serum copper and ceruloplasmin concentrations, pathologically by markedly increased concentration of copper in the brain and viscera, and clinically by signs of hepatic and neurologic dysfunction. Treatment involves the removal of excess copper, followed by maintenance of copper balance. A commonly used agent for this purpose is penicillamine (dimethylcysteine), a chelating agent that forms a ring complex with copper. It is readily absorbed from the gastrointestinal tract and rapidly excreted in the urine. A common starting dose in adults is 500 mg three or four times daily. After remission occurs, it may be possible to lower the maintenance dose, generally to not less than 1 g daily, which must thereafter be continued indefinitely. Adverse effects include nausea and vomiting, nephrotic syndrome, a lupus-like syndrome, pemphigus, myasthenia, arthropathy, optic neuropathy, and various blood dyscrasias. Treatment should be monitored by frequent urinalysis and complete blood counts. Dietary copper should also be kept below 2 mg daily. Potassium disulfide, 20 mg three times daily with meals, reduces the intestinal absorption of copper and should also be prescribed.

For those patients who are unable to tolerate penicillamine, trientine, another chelating agent, may be used in a daily dose of 1–1.5 g. Trientine appears to have few adverse effects other than mild anemia due to iron deficiency in a few patients. Zinc acetate administered orally increases the fecal excretion of copper and is sometimes used for maintenance therapy. The dose is 50 mg three times a day. Zinc sulfate (200 mg/d orally) has also been used to decrease copper absorption. Zinc blocks copper absorption from the gastrointestinal tract by induction of intestinal cell metallothionein. Its main advantage is its low toxicity compared with other anticopper agents, although it may cause gastric irritation when first introduced.

Preparations Available

**Amantadine** (Symmetrel, others)
Oral: 100 mg capsules; 10 mg/mL syrup

**Benztropine** (Cogentin, others)
Oral: 0.5, 1, 2 mg tablets
Parenteral: 1 mg/mL for injection

**Biperiden** (Akineton)
Oral: 2 mg tablets
Parenteral: 5 mg/mL for injection
**Bromocriptine** (Parlodel)
Oral: 2.5 mg tablets; 5 mg capsules

**Carbidopa** (Lodosyn)
Oral: 25 mg tablets

**Carbidopa/levodopa** (Sinemet)
Oral: 10 mg carbidopa and 100 mg levodopa, 25 mg carbidopa and 100 mg levodopa, 25 mg carbidopa and 250 mg levodopa tablets
Oral sustained-release (Sinemet CR): 25 mg carbidopa and 100 mg levodopa; 50 mg carbidopa and 200 mg levodopa

**Entacapone** (Comtan)
Oral: 200 mg tablets

**Levodopa** (Dopar, Larodopa)
Oral: 100, 250, 500 mg tablets, capsules

**Orphenadrine** (various)
Oral: 100 mg tablets
Oral sustained-release: 100 mg tablets
Parenteral: 30 mg/mL for injection

**Penicillamine** (Cuprimine, Depen)
Oral: 125, 250 mg capsules; 250 mg tablets

**Pergolide** (Permax)
Oral: 0.05, 0.25, 1 mg tablets

**Pramipexole** (Mirapex)
Oral: 0.125, 0.25, 1, 1.5 mg tablets

**Procyclidine** (Kemadrin)
Oral: 5 mg tablets

**Ropinirole** (Requip)
Oral: 0.25, 0.5, 1, 2, 5 mg tablets

**Selegiline** (deprenyl) (generic, Eldepryl)
Oral: 5 mg tablets

**Tolcapone** (Tasmar)
Oral: 100, 200 mg tablets

**Trientine** (Syprine)
Oral: 250 mg capsules

**Trihexyphenidyl** (Artane, others)
Oral: 2, 5 mg tablets; 2 mg/5 mL elixir
Oral sustained-release (Artane Sequels): 5 mg capsules

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**Chapter 29. Antipsychotic Agents & Lithium**

*Katzung PHARMACOLOGY, 9e > Section V. Drugs That Act in the Central Nervous System > Chapter 29. Antipsychotic Agents & Lithium >*

**Antipsychotic Agents**

*Deceased*

The terms **antipsychotic** and **neuroleptic** are used interchangeably to denote a group of drugs that have been used mainly for treating schizophrenia but are also effective in some other psychoses and agitated states.

**History**

Antipsychotic drugs have been used in western medicine for 50 years. Reserpine and chlorpromazine were the first drugs found to be useful in schizophrenia. Although chlorpromazine is still sometimes used for the treatment of psychoses, these forerunner drugs have been superseded by many newer agents. Their impact on psychiatry, however—especially on the treatment of schizophrenia—has been enormous: The number of patients requiring hospitalization in mental institutions has markedly decreased, and psychiatric thinking has shifted to a more biologic basis.
Nature of Psychosis & Schizophrenia

The term "psychosis" denotes a variety of mental disorders. Schizophrenia is a particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance.

The pathogenesis of schizophrenia is unknown. Largely as a result of research stimulated by the discovery of antipsychotic drugs, a genetic predisposition has been proposed as a necessary but not always sufficient condition underlying psychotic disorder. This assumption has been supported by the observed familial incidence of schizophrenia. Completion of the first phase of the human genome project increases the likelihood of identifying multiple genes that contribute to the various clinical phenotypes subsumed under the broad diagnostic classification of schizophrenia. At least one gene—that which encodes for neuregulin 1—is associated with schizophrenia in Icelandic and northern European populations. In what way it actually contributes to schizophrenia and whether it applies to other populations have yet to be determined. The molecular basis for schizophrenia thus continues to elude definition, but a great deal of effort has been expended in attempting to link the disorder with abnormalities of amine neurotransmitter function, especially that of dopamine (see The Dopamine Hypothesis). The defects of this hypothesis are significant, and it is now appreciated that the disorder is far more complex than originally supposed.

Basic Pharmacology of Antipsychotic Agents

Chemical Types

A number of chemical structures have been associated with antipsychotic properties. The drugs can be classified into several groups as shown in Figures 29–1 and 29–2.
Structural formulas of some older antipsychotic drugs: phenothiazines, thioxanthenes, and butyrophenones. Only representative members of each type are shown.

**PHENOTHIAZINE DERIVATIVES**

- **Phenothiazine nucleus**
  - **Chlorpromazine** \((2) - Cl\), \((10) - \text{CH}_2 - \text{CH}_2 - \text{CH} - \text{N} - (\text{CH}_3)_2\)
  - **Thioridazine** \((2) - \text{SC}_3\), \((10) - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3\)

**Aliphatic side chain**

- **Trifluoperazine** \((2) - \text{CF}_3\), \((10) - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3\)
- **Perphenazine** \((2) - Cl\), \((10) - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{OH}\)
- **Huphenazine** \((2) - \text{CF}_3\), \((10) - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{OH}\)

**Piperazine side chain**

- **Thiothixene** \((2) - \text{SO}_2\text{N}(\text{CH}_2)_2\)

**THIOXANTHENE DERIVATIVE**

- **Su**

**BUTYROPHENONE**

- **Haloperidol**

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Figure 29–2.
Structural formulas of some newer antipsychotic drugs.

Phenothiazine Derivatives
The Dopamine Hypothesis

The dopamine hypothesis for schizophrenia is the most fully developed of several hypotheses and is the basis for much of the rationale for drug therapy. Several lines of circumstantial evidence suggest that excessive dopaminergic activity plays a role in the disorder: (1) most antipsychotic drugs strongly block postsynaptic D2 receptors in the central nervous system, especially in the mesolimbic-frontal system; (2) drugs that increase dopaminergic activity, such as levodopa (a precursor), amphetamines (releasers of dopamine), or apomorphine (a direct dopamine receptor agonist), either aggravate schizophrenia or produce psychosis de novo in some patients; (3) dopamine receptor density has been found, postmortem, to be increased in the brains of schizophrenics who have not been treated with antipsychotic drugs; (4) positron emission tomography (PET) has shown increased dopamine receptor density in both treated and untreated schizophrenics when compared with such scans of nonschizophrenic persons; and (5) successful treatment of schizophrenic patients has been reported to change the amount of homovanillic acid (HVA), a metabolite of dopamine, in the cerebrospinal fluid, plasma, and urine.

The dopamine hypothesis is far from complete, however. If an abnormality of dopamine physiology were completely responsible for the pathogenesis of schizophrenia, antipsychotic drugs would do a much better job of treating patients—but they are only partially effective for most and ineffective for some patients. Moreover, it appears that antagonists of the NMDA receptor such as phencyclidine, when administered to nonpsychotic subjects, produce much more "schizophrenia-like" symptoms than do dopamine agonists. The recent cloning and characterization of multiple dopamine receptor types may permit more direct testing of the dopamine hypothesis if drugs can be developed that act selectively on each receptor type. The traditional antipsychotics bind D2 50 times more avidly than D1 or D3 receptors. Until recently, the main thrust in drug development was to find agents that were more potent and more selective in blocking D2 receptors. The fact that several of the atypical antipsychotic drugs have much less effect on D2 receptors and yet are effective in schizophrenia has redirected attention to the role of other dopamine receptors and to nondopamine receptors, especially serotonin receptor subtypes that may mediate synergistic effects or protect against the extrapyramidal consequences of D2 antagonism. As a result of these considerations, the direction of research has changed to a greater focus on compounds that may act on several transmitter-receptor systems. The great hope is to produce drugs with greater efficacy and fewer adverse effects, especially extrapyramidal toxicity.

Lithium & Other Mood-Stabilizing Drugs

Lithium carbonate is often referred to as an "antimanic" drug, but in many parts of the world it is considered a "mood-stabilizing" agent because of its primary action of preventing mood swings in patients with bipolar affective (manic-depressive) disorder. Discovery of its benefits was based on an incorrect hypothesis and extremely good fortune in choosing the correct dosage. Carbamazepine has also been recognized as effective in some groups of manic-depressive patients despite not being formally approved for such use. Valproate has recently been approved for the treatment of mania and is being evaluated as a mood stabilizer. Atypical antipsychotics, beginning with olanzapine, are being investigated and approved as antimanic agents and potential mood stabilizers.
Nature of Bipolar Affective Disorder

Bipolar affective (manic-depressive) disorder is a frequently diagnosed and very serious psychiatric disorder. Patients with cyclic attacks of mania have many symptoms of paranoid schizophrenia (grandiosity, bellicosity, paranoid thoughts, and overactivity). The gratifying response to lithium therapy of patients with bipolar disorder has made such diagnostic distinctions important.

The episodes of mood swings characteristic of this condition are generally unrelated to life events. The exact biologic disturbance has not been identified, but a preponderance of catecholamine-related activity is thought to be present. Drugs that increase this activity tend to exacerbate mania, whereas those that reduce activity of dopamine or norepinephrine relieve mania. Acetylcholine or glutamate may also be involved. The nature of the abrupt switch from mania to depression experienced by some patients is uncertain. Bipolar disorder has a strong familial component. Genetic studies have identified at least three possible linkages to different chromosomes.

Basic Pharmacology of Lithium

Pharmacokinetics

Lithium is a small monovalent cation. Its pharmacokinetics are summarized in Table 29–5.

<table>
<thead>
<tr>
<th>Table 29–5. Pharmacokinetics of Lithium.</th>
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<tbody>
<tr>
<td><strong>Absorption</strong></td>
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<td><strong>Distribution</strong></td>
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<tr>
<td><strong>Metabolism</strong></td>
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<tr>
<td><strong>Excretion</strong></td>
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<tr>
<td><strong>Target plasma concentration</strong></td>
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<tr>
<td><strong>Dosage</strong></td>
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Pharmacodynamics

Despite considerable investigation, the mode of action of lithium remains unclear. The major possibilities being investigated include (1) effects on electrolytes and ion transport; (2) effects on neurotransmitters and their release; and (3) effects on second messengers and intracellular enzymes that mediate transmitter action. The last of these three approaches appears to be the most promising.

Effects on Electrolytes and Ion Transport

Lithium is closely related to sodium in its properties. It can substitute for sodium in generating action potentials and in Na⁺-Na⁺ exchange across the membrane. It inhibits the latter process, i.e,
Li⁺-Na⁺ exchange is gradually slowed after lithium is introduced into the body. At therapeutic concentrations (around 1 mmol/L), it does not significantly affect the Na⁺/Ca²⁺ exchange process or the Na⁺/K⁺ ATPase sodium pump.

Effects on Neurotransmitters

Lithium appears to enhance some of the actions of serotonin, though findings have been contradictory. Its effects on norepinephrine are variable. The drug may decrease norepinephrine and dopamine turnover, and these effects, if confirmed, might be relevant to its antimanic action. Lithium also appears to block the development of dopamine receptor supersensitivity that may accompany chronic therapy with antipsychotic agents. Finally, lithium may augment the synthesis of acetylcholine, perhaps by increasing choline uptake into nerve terminals. Some clinical studies have suggested that increasing cholinergic activity may mitigate mania. However, as noted below, a second-messenger effect of lithium may obviate any effect of increased acetylcholine release.

Effects on Second Messengers

One of the best-defined effects of lithium is its action on inositol phosphates. Early studies of lithium demonstrated changes in brain inositol phosphate levels, but the significance of these changes was not appreciated until the second-messenger roles of inositol-1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG) were discovered. As described in Chapter 2: Drug Receptors & Pharmacodynamics, IP₃ and DAG are important second messengers for both α-adrenergic and muscarinic transmission. Lithium inhibits several important enzymes in the normal recycling of membrane phosphoinositides, including conversion of IP₂ to IP₁ (inositol monophosphate) and the conversion of IP to inositol (Figure 29–4). This block leads to a depletion of phosphatidylinositol-4,5-bisphosphate (PIP₂), the membrane precursor of IP₃ and DAG. Over time, the effects of transmitters on the cell will diminish in proportion to the amount of activity in the PIP₂-dependent pathways. Before therapy, such activity might be greatly increased in mania; thus, lithium could cause a selective depression of the overactive circuits.

Figure 29–4.

Effect of lithium on the IP₃ and DAG second-messenger system. The schematic diagram shows the synaptic membrane of a neuron. (PIP₂, phosphatidylinositol-4,5-bisphosphate; PLC, phospholipase-C; G, coupling protein; EFFECTS, activation of protein kinase C, mobilization of intracellular Ca²⁺, etc.) Lithium, by inhibiting the recycling of inositol substrates, may cause
Lithium may also act by other mechanisms.

Studies of noradrenergic effects in isolated brain tissue indicate that lithium can inhibit norepinephrine-sensitive adenylyl cyclase. Such an effect could relate to both its antidepressant and its antimanic effects. The relationship of these effects to lithium's actions on IP₃ mechanisms is currently unknown.

Since lithium affects second-messenger systems involving both activation of adenylyl cyclase and phosphoinositol turnover, it is not surprising that G proteins are also found to be affected. Several studies suggest that lithium may uncouple receptors from their G proteins; indeed, two of lithium's most common side effects, polyuria and subclinical hypothyroidism, may be due to uncoupling of the vasopressin and TSH receptors from their G proteins.

The major current working hypothesis for lithium's therapeutic mechanism of action supposes that its effects on phosphoinositol turnover, leading to an early relative reduction of myoinositol in human brain, are part of an initiating cascade of intracellular changes. Effects on specific isoforms of protein kinase C may be most relevant. Alterations of protein kinase C-mediated signaling alter gene expression and the production of proteins implicated in long-term neuroplastic events that could underlie long-term mood stabilization.

Clinical Pharmacology of Lithium

Bipolar Affective Disorder

Until recently, lithium carbonate was the universally preferred treatment for bipolar disorder, especially in the manic phase. With the approval of valproate and olanzapine for this indication, a smaller fraction of bipolar patients now receive lithium. This trend is reinforced by the slow onset of action of lithium, which has often been supplemented with concurrent use of antipsychotic drugs or potent benzodiazepines in severely manic patients. The overall success rate for achieving remission from the manic phase of bipolar disorder has been reported to be 60–80%. However, among patients who require hospitalization, success rates are considerably lower. A similar situation applies to maintenance treatment, which is about 60% effective overall but less in severely ill patients. These considerations have led to increased use of combined treatment in severe cases. After mania is controlled, the antipsychotic drug may be stopped, then the benzodiazepine and lithium continued as maintenance therapy.

The depressive phase of manic-depressive disorder often requires concurrent use of an antidepressant drug (see Chapter 30: Antidepressant Agents). Tricyclic antidepressant agents have been linked to precipitation of mania, with more rapid cycling of mood swings, although most patients do not show this effect. Selective serotonin reuptake inhibitors are less likely to induce mania but may have limited efficacy. Bupropion has shown some promising effects but may induce mania—like tricyclic antidepressants—at higher doses. As shown in recent controlled trials, the anticonvulsant lamotrigine is effective for many patients with bipolar depression. For some patients, however, one of the older MAO inhibitors may be the antidepressant of choice.

Unlike antipsychotic or antidepressant drugs, which exert several actions on the central or autonomic nervous system, lithium ion at therapeutic concentrations is devoid of autonomic blocking effects and of activating or sedating effects, though it can produce nausea and tremor.

Another attribute of considerable interest has been the prophylactic use of lithium in preventing
both mania and depression. It is indeed remarkable that a so-called functional psychosis can be controlled so easily by such a simple chemical as lithium carbonate.

Other Applications

Acute endogenous depression is not generally considered to be an indication for treatment with lithium. Alcohol and substance abuse have a high association with bipolar illness. However, recurrent endogenous depressions with a cyclic pattern are controlled by either lithium or imipramine, both of which are superior to a placebo.

Schizoaffective disorders are characterized by a mixture of schizophrenic symptoms and altered affect in the form of depression or excitement. Antipsychotic drugs alone or combined with lithium are used in the excited as well as in the maintenance phases; clozapine may be particularly effective. Various antidepressants are added if depression is present, but none has been adequately studied in this condition.

While lithium alone is rarely successful in treating schizophrenia, adding it to an antipsychotic may salvage an otherwise treatment-resistant patient. Carbamazepine may work equally well when added to an antipsychotic.

An interesting application of lithium that is relatively well supported by controlled studies is as an adjunct to tricyclic antidepressants and selective serotonin reuptake inhibitors in patients with unipolar depression who do not respond fully to monotherapy with the antidepressant. For this application, concentrations of lithium at the lower end of the recommended range for manic depressive illness appear to be adequate.

Monitoring Treatment

Clinicians have relied heavily on measurements of serum concentrations for assessing both the dosage required for satisfactory treatment of acute mania and the adequacy of maintenance treatment. These measurements are customarily taken 10–12 hours after the last dose, so all data in the literature pertaining to these concentrations reflect this interval.

An initial determination of serum lithium concentration should be obtained about 5 days after the start of treatment, at which time steady-state conditions should have been attained for the dosage chosen. If the clinical response suggests a change in dosage, simple arithmetic (new dose equals present dose times desired blood level divided by present blood level) should produce the desired level. The serum concentration attained with the adjusted dosage can be checked in another 5 days. Once the desired concentration has been achieved, levels can be measured at increasing intervals unless the schedule is influenced by intercurrent illness or the introduction of a new drug into the treatment program.

Maintenance Treatment

The decision to use lithium as prophylactic treatment depends on many factors: the frequency and severity of previous episodes, a crescendo pattern of appearance, and the degree to which the patient is willing to follow a program of indefinite maintenance therapy. If the present attack was the patient's first or if the patient is unreliable, one might prefer to terminate treatment after the attack has subsided. Patients who have one or more episodes of illness per year are candidates for maintenance treatment. While some patients can be maintained with serum levels as low as 0.6 meq/L, the best results in groups of patients have been obtained with higher levels, such as 0.9
meq/L.

Drug Interactions

Renal clearance of lithium is reduced about 25% by diuretics (eg, thiazides), and doses may need to be reduced by a similar amount. A similar reduction in lithium clearance has been noted with several of the newer nonsteroidal anti-inflammatory drugs that block synthesis of prostaglandins. This interaction has not been reported for either aspirin or acetaminophen. All neuroleptics tested to date, with the possible exception of clozapine and the newer antipsychotics, may produce more severe extrapyramidal syndromes when combined with lithium.

Adverse Effects & Complications

Many adverse effects associated with lithium treatment occur at varying times after treatment is started. Some are harmless, but it is important to be alert to adverse effects that may signify impending serious toxic reactions.

Neurologic and Psychiatric Adverse Effects

Tremor is one of the most frequent adverse effects of lithium treatment, occurring at therapeutic dosage levels. Propranolol and atenolol, which have been reported to be effective in essential tremor, also alleviate lithium-induced tremor. Other reported neurologic abnormalities include choreoathetosis, motor hyperactivity, ataxia, dysarthria, and aphasia. Psychiatric disturbances at toxic concentrations are generally marked by mental confusion and withdrawal or bizarre motor movements. Appearance of any new neurologic or psychiatric symptoms or signs is a clear indication for temporarily stopping treatment with lithium and close monitoring of serum levels.

Effects on Thyroid Function

Lithium probably decreases thyroid function in most patients exposed to the drug, but the effect is reversible or nonprogressive. Few patients develop frank thyroid enlargement, and fewer still show symptoms of hypothyroidism. Although initial thyroid testing followed by regular monitoring of thyroid function has been proposed, such procedures are not cost-effective. Obtaining a serum TSH concentration every 6–12 months, however, is prudent.

Renal Adverse Effects

Polydipsia and polyuria are frequent but reversible concomitants of lithium treatment, occurring at therapeutic serum concentrations. The principal physiologic lesion involved is loss of the ability of the collecting tubule to conserve water under the influence of antidiuretic hormone, resulting in excessive free water clearance (nephrogenic diabetes insipidus). Lithium-induced diabetes insipidus is resistant to vasopressin but responds to amiloride.

An extensive literature has accumulated concerning other forms of renal dysfunction during long-term lithium therapy, including chronic interstitial nephritis and minimal change glomerulopathy with nephrotic syndrome. Some instances of decreased glomerular filtration rate have been encountered but no instances of marked azotemia or renal failure.

Patients receiving lithium should avoid dehydration and the associated increased concentration of lithium in urine. Periodic tests of renal concentrating ability should be performed to detect changes.
Edema

Edema is a frequent adverse effect of lithium treatment and may be related to some effect of lithium on sodium retention. Although weight gain may be expected in patients who become edematous, water retention does not account for the weight gain observed in up to 30% of patients taking lithium.

Cardiac Adverse Effects

The bradycardia-tachycardia ("sick sinus") syndrome is a definite contraindication to the use of lithium because the ion further depresses the sinus node. T wave flattening is often observed on the ECG but is of questionable significance.

Use during Pregnancy

Renal clearance of lithium increases during pregnancy and reverts to lower levels immediately after delivery. A patient whose serum lithium concentration is in a good therapeutic range during pregnancy may develop toxic levels following delivery. Special care in monitoring lithium levels is needed at these times. Lithium is transferred to nursing infants through breast milk, in which it has a concentration about one-third to one-half that of serum. Lithium toxicity in newborns is manifested by lethargy, cyanosis, poor suck and Moro reflexes, and perhaps hepatomegaly.

The issue of dysmorphogenesis is not settled. An earlier report suggested an increase in the frequency of cardiac anomalies, especially Ebstein's anomaly, in lithium babies, but the most recent data suggest that lithium carries a relatively low risk of teratogenic effects.

Miscellaneous Adverse Effects

Transient acneiform eruptions have been noted early in lithium treatment. Some of them subside with temporary discontinuance of treatment and do not recur with its resumption. Folliculitis is less dramatic and probably occurs more frequently. Leukocytosis is always present during lithium treatment, probably reflecting a direct effect on leukopoiesis rather than mobilization from the marginal pool. This "adverse effect" has now become a therapeutic effect in patients with low leukocyte counts.

Overdoses

Therapeutic overdoses are more common than those due to deliberate or accidental ingestion of the drug. Therapeutic overdoses are usually due to accumulation of lithium resulting from some change in the patient's status, such as diminished serum sodium, use of diuretics, or fluctuating renal function. Since the tissues will have already equilibrated with the blood, the plasma concentrations of lithium may not be excessively high in proportion to the degree of toxicity; any value over 2 meq/L must be considered as indicating likely toxicity. As lithium is a small ion, it is dialyzed readily. Both peritoneal dialysis and hemodialysis are effective, though the latter is preferred. Dialysis should be continued until the plasma concentration falls below the usual therapeutic range.

Valproic Acid

Valproic acid (valproate), discussed in detail elsewhere as an antiepileptic (see Chapter 24: Antiseizure Drugs), has been demonstrated to have antimanic effects and is now being widely used for this indication in the USA. Overall, it shows efficacy equivalent to that of lithium during the
early weeks of treatment. Importantly, valproic acid has been effective in some patients who have failed to respond to lithium. Moreover, its side effect profile is such that one can rapidly increase the dose over a few days to produce blood levels in the apparent therapeutic range, with nausea being the only limiting factor in some patients. The starting dose is 750 mg/d, increasing rapidly to the 1500–2000 mg range with a recommended maximum dose of 60 mg/kg/d.

Combinations of valproic acid with other psychotropic medications likely to be used in the management of either phase of bipolar illness are generally well tolerated. Valproic acid is becoming recognized as an appropriate first-line treatment for mania, though it is not clear that it will be as effective as lithium as a maintenance treatment in all subsets of patients. Many clinicians argue for combining valproic acid and lithium in patients who do not fully respond to either agent alone.

**Carbamazepine**

Carbamazepine has been considered to be a reasonable alternative to lithium when the latter is less than optimally efficacious. It may be used to treat acute mania and also for prophylactic therapy. Adverse effects (discussed in Chapter 24: Antiseizure Drugs) are generally no greater and sometimes are less than those associated with lithium. Carbamazepine may be used alone or, in refractory patients, in combination with lithium or, rarely, valproate. The mode of action of carbamazepine is unclear, but it may reduce the sensitization of the brain to repeated episodes of mood swing. Such a mechanism might be similar to its anticonvulsant effect.

The use of carbamazepine as a mood stabilizer is similar to its use as an anticonvulsant (see Chapter 24: Antiseizure Drugs). Dosage usually begins with 200 mg twice daily, with increases as needed. Maintenance dosage is similar to that used for treating epilepsy, ie, 800–1200 mg/d. Plasma concentrations between 3 and 14 mg/L are considered desirable, though no therapeutic range has been established. Although blood dyscrasias have figured prominently in the adverse effects of carbamazepine when it is used as an anticonvulsant, they have not been a major problem with its use as a mood stabilizer. Overdoses of the drug are a major emergency and should be managed in general like overdoses of tricyclic antidepressants.

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**Preparations Available**

**Antipsychotic Agents**

**Aripiprazole** (Abilify)

Oral: 10, 15, 20, 30 mg tablets

**Chlorpromazine** (generic, Thorazine, others)

Oral: 10, 25, 50, 100, 200 mg tablets; 10 mg/5 mL syrup; 30, 100 mg/mL concentrate

Oral sustained-release: 30, 75, 150 mg capsules

Rectal: 25, 100 mg suppositories
Parenteral: 25 mg/mL for IM injection

**Clozapine** (generic, Clozaril)
Oral: 25, 100 mg tablets

**Fluphenazine** (generic, Permitil, Prolixin)
Oral: 1, 2.5, 5, 10 mg tablets; 2.5 mg/5 mL elixir; 5 mg/mL concentrate
Parenteral: 2.5 mg/mL for IM injection

**Fluphenazine esters** (generic [decanoate only], Prolixin Enanthate, Prolixin Decanoate)
Parenteral: 25 mg/mL

**Haloperidol** (generic, Haldol)
Oral: 0.5, 1, 2, 5, 10, 20 mg tablets; 2 mg/mL concentrate
Parenteral: 5 mg/mL for IM injection

**Haloperidol ester** (Haldol Decanoate)
Parenteral: 50, 100 mg/mL for IM injection

**Loxapine** (Loxitane)
Oral: 5, 10, 25, 50 mg capsules; 25 mg/mL concentrate
Parenteral: 50 mg/mL for IM injection

**Mesoridazine** (Serentil)
Oral: 10, 25, 50, 100 mg tablets; 25 mg/mL concentrate
Parenteral: 25 mg/mL for IM injection

**Molindone** (Moban)
Oral: 5, 10, 25, 50, 100 mg tablets; 20 mg/mL concentrate

**Olanzapine** (Zyprexa)
Oral: 2.5, 5, 7.5, 10, 15, 20 mg tablets; 5, 10, 15, 20 mg orally disintegrating tablets.

**Perphenazine** (generic, Trilafon)
Oral: 2, 4, 8, 16 mg tablets; 16 mg/5 mL concentrate
Parenteral: 5 mg/mL for IM or IV injection

**Pimozide** (Orap)

Oral: 1, 2 mg tablets

**Prochlorperazine** (generic, Compazine)

Oral: 5, 10, mg tablets; 5 mg/5 mL syrup

Oral sustained-release: 10, 15 mg capsules

Rectal: 2.5, 5, 25 mg suppositories

Parenteral: 5 mg/mL for IM injection

**Promazine** (generic, Sparine)

Oral: 25, 50 mg tablets

Parenteral: 25, 50 mg/mL for IM injection

**Quetiapine** (Seroquel)

Oral: 25, 100, 200, 300 mg tablets

**Risperidone** (Risperdal)

Oral: 0.25, 0.5, 1, 2, 3, 4 mg tablets; 1 mg/mL oral solution

**Thioridazine** (generic, Mellaril, others)

Oral: 10, 15, 25, 50, 100, 150, 200 mg tablets; 30, 100 mg/mL concentrate; 25, 100 mg/5 mL suspension

**Thiothixene** (generic, Navane)

Oral: 1, 2, 5, 10, 20 mg capsules; 5 mg/mL concentrate

**Trifluoperazine** (generic, Stelazine)

Oral: 1, 2, 5, 10 mg tablets; 10 mg/mL concentrate

Parenteral: 2 mg/mL for IM injection

**Triflupromazine** (Vesprin)

Parenteral: 10, 20 mg/mL for IM injection

**Ziprasidone** (Geodon)
Oral: 20, 40, 60, 80 mg capsules

Parenteral: 20 mg/mL for IM injection

Mood Stabilizers

**Carbamazepine** (generic, Tegretol, others)

Oral: 200 mg tablets, 100 mg chewable tablets; 100 mg/5 mL oral suspension.

Oral extended-release: 100, 200, 400 mg tablets; 200, 300 mg capsules

**Divalproex** (Depakote)

Oral: 125, 250, 500 mg delayed-release tablets

**Lithium carbonate** (generic, Eskalith) (Note: 300 mg lithium carbonate = 8.12 meq Li⁺.)

Oral: 150, 300, 600 mg capsules; 300 mg tablets; 8 meq/5 mL syrup

Oral sustained-release: 300, 450 mg tablets

**Valproic acid** (generic, Depakene)

Oral: 250 mg capsules; 250 mg/5 mL syrup

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**Chapter 30. Antidepressant Agents**

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**Antidepressant Agents: Introduction**

Major depression is one of the most common psychiatric disorders. At any given moment, about 5–6% of the population is depressed (point prevalence), and an estimated 10% of people may become depressed during their lives (lifetime prevalence). The symptoms of depression are often subtle and unrecognized both by patients and by physicians. Patients with vague complaints that resist explanation as manifestations of somatic disorders and those who might be simplistically described as "neurotic" should be suspected of being depressed.

Depression is a heterogeneous disorder that has been characterized and classified in a variety of ways. According to the American Psychiatric Association's fourth edition (1994) of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, several diagnoses of affective disorders are possible. Major depression and dysthymia (minor) are pure depressive syndromes, whereas bipolar disorder and cyclothymic disorder signify depression in association with mania. A simplified classification based on presumed origin is as follows: (1) "reactive" or "secondary" depression (most common), occurring in response to real stimuli such as grief, illness, etc; (2) "endogenous" depression, a genetically determined biochemical disorder manifested by inability to experience ordinary pleasure or to cope with ordinary life events; and (3) depression associated with bipolar affective (manic-depressive) disorder. Drugs discussed in this chapter are used chiefly in
management of the second type. Table 30–1 indicates how the three types may be differentiated.

<table>
<thead>
<tr>
<th>Type</th>
<th>Diagnostic Features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive</td>
<td>Loss (adverse life events). Physical illness (myocardial infarct, cancer). Drugs (antihypertensives, alcohol, hormones). Other psychiatric disorders (senility).</td>
<td>More than 60% of all depressions. Core depressive syndrome: depression, anxiety, bodily complaints, tension, guilt. May respond spontaneously or to a variety of ministrations.</td>
</tr>
<tr>
<td>Major depressive (endogenous)</td>
<td>Precipitating life event not adequate for degree of depression. Autonomous (unresponsive to changes in life). May occur at any age (childhood to old age). Biologically determined (family history).</td>
<td>About 25% of all depressions. Core depressive syndrome plus &quot;vital&quot; signs: abnormal rhythms of sleep, motor activity, libido, appetite. Usually responds specifically to antidepressants or electroconvulsive therapy. Tends to recur throughout life.</td>
</tr>
<tr>
<td>Bipolar affective (manic-depressive)</td>
<td>Characterized by episodes of mania. Cyclic; mania alone, rare; depression alone, occasional; mania-depression, usual.</td>
<td>About 10–15% of all depressions. May be misdiagnosed as endogenous if hypomanic episodes are missed. Lithium carbonate stabilizes mood. Mania may require antipsychotic drugs as well; depression managed with antidepressants.</td>
</tr>
</tbody>
</table>

An intensive effort to formalize guidelines for the treatment of depression is provided by the cross-disciplinary publication of the Depression Guideline Panel (1993) and its update on newer pharmacotherapies (Mulrow et al, 1999). Pharmacologic treatment is emphasized, though a continuing role for electroconvulsive therapy for delusional or severe forms of life-threatening depression is noted. Despite intensive research, the mechanisms of action of various pharmacologic treatments are still not understood, though most are believed to involve effects on two monoamine neurotransmitters: serotonin and norepinephrine.

The Pathogenesis of Major Depression: The Amine Hypothesis

Soon after the introduction of reserpine in the early 1950s, it became apparent that the drug could induce depression in patients being treated for hypertension and schizophrenia as well as in normal subjects. Within the next few years, pharmacologic studies revealed that the principal mechanism of action of reserpine was to inhibit the storage of amine neurotransmitters such as serotonin and norepinephrine in the vesicles of presynaptic nerve endings. Reserpine induced depression and depleted stores of amine neurotransmitters; therefore, it was reasoned, depression must be associated with decreased functional amine-dependent synaptic transmission. This idea provided the basis for what became known as the amine hypothesis of depression. A major puzzle in applying this hypothesis was the fact that although the pharmacologic actions of both tricyclic and MAO inhibitor classes of antidepressants are prompt, the clinical effects require weeks to become manifest. Attempts have been made to explain this observation by invoking slow compensatory responses to the initial blockade of amine reuptake or MAO inhibition (see below).
While the amine hypothesis is undoubtedly too simplistic, it has provided the major experimental models for the discovery of new antidepressant drugs. As a result, all the currently available antidepressant drugs—except bupropion—are classified as having their primary actions on the metabolism, reuptake, or selective receptor antagonism of serotonin, norepinephrine, or both.

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**Basic Pharmacology of Antidepressants**

**Chemistry**

A variety of different chemical structures have been found to have antidepressant activity. With the possible exception of bupropion, however, the core antidepressant action of even the newest agents derives from mechanisms engaged by antidepressants introduced 4 decades ago.

**Tricyclic Antidepressants (TCAs)**

Tricyclic antidepressants—so called because of the characteristic three-ring nucleus—have been used clinically for four decades (Figure 30–1). They closely resemble the phenothiazines chemically and, to a lesser extent, pharmacologically. Like the latter drugs, they were first thought to be useful as antihistamines with sedative properties and later as antipsychotics. The discovery of their antidepressant properties was a fortuitous clinical observation. **Imipramine** and **amitriptyline** are the prototypical drugs of the class as mixed norepinephrine and serotonin uptake inhibitors though they also have several other properties.

**Figure 30–1.**
Structural relationships between various tricyclic antidepressants (TCAs).

Heterocyclics; Second- and Third-Generation Drugs

Between 1980 and 1996, a number of heterocyclic agents denoted as second-generation and third-generation or heterocyclic antidepressants were introduced. Four of the agents classified as "second-generation" are available for clinical use in the USA and are shown in Figure 30–2. Amoxapine and maprotiline resemble the structure of the tricyclic agents, while trazodone and bupropion are distinctive. The heterocyclic agents are not notably different from the older agents in potency. Since 1990, venlafaxine, a chemically unique third-generation agent; mirtazapine, an analog of a widely used European antidepressant; and nefazodone, developed on the basis of trazodone, have been introduced. The structures of these compounds are shown in Figure 30–3.

Figure 30–2.
Second-generation antidepressants.

**Figure 30–3.**

- **Amoxapine**
- **Maprotiline**
- **Trazodone**
- **Bupropion**

Third-generation antidepressants.

Selective Serotonin Reuptake Inhibitors (SSRIs)
Among the major drawbacks of most first-generation antidepressants have been their many "irrelevant" pharmacologic actions, a trait inherited from the phenothiazine antipsychotic agents. As far as has been determined, the antimuscarinic, antihistaminic, and α-adrenoceptor-blocking actions of tricyclic antidepressants contribute only to the toxicity of these agents. Since the introduction of fluoxetine—an effective and more selective antidepressant with minimal autonomic toxicity—four more selective serotonin reuptake inhibitors have been introduced as well as the active enantiomeric form of one, (S)-citalopram. All are structurally distinct from the tricyclic molecules (Figure 30–4).

Figure 30–4.

Selective serotonin reuptake inhibitors (SSRIs).

Monoamine Oxidase (MAO) Inhibitors

MAO inhibitors may be classified as hydrazides, exemplified by the C–N–N moiety, as is the case
with **phenelzine** and **isocarboxazid** (no longer marketed); or nonhydrazides, which lack such a moiety, as with **tranylcypromine** (Figure 30–5). Tranylcypromine closely resembles dextroamphetamine, which is itself a weak inhibitor of MAO. Tranylcypromine retains some of the sympathomimetic characteristics of the amphetamines. The hydrazides appear to combine irreversibly with the enzyme, while tranylcypromine has a prolonged duration of effect even though it is not bound irreversibly. These older MAO inhibitors are nonselective inhibitors of both MAO-A and MAO-B.

![Phenelzine](image1.png)

![Tranylcypromine](image2.png)

Some monoamine oxidase inhibitors. Phenelzine is the hydrazide of phenylethylamine (Figure 9–3), while tranylcypromine has a cyclopropyl amine side chain and closely resembles dextroamphetamine (see Figure 9–4). These agents are unselective and produce an extremely long-lasting inhibition of the enzyme.

Pharmacokinetics

**Tricyclics**

Most tricyclics are incompletely absorbed and undergo significant first-pass metabolism. As a result of high protein binding and relatively high lipid solubility, volumes of distribution tend to be very large. Tricyclics are metabolized by two major routes: transformation of the tricyclic nucleus and alteration of the aliphatic side chain. Monodemethylation of tertiary amines leads to active metabolites such as desipramine and nortriptyline (which are themselves available as drugs; Figure 30–1). The pharmacokinetic parameters of various antidepressants are summarized in Table 30–2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (percent)</th>
<th>Protein Binding (percent)</th>
<th>Plasma $t_{1/2}$ (hours)</th>
<th>Active Metabolites</th>
<th>Volume of Distribution (L/kg)</th>
<th>Therapeutic Plasma Concentrations (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>31–61</td>
<td>82–96</td>
<td>31–46</td>
<td>Nortriptyline</td>
<td>5–10</td>
<td>80–200 total</td>
</tr>
<tr>
<td></td>
<td>nd</td>
<td>nd</td>
<td>8</td>
<td>7,8-Hydroxy</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>nd</td>
<td>nd</td>
<td>8</td>
<td>7,8-Hydroxy</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Bupropion</td>
<td>60–80</td>
<td>85</td>
<td>14–37</td>
<td>Hydroxy, threohydro, erythrohydro</td>
<td>20–30</td>
<td>25–100</td>
</tr>
<tr>
<td>Citalopram</td>
<td>51–93</td>
<td>70–80</td>
<td>23–75</td>
<td>Desmethyl</td>
<td>12–16</td>
<td>nd</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>nd</td>
<td>nd</td>
<td>22–84</td>
<td>Desmethyl</td>
<td>7–20</td>
<td>240–700</td>
</tr>
<tr>
<td>Desipramine</td>
<td>60–70</td>
<td>73–90</td>
<td>14–62</td>
<td>Hydroxy</td>
<td>22–59</td>
<td>&gt; 125</td>
</tr>
<tr>
<td>Doxepin</td>
<td>13–45</td>
<td>nd</td>
<td>8–24</td>
<td>Desmethyl</td>
<td>9–33</td>
<td>30–150</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>80</td>
<td>56</td>
<td>27–59</td>
<td>5-Desmethyl</td>
<td>12</td>
<td>nd</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>70</td>
<td>94</td>
<td>24–96</td>
<td>Norfluoxetine</td>
<td>12–97</td>
<td>nd</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>&gt; 90</td>
<td>77</td>
<td>7–63</td>
<td>None</td>
<td>&gt; 5</td>
<td>nd</td>
</tr>
<tr>
<td>Imipramine</td>
<td>29–77</td>
<td>76–95</td>
<td>9–24</td>
<td>Desipramine</td>
<td>15–30</td>
<td>&gt; 180 total</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>66–75</td>
<td>88</td>
<td>21–52</td>
<td>Desmethyl</td>
<td>15–28</td>
<td>200–300</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>nd</td>
<td>nd</td>
<td>20–40</td>
<td>Desmethyl</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>15–23</td>
<td>98</td>
<td>2–4</td>
<td>Hydroxy, m-chlorophenyl piperazine</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>32–79</td>
<td>93–95</td>
<td>18–93</td>
<td>10-Hydroxy</td>
<td>21–57</td>
<td>50–150</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>50</td>
<td>95</td>
<td>24</td>
<td>None</td>
<td>28–31</td>
<td>nd</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>77–93</td>
<td>90–95</td>
<td>54–198</td>
<td>nd</td>
<td>19–57</td>
<td>70–170</td>
</tr>
<tr>
<td>Sertraline</td>
<td>nd</td>
<td>98</td>
<td>22–35</td>
<td>Desmethyl</td>
<td>20</td>
<td>nd</td>
</tr>
<tr>
<td>Trazodone</td>
<td>nd</td>
<td>nd</td>
<td>4–9</td>
<td>m-Chloro-phenyl-piperazine</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>nd</td>
<td>27–30</td>
<td>4–10</td>
<td>O-Desmethyl</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

1. Range includes active metabolites.
2. nd = no data found.

**Heterocyclics**

The pharmacokinetcs of these drugs are similar to those of the tricyclics (Table 30–2). Some may have active metabolites. Trazodone and venlafaxine have short plasma half-lives, which mandates divided doses during the day when beginning treatment, though once-a-day dosing may be possible later. Extended-release forms of bupropion and venlafaxine allow for once-a-day dosing in some patients from the outset.

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

The pharmacokinetic parameters of these drugs are summarized in Table 30–2. Fluoxetine is notable for the long half-life of its active metabolite, norfluoxetine (7–9 days at steady state). This long \( t_{1/2} \) has allowed for the introduction of a formulation for once-weekly dosing. Fluoxetine
inhibits various drug-metabolizing enzymes, which has led to a number of significant drug-drug interactions with other antidepressants and with other drugs as well. Sertraline and paroxetine have pharmacokinetic parameters similar to those of tricyclics. Citalopram and fluvoxamine resemble fluoxetine.

MAO Inhibitors

The monoamine oxidase inhibitors (MAOIs) are readily absorbed from the gastrointestinal tract. The hydrazide inhibitor phenelzine is acetylated in the liver and manifests differences in elimination depending on the acetylation phenotype of the individual (see Chapter 4: Drug Biotransformation). However, inhibition of MAO persists even after these drugs are no longer detectable in plasma. Therefore, conventional pharmacokinetic parameters (half-life, etc) are not very helpful in governing dosage. It is prudent to assume that the drug effect will persist for from 7 days (tranylcypromine) to 2 or 3 weeks (phenelzine) after discontinuance of the drug.

Pharmacodynamics

Action of Antidepressants on Biogenic Amine Neurotransmitters

The amine hypothesis was buttressed by studies on the mechanism of action of various types of antidepressant drugs (Figure 30–6). Tricyclics block the amine (norepinephrine or serotonin) reuptake pumps, which terminate amine neurotransmission (see Table 30–3 and Chapter 6: Introduction to Autonomic Pharmacology). Such an action presumably permits a longer sojourn of neurotransmitter at the receptor site. MAO inhibitors block a major degradative pathway for the amine neurotransmitters, which permits more amines to accumulate in presynaptic stores and more to be released. Some of the second-generation antidepressants have similar effects on amine neurotransmitters, while others have mild or minimal effects on reuptake or metabolism. In contrast, trazodone, nefazodone, and mirtazapine stand out as agents in which antagonism of subtypes of serotonin receptors (5-HT2A or 5-HT2C) may be important in their action. Mirtazapine is unique in including antagonism of α2 norepinephrine receptors as presumably contributing to its therapeutic effects. Bupropion has been found to alter the output of norepinephrine in humans following chronic administration through some as yet unidentified primary mechanism as well as occupying about 25% of dopamine uptake pumps in the brain as revealed by positron emission tomography. Since it has been shown that effective doses of SSRIs occupy 80% of serotonin uptake sites, the clinical relevance of 25% dopamine uptake occupancy is uncertain. Thus, even the newest antidepressants can still be categorized as working through serotonergic and noradrenergic effects with the possibility of a role for dopamine. A potential dopaminergic mechanism has often been invoked as relevant to the efficacy of MAOIs.

Figure 30–6.
Schematic diagram showing some of the potential sites of action of antidepressant drugs. Chronic therapy with these drugs has been proved to reduce reuptake of norepinephrine or serotonin (or both), reduce the number of postsynaptic receptors, and reduce the generation of cAMP. The MAO inhibitors act on MAO in the nerve terminals and cause the same effects on receptors and cAMP generation.

Receptor and Postreceptor Effects

Considerable attention has been paid to the ultimate postsynaptic effects of increased neurotransmitters in the synapses. In tests of postsynaptic effects, cAMP concentrations have consistently decreased rather than increased, in spite of the presumably longer duration of action of the transmitters. In addition, the number of postsynaptic β-adrenoceptors has shown a measurable decrease that follows the same delayed time course as clinical improvement in patients. Thus, the initial increase in neurotransmitter seen with some antidepressants appears to produce, over time, a compensatory decrease in receptor activity, ie, down-regulation of receptors. Decreases in norepinephrine-stimulated cAMP and in β-adrenoceptor binding have been conclusively shown for selective norepinephrine uptake inhibitors, those with mixed action on norepinephrine and serotonin, monoamine oxidase inhibitors, and even electroconvulsive therapy. Such changes do not consistently occur after the selective serotonin uptake inhibitors, α2 receptor antagonists, and mixed serotonin antagonists.

It has also been emphasized that enhanced serotonergic transmission, albeit mediated through diverse mechanisms, might be a common (but not universal) long-term effect of antidepressants. This could occur, for instance, without increasing the concentration of neurotransmitter at the receptor site if there were an increase in serotonin receptor sensitivity. Thus, chronic treatment with tricyclic agents or electroconvulsive shock increases the electrophysiologic response to microiontophoretically applied serotonin in various areas of the rat brain. And selective receptor antagonism of either norepinephrine or serotonin receptors may lead to enhanced extracellular serotonin due to the complex manner in which these neurotransmitters are interregulated. One current hypothesis holds that enhanced stimulation or responsiveness of postsynaptic 5-HT1A receptors is particularly important in the action of antidepressants.
Most recently, long-term intracellular changes involving phosphorylation of various regulatory elements, including those within the nucleus, have been implicated as relevant to antidepressant action. It is possible that effects on certain neurotrophic factors—factors critical to sustained survival and function of neurons in the adult nervous system—may be central to the actions of antidepressants.

No clinical studies have directly tested the relevance of these findings from animals for norepinephrine and serotonin function in humans and their relationship to the mode of action of antidepressants. One of the most interesting approaches has been to reduce the amino acid precursor of serotonin, tryptophan, in the diet and, by implication, the amount of available neurotransmitter in the brain, since tryptophan availability can be rate-limiting in the formation of serotonin under certain experimental conditions. Using this approach, it was found that a tryptophan-depleted diet produces low plasma tryptophan and acutely reverses antidepressant responses to SSRIs but not to selective or mixed norepinephrine uptake inhibitors. Similarly, depletion of the norepinephrine amino acid precursor tyrosine can reverse antidepressant effects of the relatively selective norepinephrine reuptake inhibitor, desipramine. These findings indirectly support the hypothesis that enhanced serotonin throughput is necessary for the antidepressant action of serotonin but not norepinephrine uptake inhibitors. The same appears to be true of norepinephrine throughput and norepinephrine reuptake inhibitors. However, tryptophan depletion does not consistently worsen the condition of unmedicated depressed patients. Thus, there is no clear relationship between serotonin and depression or antidepressant mechanisms in general.

Effects of Specific Antidepressants

Tricyclics

The first-generation antidepressants demonstrate varying degrees of selectivity for the reuptake pumps for norepinephrine and serotonin (Table 30–3). They also have numerous autonomic actions, as described below under Adverse Effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedative Action</th>
<th>Antimuscarinic Action</th>
<th>Serotonin</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0</td>
<td>0</td>
<td>+, 0</td>
<td>+, 0</td>
<td>+</td>
</tr>
<tr>
<td>Citalopram</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>0, +</td>
<td>0, +</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>---------------</td>
<td>----</td>
<td>----</td>
<td>-----</td>
<td>----</td>
<td>---</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Mirtazapine²</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>++</td>
<td>+++</td>
<td>±, 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>0</td>
<td>++</td>
<td>?</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trazodone</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>0, +</td>
</tr>
</tbody>
</table>

0 = none; + = slight; ++ = moderate; +++ = high; ? = uncertain.

²Significant α₂-adrenoceptor antagonism.

Second-Generation Agents

Amoxapine is a metabolite of the antipsychotic drug loxapine and retains some of its antipsychotic action and dopamine receptor antagonism. A combination of antidepressant and antipsychotic actions might make it a suitable drug for depression in psychotic patients. However, the dopamine antagonism may cause akathisia, parkinsonism, amenorrhea-galactorrhea syndrome, and perhaps tardive dyskinesia.

Maprotiline (a tetracyclic drug) is most like desipramine in terms of its potent norepinephrine uptake inhibition. Like the latter drug, it has fewer sedative and antimuscarinic actions than the older tricyclics.

Clinical experience with trazodone has indicated unpredictable efficacy for depression though it has proved very useful as a hypnotic, sometimes being combined with MAOIs, which disturb sleep.

Third-Generation Agents

Three antidepressants—nefazodone, venlafaxine, and mirtazapine—are all related to earlier agents in either structure or mechanism of action. Nefazodone is closely related to trazodone but is less sedating. It produces fewer adverse sexual effects than the SSRIs but is a potent inhibitor of CYP3A4. (Fluvoxamine causes the same inhibition of CYP3A4.)

Venlafaxine is a potent inhibitor of serotonin reuptake and a weaker inhibitor of norepinephrine transport such that at lower therapeutic doses it behaves like an SSRI. At high doses (more than 225 mg/d) it produces mild to moderate increases of heart rate and blood pressure attributable to norepinephrine reuptake inhibition. Doses in the range of 300 mg/d or greater may confer broader therapeutic effects than SSRIs, but a careful titration up to these doses is needed to control adverse effects.

Mirtazapine, a drug derived from mianserin—an antidepressant available outside the USA—is a
potent antihistaminic with greater sedating effects than the other second- and third-generation antidepressants. Its use is also more likely to be associated with weight gain. The hypothesized mechanism of action of mirtazapine combines 5-HT2 receptor and α-adrenoceptor antagonism and, if established in humans, would be unique among available drugs. Thus, mirtazapine may prove beneficial in patients who can tolerate its sedative effects and do not respond well to SSRIs or cannot tolerate the sexual or other adverse effects of the other antidepressants.

Selective Serotonin Reuptake Inhibitors

Fluoxetine was the first SSRI to reach general clinical use. Paroxetine and sertraline differ mainly in having shorter half-lives and different potencies as inhibitors of specific P450 isoenzymes. While the SSRIs have not been shown to be more effective overall than prior drugs, they lack many of the toxicities of the tricyclic and heterocyclic antidepressants. Thus, patient acceptance has been high despite adverse effects such as nausea, decreased libido, and even decreased sexual function.

A dangerous pharmacodynamic interaction may occur when fluoxetine or one of the newer selective serotonin reuptake inhibitors is used in the presence of a monoamine oxidase inhibitor. The combination of increased stores of the monoamine plus inhibition of reuptake after release is thought to result in marked increases of serotonin in the synapses, leading to a serotonin syndrome. This sometimes fatal syndrome includes hyperthermia, muscle rigidity, myoclonus, and rapid changes in mental status and vital signs.

MAO Inhibitors

MAO-A (isoform A) is the amine oxidase primarily responsible for norepinephrine, serotonin, and tyramine metabolism. MAO-B is more selective for dopamine. The irreversible inhibitors available in the USA are nonselective and block both forms of the enzyme. Irreversible block of MAO, characteristic of the older MAO inhibitors, allows significant accumulation of tyramine and loss of the first-pass metabolism that protects against tyramine in foods. As a result, the irreversible MAO inhibitors are subject to a very high risk of hypertensive reactions to tyramine ingested in food. From the evidence available to date, the reversible, short-acting MAO inhibitor moclobemide, which is available in several countries (but not the USA), appears to be relatively free of this interaction. (The selective MAO-B inhibitor selegiline loses selectivity at antidepressant dosage. Because its action is on the enzyme that metabolizes dopamine, it is most useful in the treatment of Parkinson's disease [Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders].)

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Clinical Pharmacology of Antidepressants

Clinical Indications

The major indication for these drugs is to treat depression, but a number of other uses have been established by clinical experience and controlled trials.

Depression

This indication has been kept broad deliberately, even though evidence from clinical studies strongly suggests that the drugs are specifically useful only in major depressive episodes. Major
depressive episodes are diagnosed not so much by their severity as by their quality. Formerly, they were referred to as "endogenous," "vital," or "vegetative"—reflecting the characteristic disturbances of major body rhythms of sleep, hunger and appetite, sexual drive, and motor activity. The diagnosis of major depression may be uncertain in individual patients, so that on balance this condition is underdiagnosed and undertreated. The depressed phase of bipolar illness definitely requires pharmacologic treatment given the high rate of suicide in persons with this disorder. Standard antidepressants are usually added to lithium or another antimanic agent; SSRIs are less likely to induce mania than the older tricyclic agents. There are, however, few controlled studies on their relative efficacy or proper duration of use. Recent controlled studies provide evidence that the anticonvulsant lamotrigine may have special promise in bipolar depression.

Panic Disorder

Imipramine was first shown in 1962 to have a beneficial effect in the acute episodes of anxiety that have come to be known as panic attacks. Recent studies have shown it to be as effective as MAO inhibitors and benzodiazepines. It has also been demonstrated that SSRIs are effective in panic disorder. In some instances, benzodiazepines are preferred, as they are well tolerated and their clinical effects become evident promptly. Alternatively, if one wishes to avoid the physiologic dependence associated with chronic benzodiazepine use, SSRIs are acceptable for many patients though they require several weeks to produce full therapeutic effects.

Obsessive-Compulsive Disorders

The serotonin reuptake inhibitors have been shown to be uniquely effective for treating these disorders. Recent studies have focused on fluoxetine and other selective serotonin reuptake-inhibiting drugs, although clomipramine, a mixed serotonin and norepinephrine uptake inhibitor, may be more potent. Fluvoxamine is marketed exclusively for this disorder in the United States.

Enuresis

Enuresis is an established indication for tricyclics. Proof of efficacy for this indication is substantial, but drug therapy is not the preferred approach. The beneficial effect of drug treatment lasts only as long as drug treatment is continued. Institutionalized elderly patients with incontinence are often treated with imipramine. Unfortunately, this age group is also the most sensitive to the anticholinergic hallucinogenic effects of the drug.

Chronic Pain

Clinicians in pain clinics have found tricyclics to be especially useful for treating a variety of chronically painful states that often cannot be definitively diagnosed. Whether such painful states represent depressive equivalents or whether such patients become secondarily depressed after some initial pain-producing insult is not clear. It is even possible that the tricyclics work directly on pain pathways.

Controlled studies of higher doses of venlafaxine, which inhibit both norepinephrine and serotonin uptake, show efficacy in pain. Duloxetine, a mixed uptake inhibitor soon to be marketed, has similar effects. SSRIs, however, are not effective for chronic pain.

Other Indications

Certain antidepressants have been shown to be effective for eating disorders, especially bulimia.
(fluoxetine), and attention deficit hyperkinetic disorder (imipramine, desipramine). **Atomoxetine** was recently introduced for the treatment of attention deficit hyperactivity disorder (ADHD). This selective inhibitor of norepinephrine reuptake was shown to be as effective as a standard drug in this condition (methylphenidate; see Chapter 9: Adrenoceptor-Activating & Other Sympathomimetic Drugs) and possibly better tolerated. This drug should not be used concurrently with MAO inhibitors.

SSRIs show efficacy in social phobia, and combined serotonin and norepinephrine uptake inhibitors are effective in generalized anxiety disorder.

**Drug Choice**

Controlled comparisons of the available antidepressants have usually led to the conclusion that they are roughly equivalent drugs. Although this may be true for groups of patients, individual patients may for uncertain reasons fare better on one drug than on another. European studies show that patients depressed enough to be hospitalized respond better to classic tricyclics than to monotherapy with SSRIs. Meta-analyses of outpatient studies also show greater efficacy of tricyclics than SSRIs in patients who complete trials. The greater tolerability of the SSRIs, however, makes them the preferred agent for most patients. At high doses (> 225 mg), venlafaxine also shows greater efficacy than the SSRIs. Thus, finding the right drug and the right dose for the individual patient must be accomplished empirically. The past history of the patient's drug experience is the most valuable guide. At times such a history may lead to the exclusion of tricyclics, as in the case of patients who have responded well in the past to MAO inhibitors.

Tricyclics and the second- and third-generation agents differ mainly in the degree of sedation they produce (greatest with amitriptyline, doxepin, trazodone, and mirtazapine) and their antimuscarinic effects (greatest with amitriptyline and doxepin; Table 30–3). SSRIs are generally free of sedative effects and remarkably safe in overdose. Combined with the ease of once-a-day dosing, these qualities may explain why they have become the most widely prescribed antidepressants.

None of the newer antidepressants have been shown to be more effective overall than the tricyclics with which they have been compared. Solid evidence to support a claim of more rapid onset of action has been difficult to obtain. Amoxapine and maprotiline seem to have as many sedative and autonomic actions as most tricyclics; more recently introduced antidepressants such as bupropion and venlafaxine have fewer, although nefazodone and mirtazapine are very sedating. Amoxapine and maprotiline are at least as dangerous as the tricyclics when taken in overdoses; the other newer agents seem to be safer.

No special indications for particular types of depression have been found for the selective serotonin reuptake inhibitors or other newer antidepressants. The popularity of these drugs, despite their higher cost, is due principally to their greater acceptance by patients. A provocative clinical report that fluoxetine use increased suicidal or aggressive ideation was not supported by subsequent analyses of massive data bases. Suicidal thoughts are part of the depressive syndrome.

Clinical reports, prescription databases, and a few trials support the use of selective serotonin reuptake inhibitors in combination with the older tricyclics, especially desipramine; with bupropion; and, most recently, with mirtazapine in patients who do not show an adequate response to a single agent.

MAO inhibitors are helpful in patients described as having "atypical" depressions—usually patients with considerable attendant anxiety, phobic features, and hypochondriasis.
Few clinicians use lithium, an antimanic agent, as primary treatment for depression. However, some have found that lithium along with one of the other antidepressants may achieve a favorable response not obtained by the antidepressant alone. Another potential use of lithium is to prevent relapses of depression.

Dosages

The usual daily dose ranges of antidepressants are shown in Table 30–4. Doses are almost always determined empirically; the patient's acceptance of adverse effects is the usual limiting factor. Tolerance to some of the objectionable effects may develop, so that the usual pattern of treatment has been to start with small doses, increasing either to a predetermined daily dose, or to one that produces relief of depression, or to the maximum tolerated dose (except in the case of nortriptyline, which loses efficacy at plasma concentrations over 150 ng/mL).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>75–200</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>75–300</td>
</tr>
<tr>
<td>Desipramine</td>
<td>75–200</td>
</tr>
<tr>
<td>Doxepin</td>
<td>75–300</td>
</tr>
<tr>
<td>Imipramine</td>
<td>75–200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>75–150</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>20–40</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>75–200</td>
</tr>
<tr>
<td><strong>Second- and third-generation agents</strong></td>
<td></td>
</tr>
<tr>
<td>Amoxapine</td>
<td>150–300</td>
</tr>
<tr>
<td>Bupropion</td>
<td>200–400</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>75–300</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15–60</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>200–600</td>
</tr>
<tr>
<td>Trazodone</td>
<td>50–600</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75–225</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>45–75</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>30–60</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>20–60</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10–30</td>
</tr>
</tbody>
</table>
MAO inhibitors, bupropion, fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine are customarily given early in the day when initiating treatment, as they can be somewhat stimulating and may cause insomnia if given late. After a few weeks on the drug, however, any such effects should disappear and time of day administered is rarely important. Virtually all the other antidepressants have varying degrees of sedative effects and are best given near bedtime. Autonomic adverse effects also tend to be less troublesome if the dose is given late.

Maintenance Treatment

Whether or not to undertake long-term maintenance treatment of a depressed patient depends entirely on the natural history of the disorder. If the depressive episode was the patient's first and if it responded quickly and satisfactorily to drug therapy, it is rational to gradually withdraw treatment over a period of a few weeks after treating for 6–9 months. If relapse does not occur, drug treatment can be stopped until another episode occurs, which is unpredictable but highly probable. Pooled data from randomized trials covering 6–36 months reveal more than 50% reduction in relapses or recurrences if patients are maintained on an antidepressant. Thus, a patient who has had previous episodes of depression—especially if each succeeding one was more severe and more difficult to treat—is a candidate for maintenance therapy. Maintenance therapy requires the full dosage used to obtain the initial response. The duration of treatment varies, though many patients require maintenance treatment indefinitely.

Monitoring Plasma Concentrations

Routine monitoring of plasma concentrations of antidepressants, while technically feasible for most drugs, is of uncertain value (except for nortriptyline). However, studies suggest that at least 20% of patients become noncompliant at some time or other. Thus, a "poor response" in a patient for whom an adequate dosage of drug has been prescribed may be shown by measurement of the plasma drug concentration to be due merely to failure to take the drug.

Unresponsive Patients

One third or more of patients do not respond (defined as 50% or more improvement), and over half fail to achieve or maintain full remission on any single treatment. In evaluating a patient's resistance to treatment, one should consider the five D's: diagnosis, drug, dose, duration of treatment, and different treatment.

Diagnosis might be reassessed if the patient shows little response over a period of 2–3 weeks of adequate dosage or plasma concentrations. Whether or not the patient is bipolar, lithium might be added (see Chapter 29: Antipsychotic Agents & Lithium); if psychotic, treatment might be augmented with an antipsychotic. Combination of an SSRI with desipramine or bupropion appears relatively safe and effective for some patients. Similarly, mirtazapine can be effectively combined with SSRIs. There is no good pharmacologic rationale for combining venlafaxine with SSRIs since it is itself a potent serotonin reuptake inhibitor; rather, it might be considered for combination with bupropion or mirtazapine. Some clinicians believe that several weeks or months of treatment should
be tried before giving up on a drug or combination. The morbidity of depression, however, is such that long delays in attaining relief are demoralizing.

A generally accepted strategy is to begin treatment with an SSRI in mild to moderate outpatient depression and then augment by adding a drug of a different class for more impaired patients. Otherwise, switch to a drug of different class. Most clinicians would prefer to move through various antidepressant drug classes in the search for the right drug rather than through various drugs within a class.

Dose and duration of treatment must be considered. Many treatment failures are due to inadequate dosage, which should be pushed to the limits of the patient's tolerance in refractory cases. The duration of treatment before giving up on a drug is a matter of clinical judgment.

Finally, some patients may need a completely different type of treatment, such as electroconvulsive therapy (ECT). ECT is often viewed as a treatment of last resort, but it should not be withheld from patients with this disorder who cannot be helped by drug therapy. For patients with psychotic depression, ECT may be a treatment of first choice.

Noncompliance is an important cause of lack of response to drugs. Patients should be warned also that noticeable improvement may be slow, perhaps taking 3 weeks or more. Inability to tolerate adverse effects and discouragement with treatment are two major causes for noncompliance and for failure of antidepressants to show efficacy.

Adverse Effects

Adverse effects of various antidepressants are summarized in Table 30–5. Most common unwanted effects are minor, but they may seriously affect patient compliance; the more seriously depressed the patient is, the more likely it is that unwanted effects will be tolerated. Most normal persons find that even moderate doses of many antidepressants cause disagreeable symptoms, especially the classic tertiary amine tricyclics: amitriptyline, imipramine, clomipramine, and doxepin. With the SSRIs, transient nausea is the most frequent complaint, and decreased libido and sexual dysfunction create the greatest concerns during maintenance treatment.

<table>
<thead>
<tr>
<th>Table 30–5. Adverse Effects of Antidepressants.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
</tr>
<tr>
<td>Sedation (sleepiness, additive effects with other sedative drugs)</td>
</tr>
<tr>
<td>Sympathomimetic (tremor, insomnia)</td>
</tr>
<tr>
<td>Antimuscarinic (blurred vision, constipation, urinary hesitancy, confusion)</td>
</tr>
<tr>
<td>Cardiovascular (orthostatic hypotension, conduction defects, arrhythmias)</td>
</tr>
<tr>
<td>Psychiatric (aggravation of psychosis, withdrawal syndrome)</td>
</tr>
<tr>
<td>Neurologic (seizures)</td>
</tr>
<tr>
<td>Metabolic-endocrine (weight gain, sexual disturbances)</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
</tr>
<tr>
<td>Sleep disturbances, weight gain, postural hypotension, sexual disturbances (phenelzine)</td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Amoxapine</td>
</tr>
<tr>
<td>Maprotiline</td>
</tr>
<tr>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Trazodone, nefazodone</td>
</tr>
<tr>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Bupropion</td>
</tr>
<tr>
<td>Fluoxetine and other serotonin reuptake inhibitors</td>
</tr>
</tbody>
</table>

Drug Interactions

Pharmacodynamic Interactions

Many of the pharmacodynamic interactions of antidepressants with other drugs have already been discussed. Sedative effects may be additive with other sedatives, especially alcohol. Patients taking tricyclics should be warned that use of alcohol may lead to greater than expected impairment of driving ability. MAO inhibitors, by increasing stores of catecholamines, sensitize the patient to indirectly acting sympathomimetics such as tyramine, which is found in some fermented foods and beverages, and to sympathomimetic drugs such as diethylpropion, phenylpropanolamine, or botanicals containing ephedrine. Such sensitization can result in dangerous and—rarely—fatal hypertensive reactions. The serious interaction between MAO inhibitors and selective serotonin reuptake inhibitors has been mentioned; the serotonin syndrome is potentially lethal and must be avoided.

Pharmacokinetic Interactions

The most likely pharmacokinetic interactions are between the potent inhibitors of P450 2D6, paroxetine and fluoxetine, and those drugs highly dependent on this pathway for clearance (eg, desipramine, nortriptyline, flecainide; see also Chapter 4: Drug Biotransformation). Actual instances of clinically significant interactions are extremely rare, there being only a handful of case reports after cumulative exposure of more than 50 million patients to these SSRI drugs. Inhibition of P450 3A4 could possibly occur at high concentrations of nefazodone and fluvoxamine and block the metabolism of the many substrates of this isoform.

Overdoses

Tricyclics

Tricyclics are extremely dangerous when taken in overdose quantities, and depressed patients are more likely than others to be suicidal. Prescriptions should therefore be limited to amounts less than 1.25 g, or 50 dose units of 25 mg, on a "no refill" basis. If suicide is a serious possibility, the tablets should be entrusted to a family member. The drugs must be kept away from children. Both
accidental and deliberate overdoses continue to occur and are serious medical emergencies. Major
effects and management of overdosage are discussed in Chapter 59: Management of the Poisoned
Patient.

Second- and Third-Generation Drugs

Overdoses of amoxapine are characterized by severe neurotoxicity, with seizures that are difficult to
control. Overdoses of maprotiline also have a tendency to cause seizures as well as cardiotoxicity.
Overdoses of the other heterocyclic drugs appear to create only minor problems and can usually be
managed with purely supportive measures. For example, in one recorded case even 11 g of
nefazodone failed to cause serious injury.

MAO Inhibitors

Intoxication with MAO inhibitors is unusual. Agitation, delirium, and neuromuscular excitability
are followed by obtunded consciousness, seizures, shock, and hyperthermia. Supportive treatment is
usually all that is required, though sedative phenothiazines with adrenoceptor-blocking action,
such as chlorpromazine, may be useful.

Selective Serotonin Reuptake Inhibitors

A few deaths have occurred during overdosage of SSRIs when other drugs were also being taken.
The likelihood of fatalities from SSRI overdoses is extremely low. In case of overdose, only
supportive treatment can be offered, since the high volume of distribution, as with other
antidepressants, rules out removal of drug by dialysis. As much as 2.6 g of sertraline has been taken
with survival. Overdoses of paroxetine are relatively benign: Up to 850 mg has been taken with no
evidence of cardiotoxicity.

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System > Chapter 30. Antidepressant Agents >

Preparations Available

Tricyclics

**Amitriptyline** (generic, Elavil, others)

Oral: 10, 25, 50, 75, 100, 150 mg tablets

Parenteral: 10 mg/mL for IM injection

**Clomipramine** (generic, Anafranil; labeled only for obsessive-compulsive disorder)

Oral: 25, 50, 75 mg capsules

**Desipramine** (generic, Norpramin, Pertofrane)

Oral: 10, 25, 50, 75, 100, 150 mg tablets
**Doxepin** (generic, Sinequan, others)
Oral: 10, 25, 50, 75, 100, 150 mg capsules; 10 mg/mL concentrate

**Imipramine** (generic, Tofranil, others)
Oral: 10, 25, 50 mg tablets (as hydrochloride); 75, 100, 125, 150 mg capsules (as pamoate)
Parenteral: 25 mg/2 mL for IM injection

**Nortriptyline** (generic, Aventyl, Pamelor)
Oral: 10, 25, 50, 75 mg capsules; 10 mg/5 mL solution

**Protriptyline** (generic, Vivactil)
Oral: 5, 10 mg tablets

**Trimipramine** (Surmontil)
Oral: 25, 50, 100 mg capsules

Second- & Third-Generation Drugs

**Amoxapine** (generic, Asendin)
Oral: 25, 50, 100, 150 mg tablets

**Bupropion** (generic, Wellbutrin)
Oral: 75, 100 mg tablets; 100, 150 mg sustained-release tablets

**Maprotiline** (generic, Ludiomil)
Oral: 25, 50, 75 mg tablets

**Mirtazapine** (Remeron)
Oral: 15, 30, 45 mg tablets

**Nefazodone** (Serzone)
Oral: 50, 100, 150, 200, 250 mg tablets

**Trazodone** (generic, Desyrel)
Oral: 50, 100, 150, 300 mg tablets

**Venlafaxine** (Effexor)
Oral: 25, 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg extended-release tablets

Selective Serotonin Reuptake Inhibitors

**Citalopram** (Celexa)
Oral: 20, 40 mg tablets

**Escitalopram** (Lexapro)
Oral: 5, 10, 20 mg tablets

**Fluoxetine** (generic, Prozac)
Oral: 10, 20 mg pulvules; 10 mg tablets; 20 mg/5 mL liquid
Oral delayed release (Prozac Weekly): 90 mg capsules

**Fluvoxamine** (Luvox, labeled only for obsessive-compulsive disorder)
Oral: 25, 50, 100 mg tablets

**Paroxetine** (Paxil)
Oral: 10, 20, 30, 40 mg tablets; 10 mg/5 mL suspension; 12.5, 25, 37.5 mg controlled-release tablets

**Sertraline** (Zoloft)
Oral: 25, 50, 100 mg tablets

Monoamine Oxidase Inhibitors

**Phenelzine** (Nardil)
Oral: 15 mg tablets

**Tranylcypromine** (Parnate)
Oral: 10 mg tablets

Other

**Atomoxetine** (Strattera)
Oral: 10, 18, 25, 40, 60 mg capsules
Chapter 31. Opioid Analgesics & Antagonists

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 Sertturner in 1803 isolated the pure alkaloid morphine—named 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 include synthetic surrogates, other opioid-like drugs whose actions are blocked by the nonselective antagonist naloxone, plus several endogenous peptides that interact with the several subtypes of opioid receptors.

Basic Pharmacology of the Opioid Analgesics

Source

Incision of the poppy seed pod reveals a white substance that turns into a brown gum that is crude opium. Opium contains many alkaloids, the principle one being morphine which is present in a concentration of about 10%. Codeine is synthesized commercially from morphine.

Classification & Chemistry

Opioid drugs include full agonists, partial agonists, and antagonists (see Chapter 2: Drug Receptors & Pharmacodynamics for definitions). Figure 31–1 shows the chemical structures of morphine, a natural opioid; codeine, a semisynthetic opioid; fentanyl, a pharmacologically similar synthetic; and naloxone, a nonselective opioid antagonist. Morphine is a full agonist at the μ (mu) opioid receptor, whereas codeine functions as a partial (or "weak") μ receptor agonist. As shown in Figure 31–1, 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. Some opioids, eg, nalmephine, are capable of producing an agonist (or partial agonist) effect at one opioid receptor subtype and an antagonist effect at another. Not only can the activating properties of opioid analgesics be manipulated by pharmaceutical chemistry, certain opioid analgesics are modified in the liver resulting in compounds with greater analgesic action (see below, Pharmacokinetics, Metabolism).
Endogenous Opioid Peptides

Opioid alkaloids (eg, morphine) produce analgesia through actions at regions in the brain that contain peptides which have opioid-like pharmacologic properties. The general term currently used for these endogenous substances is endogenous opioid peptides, which replaces the previous term endorphin.

Three families of endogenous opioid peptides have been described in detail. The best-characterized of the opioid peptides possessing analgesic activity are the pentapeptides methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin). Leu- and met-enkephalin have slightly higher affinity for the \( \delta \) (delta) than for the \( \mu \) (mu) opioid receptor (Table 31–1). These 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, \( \beta \)-endorphin, and several nonopioid peptides, including adrenocorticotropic hormone (ACTH), \( \beta \)-lipotropin, and melanocyte-stimulating hormone. Preproenkephalin contains six copies of met-enkephalin and one copy of leu-enkephalin. Preprodynorphin yields several active opioid peptides that contain the leu-enkephalin sequence. These are dynorphin A, dynorphin B, and \( \varepsilon \) and \( \eta \) neoeンドorphins. More recently, the endogenous peptides endomorphin-1 and endomorphin-2, have been found to possess many of the properties of opioid peptides, notably analgesia and high affinity binding to the \( \varepsilon \) receptor. Current research is focused on whether endomorphins selectively activate \( \varepsilon \) receptor subtypes. Both the endogenous opioid precursor molecules and the endomorphins are present at central nervous system (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 to diminish the sensation of noxious stimuli.

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Functions</th>
<th>Endogenous Opioid Peptide Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) (mu)</td>
<td>Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed GI transit; modulation of hormone and neurotransmitter release</td>
<td>Endorphin &gt; enkephalins &gt; dynorphins</td>
</tr>
</tbody>
</table>
Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release

\( \delta \) (delta)

- Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release
- Enkephalins >> endorphins and dynorphins

\( \kappa \) (kappa)

- Supraspinal and spinal analgesia; psychotomimetic effects; slowed GI transit
- Dynorphins >> endorphin and enkephalins

GI, gastrointestinal.

In contrast to the analgesic role of leu- and met-enkephalin, an analgesic action of dynorphin A—through its binding to \( \kappa \) (kappa) opioid receptors—remains controversial. Dynorphin A is also found in the dorsal horn of the spinal cord where it plays a critical role in the sensitization of nociceptive neurotransmission. Increased levels of dynorphin can be found in the dorsal horn following tissue injury and inflammation. This elevated dynorphin level is believed to increase pain and induce a state of long-lasting hyperalgesia. The pro-nociceptive action of dynorphin in the spinal cord appears to be independent of the opioid receptor system. Rather, dynorphin A can bind and activate the \( \mathrm{N} \)-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 principle receptor for this system is the G protein-coupled orphanin opioid-receptor-likesubtype 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 but acts only at the ORL1 receptor. Although widely expressed in the CNS and periphery, this system has a diverse pharmacology, capable of opposing classic receptor-mediated analgesia as well as modulating drug reward, reinforcement, learning, and memory processes.

Pharmacokinetics

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

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Approximate Dose (mg)</th>
<th>Oral:Parenteral Potency Ratio</th>
<th>Duration of Analgesia (hours)</th>
<th>Intrinsic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine(^1)</td>
<td></td>
<td>10</td>
<td>Low</td>
<td>4–5</td>
<td>High</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Dilaudid</td>
<td>1.5</td>
<td>Low</td>
<td>4–5</td>
<td>High</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Numorphan</td>
<td>1.5</td>
<td>Low</td>
<td>3–4</td>
<td>High</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dolophine</td>
<td>10</td>
<td>High</td>
<td>4–6</td>
<td>High</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Demerol</td>
<td>60–100</td>
<td>Medium</td>
<td>2–4</td>
<td>High</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Sublimaze</td>
<td>0.1</td>
<td>Low</td>
<td>1–1.5</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 31–2. Common Opioid Analgesics.
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Brand</th>
<th>Route</th>
<th>Initial Dose</th>
<th>Peak Dose</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>Sufenta</td>
<td>Parenteral</td>
<td>0.02</td>
<td>1–1.5</td>
<td>High</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Alfenta</td>
<td>Parenteral</td>
<td>Titrated</td>
<td>0.25–0.75</td>
<td>High</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Levo-Dromoran</td>
<td>Parenteral</td>
<td>2–3</td>
<td>4–5</td>
<td>High</td>
</tr>
<tr>
<td>Codeine</td>
<td>Dromoran</td>
<td>Parenteral</td>
<td>30–60⁴</td>
<td>3–4</td>
<td>Low</td>
</tr>
<tr>
<td>Hydrocodone²</td>
<td></td>
<td>Parenteral</td>
<td>5–10</td>
<td>4–6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oxycodone¹³</td>
<td>Percodan</td>
<td>Parenteral</td>
<td>4.5⁴</td>
<td>3–4</td>
<td>Moderate</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
<td>Parenteral</td>
<td>60–120³⁴</td>
<td>4–5</td>
<td>Very low</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Talwin</td>
<td>Parenteral</td>
<td>30–50⁴</td>
<td>3–4</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Nubain</td>
<td>Parenteral</td>
<td>10</td>
<td>3–6</td>
<td>High</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Buprenex</td>
<td>Parenteral</td>
<td>0.3</td>
<td>4–8</td>
<td>High</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Stadol</td>
<td>Parenteral</td>
<td>2</td>
<td>3–4</td>
<td>High</td>
</tr>
</tbody>
</table>

¹ Available in sustained-release forms, morphine (MSContin); oxycodone (OxyContin).
² Available in tablets containing acetaminophen (Norco, Vicodin, Lortab, others).
³ Available in tablets containing acetaminophen (Percocet); aspirin (Percodan).
⁴ Analgesic efficacy at this dose not equivalent to 10 mg of morphine. See text for explanation.

**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, which is primarily due to a methyl group on their aromatic hydroxyl group. Nasal insufflation of certain opioids can result in rapid therapeutic blood levels by avoiding first-pass metabolism. Other routes of opioid administration include oral mucosal and the application of transdermal patches, which can provide delivery of potent analgesics over days.

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

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. Moreover, approximately 10% of morphine is metabolized to morphine-6-glucuronide (M6G), an active metabolite with greater analgesic potency than morphine. Despite their limited ability to cross the blood-brain barrier, accumulation of these metabolites may produce unexpected side effects in patients with renal failure or when exceptionally large doses of morphine are administered. This can result in M3G-induced CNS excitation (seizures) or enhanced and prolonged opioid action produced by M6G. Similarly, hydromorphone is metabolized to hydromorphone-3-glucuronide (H3G), which has CNS excitatory properties. However, hydromorphone has not been shown to form the 6-glucuronide metabolite.

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 (fentanyl, alfentanil, sufentanil) and eventually leaves only small quantities of the parent compound unchanged for excretion. 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. Genetic polymorphism of CYP2D6 has been documented and linked to the variation in analgesic response seen among patients. Nevertheless, these metabolites may be of minor consequence because the parent compounds (codeine, oxycodone, hydrocodone) are currently believed to be directly responsible for the majority of their analgesic actions.

Accumulation of a demethylated metabolite of meperidine, normeperidine, may occur in patients with decreased renal function or those receiving multiple high doses of the drug. In sufficiently high concentrations, normeperidine may cause seizures.

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. Glucuronide conjugates are also found in the bile, but enterohepatic circulation represents only a small portion of the excretory process.

Pharmacodynamics

Mechanism of Action

Opioid agonists produce analgesia by binding to specific G protein-coupled receptors, located primarily in brain and spinal cord regions involved in the transmission and modulation of pain.
Receptor Types

As noted above, 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 μ₁, μ₂, δ₁, δ₂, κ₁, κ₂, and κ₃. 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. Since an opioid drug 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.

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 Ca²⁺ disposition, and alter protein phosphorylation (see Chapter 2: Drug Receptors & Pharmacodynamics). The opioids have two well-established direct actions on neurons: (1) they close voltage-gated Ca²⁺ channels on presynaptic nerve terminals and thereby reduce transmitter release and (2) they hyperpolarize and thus inhibit postsynaptic neurons by opening K⁺ channels. Figure 31–2 schematically illustrates the presynaptic action at all three receptor types and the postsynaptic effect at μ receptors on nociceptive afferents in the spinal cord. The presynaptic action—depressed transmitter release—has been demonstrated for release of a large number of neurotransmitters including glutamate, the principle excitatory amino acid released from nociceptive nerve terminals, as well as acetylcholine, norepinephrine, serotonin, and substance P.

Relation of Physiologic Effects to Receptor Type

The majority of currently available opioid analgesics act primarily at the μ opioid receptor. Analgesia, as well as the euphoriant, respiratory depressant, and physical dependence properties of
morphine result principally from actions at \( \mu \) receptors. In fact, the \( \mu \) 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 \( \delta \) and \( \kappa \) receptors. This is supported by the study of genetic knockouts of the \( \mu \), \( \delta \), and \( \kappa \) genes in mice. Delta receptor agonists retain analgesic properties in \( \mu \) receptor knockout mice. The development of \( \delta \)-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 \( \mu \)-receptor agonists, such as morphine. Although morphine does act at \( \delta \) and \( \kappa \) 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 \( \delta \) and \( \kappa \) receptors (Table 31–1). For example, leu-enkephalin has a high affinity for the \( \delta \) receptor and dynorphin for the \( \kappa \) receptor.

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 \( \kappa \) 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. Interestingly, butorphanol has also been shown to cause significantly greater analgesia in women than in men. The reason for this difference is not known.

Receptor Distribution and Neural Mechanisms of Analgesia

Opioid receptor binding sites have been localized autoradiographically using high-affinity radioligand binding 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 (site \( B \), Figure 31–3). Receptors are present both on spinal cord pain transmission neurons and on the primary afferents that relay the pain message to them (Figure 31–3, left side). Opioid agonists inhibit the release of excitatory transmitters from these primary afferents, and they directly inhibit the dorsal horn pain transmission neuron. Thus, opioids exert a powerful analgesic effect directly upon 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.

Figure 31–3.
Under most circumstances, opioids are given systemically and so act simultaneously at both spinal and supraspinal sites; interaction at these two sites tends to increase their overall analgesic efficacy. Different combinations of opioid receptors are found in the supraspinal regions implicated in pain transmission and modulation (Figure 31–3). Of particular importance are opioid binding sites in pain-modulating descending pathways (Figure 31–3, right), including the rostral ventral medulla, the locus ceruleus, and the midbrain periaqueductal gray area. At these sites as at others, opioids directly inhibit neurons, yet neurons that send processes to the spinal cord and inhibit pain transmission neurons are activated by the drugs. This activation has been shown to result from the inhibition of inhibitory neurons in several locations (Figure 31–4).
When pain-relieving opioid drugs are given systemically, they presumably act upon brain 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 identification of functional μ receptors on the peripheral terminals of sensory neurons supports this hypothesis. Furthermore, activation of peripheral μ receptors results in a decrease in sensory neuron activity and transmitter release. Peripheral administration of opioids, eg, into the knees of patients undergoing arthroscopic knee surgery, has shown some clinical benefit. If they can be developed, opioids selective for a peripheral site would be useful adjuncts in the treatment of inflammatory pain (see Ion Channels & Novel Analgesics). Moreover, new peripherally acting dynorphins may provide a novel means to treat visceral pain.

Tolerance and Physical Dependence

With frequently repeated administration of therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness, ie, tolerance. To reproduce the original response, a larger dose must be administered. Along with tolerance, physical dependence develops. Physical dependence is defined as the occurrence of a characteristic withdrawal or abstinence syndrome when the drug is stopped or an antagonist is administered.

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 or a down-regulation and recycling of μ receptors from the cell surface to cryptic
intracellular sites. Although these processes are associated with tolerance, they are not sufficient to explain it. Recent research suggests that the \( \mu \) opioid receptor is an important 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 \( \mu \) receptor and G-proteins, second messenger systems, and their target ion channels. Moreover, a particular ion channel complex, the NMDA receptor, has been shown to play a critical role in tolerance development and maintenance because NMDA receptor antagonists such as ketamine can block tolerance development. The development of novel NMDA receptor antagonists or other strategies to recouple \( \mu \) 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. Spinal dynorphin is a leading candidate for the mediation of opioid-induced pain and hyperalgesia.

**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 even though some variation between individual agents does occur. Agents with partial agonist or mixed receptor effects, when given to a patient who has not recently received an agonist agent, also produce analgesia but with minor additional variations in effects as noted below. Characteristics of specific members of these two groups are discussed below. When given to a subject who has received an agonist, the pure antagonists and the mixed agents have very different effects from those observed in a subject who has not received an agonist. This is discussed further at the end of this chapter.

**Central Nervous System Effects**

The principal effects of opioid analgesics with affinity for \( \mu \) 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).

| 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                           |                 |                 |

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 aspect.

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.

Sedation

Drowsiness and clouding of mentation are frequent concomitants of opioid action. There is little or no amnesia. Sleep is induced by opiates 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 REM and non-REM sleep patterns. This disrupting effect is probably characteristic of all opioids. In contrast to humans, a number of species (cats, horses, cows, pigs) may manifest excitation rather than sedation when given opioids. These paradoxic effects are at least partially dose-dependent.

Respiratory Depression

All of the opioid analgesics can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms. Alveolar PCO₂ 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 PaCO₂ 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.

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.

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 will be seen. This action, which can be blocked by opioid antagonists, is mediated by parasympathetic pathways, which, in turn, can be blocked by atropine.
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) 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.

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.

Peripheral Effects

Cardiovascular System

Most opioids have no significant direct effects on the heart and no major effects on cardiac rhythm (except bradycardia). Meperidine is an exception to this generalization because its antimuscarinic action may 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, since the above mechanisms make these patients quite susceptible to hypotension. Opioid analgesics affect cerebral circulation minimally except when PCO$_2$ rises as a consequence of respiratory depression. Increased PCO$_2$ leads to cerebral vasodilation associated with a decrease in cerebral vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

Gastrointestinal Tract

Constipation has long been recognized as an effect of opioids. Opioid receptors exist in high density in the gastrointestinal tract, and the constipating effects of the opioids are mediated through an action on the local enteric nervous system (see Chapter 6: Introduction to Autonomic Pharmacology) 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 management of diarrhea.

Biliary Tract

The opioids constrict biliary smooth muscle, which may 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.

Renal

Renal function is depressed by opioids. It is believed that in humans this is chiefly due to decreased renal plasma flow. Opioids can decrease systemic blood pressure and glomerular filtration rate. In addition, opioids have been found to have an antidiuretic effect in humans. Mechanisms may involve both the CNS and peripheral sites, but the relative contributions of each are unknown. 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.

Uterus

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

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, play regulatory roles in these systems (Table 31–1).

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.

Miscellaneous

The opioids may modulate the actions of the immune system by effects on lymphocyte proliferation, antibody production, and chemotaxis. 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.

Effects of Drugs with Both Agonist and Antagonist Actions

Buprenorphine is an opioid agonist that displays high binding affinity but low intrinsic activity at the receptor. Its slow rate of dissociation from the receptor has also made it an attractive alternative to methadone for the management of opioid withdrawal. It functions as an antagonist at the and 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 agonists such as morphine. Buprenorphine also binds to ORL1, the orphanin receptor. Whether this property also participates in opposing 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 following use of drugs with mixed agonist-antagonist actions.

Even the most severe acute pain (that lasting hours to days) can usually be well controlled—with significant but tolerable adverse effects—with 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, presynaptic 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 (Basbaum, 1999; Woolf, 2000).

In the effort to discover better analgesic drugs for chronic pain, renewed attention is being paid to synaptic transmission in nociception and sensory processing. Potentially important ion channels associated with these processes in the periphery include members of the transient receptor potential potential family as TRPV1 (capsaicin receptor) that is activated by heat and products of inflammation as well as P2X receptors (responsive to purines released from tissue damage). A special type of tetrodotoxin-resistant voltage-gated sodium channel (Nav1.8), also known as the PN3/SNS channel, is apparently uniquely associated with nociceptive neurons in dorsal root ganglia. Mexiletine, which is useful in some chronic pain states, may act by blocking this channel. Certain blockers of voltage-gated N-type calcium channels have shown analgesic effects. A synthetic peptide related to the marine snail toxin α-conotoxin, which selectively blocks these calcium channels, is in clinical trials as an analgesic. Gabapentin, an anticonvulsant analog of GABA (see Chapter 24: Antiseizure Drugs), is an effective treatment for neuropathic (nerve injury) pain. It has recently been shown to block the pain and hyperalgesia associated with inflammation. Potential sites of action of gabapentin include the alpha-2-delta family of calcium channels.

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 side effects or neurotoxicity. 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. A nicotinic agonist found in certain frogs (epibatidine) has significant analgesic effect.

Although none of the studies described has yet yielded an approved analgesic drug, they have already provided a better understanding of nociception and analgesia.
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 described in terms of a numeric visual analog scale (VAS) with word descriptors ranging from no pain (0) to excruciating pain (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).

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 unwanted side effects, and the patient's past experience with opioids should all be addressed. One of the principal errors made by physicians in this setting is a 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, where 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

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 will be 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 (MSContin) 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 episodes of breakthrough pain (see Alternative Routes of Administration, below). 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 this 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.

Acute Pulmonary Edema

The relief produced by intravenous morphine in dyspnea from pulmonary edema associated with left ventricular failure is remarkable. The mechanism is not clear but probably involves reduced perception of shortness of breath and reduced patient anxiety as well as reduced cardiac preload (reduced venous tone) and afterload (decreased peripheral resistance). Morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema.

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.

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, are used. Several preparations are available specifically for this purpose.

Applications in Anesthesia

The opioids are frequently used as premedicant drugs before anesthesia and surgery because of their sedative, anxiolytic, and analgesic properties. The opioids 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: General Anesthetics), most commonly in cardiovascular surgery and other types of high-risk surgery where 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 may occur after the drug is injected into the epidural space and may require reversal with naloxone. Other 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 because adverse effects are less common. Morphine is the most frequently used agent, but the use of low doses of local anesthetics in combination with fentanyl infused through a thoracic epidural catheter has also become an accepted method of pain control in patients recovering from 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.

Alternative Routes of Administration

**Rectal suppositories** of morphine and hydromorphone have long 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 finds great use in patients experiencing chronic pain. 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. With PCA, the patient controls a parenteral (usually intravenous) infusion device by depressing 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 respiratory depression with hypoxia that requires careful monitoring of vital signs and sedation level.

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, as well as contraindications must be considered.

<table>
<thead>
<tr>
<th>Table 31–4. Adverse Effects of the Opioid Analgesics.</th>
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<tbody>
<tr>
<td>Behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions)</td>
</tr>
<tr>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
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<tr>
<td>Postural hypotension accentuated by hypovolemia</td>
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<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Itching around nose, urticaria (more frequent with parenteral and spinal administration)</td>
</tr>
</tbody>
</table>
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 psychologic dependence and the severity of withdrawal effects. For example, withdrawal from dependence upon 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 psychologic dependence of the partial agonist-antagonist opioids appear to be less than that of the agonist drugs.

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. 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 nontolerant 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 develops also 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 nor to those of the pure antagonists.

Cross-tolerance is an extremely important characteristic of the opioids, ie, patients tolerant to morphine 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, dextromethorphan) have shown promise in preventing or reversing opioid-induced tolerance in animals and humans. Routine use of these agents awaits the outcome of well-controlled studies to determine their clinical effectiveness in reducing postoperative pain and morphine requirements.

Physical 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 (see Chapter 32: Drugs of Abuse). 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 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. After the abstinence syndrome subsides, tolerance also disappears as evidenced by a restoration in sensitivity to the opioid agonist. However, despite the loss of physical dependence on the opioid, craving for it may persist for many months.

A transient, explosive abstinence syndrome—antagonist-precipitated withdrawal—can be induced in a subject physically dependent on opioids by administering naloxone or other 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.

Psychologic Dependence

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.

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 should be included in this process.

Once a therapeutic dose is established, attempt to limit dosage to this level. This goal is facilitated by use of a written treatment contract which 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.

**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 following Antagonists section and Chapter 59: Management of the Poisoned Patient.

**Contraindications and Cautions in Therapy**

**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.

**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.

**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 will 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 with 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.

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.

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.

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.

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.

Table 31–5. Opioid Drug Interactions.

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Interaction With Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative-hypnotics</td>
<td>Increased central nervous system depression, particularly respiratory depression.</td>
</tr>
<tr>
<td>Antipsychotic tranquilizers</td>
<td>Increased sedation. Variable effect on respiratory depression. Accentuation of cardiovascular effects (antimuscarinic and α-blocking actions).</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexic coma; hypertension has also been reported.</td>
</tr>
</tbody>
</table>

MAO, monoamine oxidase.

Specific Agents

The following section describes the most important 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. **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, and rectal routes. It is well absorbed from the gastrointestinal tract and its bioavailability far exceeds that of oral morphine. Methadone is not only a potent receptor agonist but its racemic mixture of d- and l-methadone isomers can block both NMDA receptors and monoaminergic reuptake. 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 at least every 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 side effects, such as respiratory depression.

Methadone is widely known for its use 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 that 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 due to the increased risk of overdose death secondary to respiratory arrest. **Buprenorphine**, a partial 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

**Meperidine** and **fentanyl** are the most widely used agents in this family of synthetic opioids. Meperidine has significant antimuscarinic effects, which may be a contraindication if tachycardia would be a problem. It is also reported to have a negative inotropic action on the heart. The potential for producing seizures secondary to accumulation of normeperidine in patients receiving high doses of meperidine or with renal compromise must be considered. The fentanyl subgroup now includes *sufentanil, alfentanil,* and *remifentanil* in addition to the parent compound, 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, 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.

Morphinans

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

Mild to Moderate Agonists

Phenanthrenes

**Codeine** (Figure 31–1), **oxycodone, dihydrocodeine,** and **hydrocodone** are all somewhat less efficacious than morphine (they are partial agonists) or have adverse effects that limit the maximum tolerated dose when one attempts to achieve analgesia comparable to that of morphine. These compounds are rarely used alone but are combined in formulations containing aspirin or acetaminophen and other drugs.

Phenylethylamines

**Propoxyphene** is chemically related to methadone but has low analgesic activity. Various studies have reported its potency at levels ranging from no better than placebo to half as potent as codeine, ie, 120 mg propoxyphene = 60 mg codeine. Its true potency probably lies somewhere between these extremes, and its analgesic effect is additive to that of an optimal dose of aspirin. However, its low efficacy makes it unsuitable, even in combination with aspirin, for severe pain. Although propoxyphene has a low abuse liability, the increasing incidence of deaths associated with its misuse has caused it to be scheduled as a controlled substance with low potential for abuse.

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. 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.

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 $\kappa$ receptor agonist and a $\mu$ 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 $\mu$ receptor agonist. Its long duration of action is due to its slow dissociation from $\mu$ 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.

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 $\kappa$ agonist. However, it may also act as a partial agonist or antagonist at the $\mu$ receptor.

Benzomorphans

**Pentazocine** is a $\kappa$ agonist with weak $\mu$ 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.

**Dezocine** is a compound structurally related to pentazocine. It has its highest affinity for $\kappa$ receptors and less interaction with $\mu$ receptors. Although it is said to be equivalent in efficacy to morphine, its use is associated with the same problems observed with all opioids that have mixed receptor actions.

Miscellaneous

**Tramadol** is a central-acting analgesic whose mechanism of action is predominantly based on enhanced serotonergic neurotransmission. As such, its analgesic effectiveness can be blocked by coadministration of the serotonin (5-HT$_3$) receptor antagonist ondansetron. Tramadol also inhibits norepinephrine transporter function and is a weak $\mu$ receptor agonist, since it is only partially antagonized by naloxone. 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. Other side effects include nausea and dizziness, but these symptoms typically abate following several days of therapy. Surprisingly, no clinically relevant 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 $\mu$
receptor action, this agent may be useful in atypical pain such as chronic neuropathic pain.

**Antitussives**

As noted above, 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 is 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). While these agents (other than codeine) are largely free of the adverse effects associated with the opioids, they should be used with caution in patients taking monoamine oxide (MAO) inhibitors (see Table 31–5). Antitussive preparations usually also contain expectorants to thin and liquefy respiratory secretions.

**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 receptor agonists.

**Codeine**, as noted above, 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** (Figure 31–1), **naltrexone**, and **nalmefene** are morphine derivatives with bulkier substituents at the N17 position. These agents have a relatively high affinity for opioid binding sites. They have lower affinity for the other receptors but can also reverse agonists at δ and σ sites.

**Pharmacokinetics**

Naloxone has poor efficacy when given by the oral route and a short duration of action (1–2 hours) when given by injection. 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 will block 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 effects.

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

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 59: Management of the Poisoned Patient). 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. Treatment 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 µg/kg and to consider a second dose of up to a total of 25 µg/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 the use of intravenous or epidural opioids. Careful titration of the naloxone dosage can often eliminate the itching, nausea, and vomiting while sparing the analgesia. Oral naloxone, and more recently developed nonabsorbable analogs of naloxone, have been shown to be efficacious in the treatment of opioid-induced ileus or constipation. The principal mechanism behind this selective therapeutic effect is believed to be local inhibition of µ receptors in the gut with minimal systemic absorption.

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. There is evidence that naltrexone decreases craving for alcohol in chronic alcoholics, and it has been approved by the US Food and Drug Administration for this purpose (see Chapter 23: The Alcohols).

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Preparations Available¹

**Analgesic Opioids**

**Alfentanil** *(Alfenta)*
- Parenteral: 0.5 mg/mL for injection

**Buprenorphine** *(Buprenex, others)*
- Oral: 2, 8 mg sublingual tablets
- 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: 30, 60 mg/mL for injection

**Dezocine** *(Dalgan)*
- Parenteral: 5, 10, 15 mg/mL for injection

**Fentanyl**
- Parenteral *(generic, Sublimaze)*: 50 mg/mL for injection
- Fentanyl Transdermal System *(Duragesic)*: 25, 50, 75, 100 μg/h delivery
- Fentanyl Oralet: 100, 200, 300, 400 μg oral lozenge
- Fentanyl Actiq: 200, 400, 600, 800, 1200, 1600 μg lozenge on a stick

**Hydromorphone** *(generic, Dilaudid)*
- Oral: 1, 2, 3, 4, 8 mg tablets; 5 mg/mL liquid
- Parenteral: 1, 2, 4, 10 mg/mL for injection
- Rectal: 3 mg suppositories

**Levomethadyl acetate** *(Orlaam)*
Oral: 10 mg/mL solution. Note: 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: 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: 10, 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 (Kadian): 20, 50, 100 mg capsules

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 mg tablets, capsules; 1, 20 mg/mL solutions

Oral sustained-release (OxyContin): 10, 20, 40, 80, 100 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

**Propoxyphene** (generic, Darvon Pulvules, others)

Oral: 65 mg capsules, 100 mg tablets. Note: This product is not recommended.

**Remifentanil** (Ultiva)

Parenteral: 3, 5, 10 mg powder for reconstitution for injection

**Sufentanil** (generic, Sufenta)

Parenteral: 50 μg/mL for injection

**Tramadol** (Ultram)

Oral: 50 mg tablets

Analgesic Combinations^2

**Codeine/acetaminophen** (generic, Tylenol w/ 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). *Note:* High-dose acetaminophen has potential for hepatic toxicity with repeated use.

Oral: 5 mg oxycodone plus 325 or 500 mg acetaminophen tablets

**Oxycodone/aspirin** (generic, Percodan)

Oral: 4.9 mg oxycodone plus 325 mg aspirin

**Propoxyphene/aspirin or acetaminophen** (Darvon Compound-65, others). *Note:* This product is not recommended.
Oral: 65 mg propoxyphene plus 389 mg aspirin plus 32.4 mg caffeine; 50, 65, 100 mg propoxyphene plus 325 or 650 mg acetaminophen.

Opioid Antagonists

**Nalmefene** (Revex)

Parenteral: 0.1, 1 mg/mL for injection

**Naloxone** (Narcan, various)

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

**Naltrexone** (ReVia, Depade)

Oral: 50 mg tablets

Antitussives

**Codeine** (generic, others)

Oral: 15, 30, 60 mg tablets; constituent of many proprietary syrups

**Dextromethorphan** (generic, Benylin DM, Delsym, others)

Oral: 2.5, 5, 7.5, 15 mg lozenges; 3.5, 5, 7.5, 10, 15 mg/5 mL syrup; 30 mg sustained-action liquid; constituent of many proprietary syrups

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1 Antidiarrheal opioid preparations are listed in Chapter 63: Drugs Used in the Treatment of Gastrointestinal Diseases.

2 Dozens of combination products are available; only a few of the most commonly prescribed ones 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 damage with acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs contained in these analgesic combinations.

**Chapter 32. Drugs of Abuse**

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Drugs of Abuse: Introduction

The term "drug abuse" is unfortunate because it connotes social disapproval and may have different meanings to different people. One must also distinguish drug abuse from drug misuse. Abuse of a drug might be construed as any use of a drug for nonmedical purposes, usually for altering consciousness but also for bodybuilding. To misuse a drug might be to take it for the wrong indication, in the wrong dosage, or for too long a period, to mention only a few obvious examples. In the context of drug abuse, the drug itself is of less importance than the pattern of use. For example, taking 50 mg of diazepam to heighten the effect of a daily dose of methadone is an abuse...
of diazepam. On the other hand, taking the same excessive daily dose of the drug but only for its anxiolytic effect is misusing diazepam.

**Dependence** is a biologic phenomenon often associated with "drug abuse." **Psychologic dependence** is manifested by compulsive drug-seeking behavior in which the individual uses the drug repetitively for personal satisfaction, often in the face of known risks to health. Cigarette smoking is an example. Deprivation of the agent for a short period of time typically results in a strong desire or craving for it. **Physiologic dependence** is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. It has been suggested that the body adjusts to a new level of homeostasis during the period of drug use and reacts in opposite fashion when the new equilibrium is disturbed. Alcohol withdrawal syndrome is perhaps the best-known example, but milder degrees of withdrawal may be observed in people who drink a lot of coffee every day. Psychologic dependence almost always precedes physiologic dependence but does not inevitably lead to it. **Addiction** is usually taken to mean a state of physiologic and psychologic dependence, but the word is too imprecise for scientific usage.

**Tolerance** signifies a decreased response to the effects of the drug, necessitating ever larger doses to achieve the same effect. Tolerance is closely associated with the phenomenon of physiologic dependence. It is largely due to compensatory responses that mitigate the drug's pharmacodynamic action. **Metabolic tolerance** due to increased disposition of the drug after chronic use is occasionally reported. **Behavioral tolerance**, an ability to compensate for the drug's effects, is another possible mechanism of tolerance. **Functional tolerance**, which may be the most common type, is due to compensatory changes in receptors, effector enzymes, or membrane actions of the drug.

A number of experimental techniques have been devised to predict the ability of a drug to produce dependence and to assess its likelihood for abuse. Most of these techniques employ self-administration of the drug by animals. The rates of reinforcement can be altered so as to make the animal work harder for each dose of drug, providing a semiquantitative measure as well. Comparisons are made against a standard drug in the class, eg, morphine among the opioids. Withdrawal of dependent animals from drugs assesses the nature of the withdrawal syndrome and can be used to test drugs that might cross-substitute for the standard drug. Most agents with significant potential for psychologic or physiologic dependence can be readily detected by these techniques. The actual abuse liability, however, is difficult to predict, since many variables enter into the decision to abuse drugs.

**Cultural Considerations**

Each society accepts certain drugs as licit and condemns others as illicit. In the USA and most of Western Europe, the "national drugs" are caffeine, nicotine, and alcohol. In the Middle East, cannabis may be added to the list of licit drugs, whereas alcohol is forbidden. Among certain Native American tribes, peyote, a hallucinogen, may be used licitly for religious purposes. In the Andes of South America, cocaine is used to allay hunger and enhance the ability to perform arduous work at high altitudes. Thus, which drugs are licit or illicit or—to use other terminology—"used" or "abused" is a social judgment. A major social cost of relegating any substance to the illicit category is the criminal activity that often results, since purveyors of the substance are lured into illegal traffic by the opportunity to make large profits, while dependent users may resort to robbery, prostitution, and other types of antisocial behavior to support their habits. A major social and medical cost associated with parenteral abuse of drugs is the high incidence of transmission of HIV and hepatitis virus through the sharing of needles.
Current attitudes in the USA to drugs of this type are reflected in the Schedule of Controlled Drugs. This schedule is quite similar to those published by international control bodies. Such schedules affect principally ethical and law-abiding manufacturers and prescribers of the drugs and have little deterrent effect on illicit manufacturers or suppliers. Such schedules have been circumvented by the synthesis of "designer" drugs that make small modifications of the chemical structures of drugs with little or no change in their pharmacodynamic actions. Thus, schedules must constantly be revised to include these attempts to produce compounds not currently listed.

Because of the high social cost of drug abuse, many countries attempt to interdict their entry across borders. While surveys may indicate that the use of drugs such as cocaine and marijuana is increasing or decreasing, it is difficult to attribute such changes to law enforcement policies. Little progress has been made in decreasing the demand for illicit drugs. Some persons have argued that the only reasonable solution to the problem is legalization of the drugs. Such proposals are obviously highly controversial.

Any use of mind-altering drugs is based on a complicated interplay between three factors: the user, the setting in which the drug is taken, and the drug. Thus, the personality of the user and the setting may have a strong influence on what the user experiences. Nonetheless, it is usually possible to identify a pharmacologic "core" of drug effects that will be experienced by almost anyone under almost any circumstances if the dosage is adequate.

Schedule of Controlled Drugs

**SCHEDULE I**
(All nonresearch use illegal under federal law.)

- **Flunitrazepam** (Rohypnol)
- **Narcotics:** Heroin and many nonmarketed synthetic narcotics
- **Hallucinogens:**
  - LSD
  - MDA, STP, DMT, DET, mescaline, peyote, bufotenine, ibogaine, psilocybin, hencyclidine (PCP; veterinary drug only)
- **Marijuana**
- **Methaqualone**

**SCHEDULE II**
(No telephone prescriptions, no refills.)

- **Opioids:**
  - Opium
  - Opium alkaloids and derived phenanthrene alkaloids: morphine, hydromorphone (Dilaudid), oxymorphone (Numorphan), oxycodone (dihydroxycodeinone, a component of Percodan, Percocet, Roxicodone, Tylox)
  - Designated synthetic drugs: levomethadyl (Orlaam), meperidine (Demerol), methadone, levorphanol (Levo-Dromoran), fentanyl (Sublimaze, Duragesic, Actiq), alphaprodine, alfentanil (Alfenta), sufentanil (Sufenta), remifentanil (Ultiva)
- **Stimulants:**
  - Coca leaves and cocaine
  - Amphetamine
  - Amphetamine complex (Biphetamine)
  - Amphetamine salts (Adderall)
  - Dextroamphetamine (Dexedrine)
  - Methamphetamine (Desoxyn)
  - Phenmetrazine (Preludin)
Methylphenidate (Ritalin)
Above in mixtures with other controlled or uncontrolled drugs

**Depressants:**
- Amobarbital (Amytal)
- Pentobarbital (Nembutal)
- Secobarbital (Seconal)
- Mixtures of above (eg, Tuinal)

**SCHEDULE III**
(Prescription must be rewritten after 6 months or five refills.)

**Opioids:**
- Buprenorphine (Buprenex, Subutex, Suboxone)
  The following opioids in combination with one or more active nonopioid ingredients, provided the amount does not exceed that shown:
  - Codeine and dihydrocodeine: not to exceed 1800 mg/dL or 90 mg/tablet or other dosage unit
  - Dihydrocodeinone (hydrocodone in Hycodan, Vicodin, and Lortab): not to exceed 300 mg/dL or 15 mg/tablet
  - Opium: 500 mg/dL or 25 mg/5 mL or other dosage unit (paregoric)

**Stimulants:**
- Benzphetamine (Didrex)
- Phendimetrazine (Plegine)

**Depressants:**
- Schedule II barbiturates in mixtures with noncontrolled drugs or in suppository dosage form
  - Butabarbital (Butisol)
  - Ketamine (Kentalar)
  - Thiopental (Pentothal)

**Cannabinoids:**
- Dronabinol (Marinol)

**Anabolic Steroids:**
- Fluoxymesterone (Halotestin)
- Methyltestosterone (Android, Testred)
- Nandrolone decanoate (Dec-Durabolin)
- Nandrolone phenpropionate (Durabolin)
- Oxandrolone (Oxandrin)
- Oxymetholone (Androl-50)
- Stanozolol (Winstrol)
- Testolactone (Teslac)
- Testosterone and its esters

**SCHEDULE IV**
(Prescription must be rewritten after 6 months or five refills; differs from Schedule III in penalties for illegal possession.)

**Opioids:**
- Butorphanol (Stadol)
- Difenoxin (Motofen)
- Pentazocine (Talwin)
- Propoxyphene (Darvon)

**Stimulants:**
- Diethylpropion (Tenuate)
- Mazindol (Sanorex)
- Modafinil (Provigil)
Phentermine (Ionamin)
Pemoline (Cylert)
Sibutramine (Merida)

**Depressants:**
Benzodiazepines
Alprazolam (Xanax)
Chlordiazepoxide (Librium)
Clonazepam (Klonopin)
Clorazepate (Tranxene)
Diazepam (Valium)
Estazolam (ProSom)
Flurazepam (Dalmane)
Halazepam (Paxipam)
Lorazepam (Ativan)
Midazolam (Versed)
Oxazepam (Serax)
Prazepam (Centrax)
Quazepam (Doral)
Temazepam (Restoril)
Triazolam (Halcion)
Chloral hydrate
Ethchlorvynol (Placidyl)
Meprobamate (Equanil, Miltown, etc)
Mephobarbital (Mebaral)
Methohexital (Brevital)
Paraldehyde
Phenobarbital
Zaleplon (Sonata)
Zolpidem (Ambien)

**SCHEDULE V**
(As any other nonopioid prescription drug; may also be dispensed without prescription unless additional state regulations apply.)

**Opioids:**
Diphenoxylate (not more than 2.5 mg and not less than 0.025 mg of atropine per dosage unit, as in Lomotil)

The following drugs in combination with other active nonopioid ingredients and provided the amount per 100 mL or 100 g does not exceed that shown:
Codeine: 200 mg
Dihydrocodeine: 100 mg


2Emergency prescriptions may be telephoned if followed within 7 days by a valid written prescription annotated to indicate it was previously placed by telephone.

**Neurobiology of Abused Drugs**

During the last 20 years, substantial progress has been made in elucidating the neurobiology of abused drugs and their effects not only on neurotransmitter receptors and reuptake carriers but also on the cascade of second, third, and fourth intracellular messenger systems (Nestler, 2001). Many abused drugs act through G protein-linked receptors such as the opioid, cannabinoid, and dopamine...
receptors. These G proteins frequently are coupled to the cyclic adenosine monophosphate (cAMP) second messenger system, and through phosphorylation of various intracellular proteins a cascade of changes occurs in the cytoplasm and nucleus. Immediate early genes such as c-fos and c-jun are activated followed by regulation of other genes with more sustained effects on protein transcription that may lead to the observed down-regulation of receptor numbers and up-regulation of second messenger systems. These effects on DNA are also reflective of genetic risk factors for drug dependence; it is estimated that up to 50% of the risk for dependence is due to polygenic inheritance. Extensive studies are underway for alcohol, opioids, and stimulants including nicotine in order to identify specific genes associated with this risk.

For each of the classes of abused drugs a complex molecular biology has been described, including specific neuroanatomic substrates linked to different neurotransmitters during acute intoxication and during withdrawal after dependence is established. Acute reinforcing effects of abused drugs are clearly a function of specific receptor binding but are also related to the rate of change in synaptic levels of dopamine, a key neurotransmitter involved in reinforcement in the nucleus accumbens. The chronic effects of abused drugs include tolerance and sensitization as well as the neurobiologic substrates for withdrawal symptoms. Much has been learned about these neurobiologic substrates for withdrawal in opioid dependence, including the activation of adrenergic brain systems such as the locus ceruleus during withdrawal. The latter findings have important treatment implications, such as the use of clonidine for opioid withdrawal.

Other drug classes, such as the benzodiazepines, have specific receptors on chloride channels associated with the neurotransmitter γ-aminobutyric acid (GABA), while other abused drugs, such as phencyclidine, bind to sites on excitatory amino acid receptor-channel complexes. The functions of other receptors that bind abused drugs such as opioid and cannabinoid receptors also have been clarified with the identification of endogenous ligands for these receptors, such as δ-endorphin for the μ-opioid receptor and anandamide for the cannabinoid receptor. These binding sites appear to be critical for the acute effects of these abused drugs, and substantial progress has been made in understanding the neurotransmitter basis for reinforcement of most abused drugs including recent work with the inhalant toluene (Riegel and French, 2002). The dopamine neurons connecting the ventral tegmental area to the nucleus accumbens have been considered the major reinforcement pathway for a wide range of abused drugs, but their role in reinforcement has been most clearly established for cocaine and amphetamine and less clearly for other drugs, particularly inhalants and several hallucinogens.

The neurobiologic findings in animal models have been increasingly confirmed in human studies. These human studies include pharmacologic challenges with neuroendocrine and behavioral outcomes, assessments of endogenous ligands in cerebrospinal fluid from drug-dependent patients, and neuroimaging studies, particularly neuroreceptor imaging. Available radioligands have permitted examination in humans of dopamine receptors and transporters, opioid receptors, and functional brain activity based on blood flow or glucose utilization. These receptor-neuroimaging studies have demonstrated that chronic abuse of drugs which can produce tolerance, dependence, and sensitization may have associated effects on receptor numbers (eg, dopamine D$_2$ receptors decrease in cocaine abusers) and on transporter numbers (eg, dopamine transporters increase in cocaine abusers). Blood flow and glucose utilization studies have shown that acute drug use is associated with substantial reductions in cerebral metabolic activity and that the rate of change is a correlate of the reinforcing effects of abused drugs.

In the following sections, we review current knowledge about the molecular neurobiology of each class of abused drugs and their clinical pharmacology.
Opioids

History

The nepenthe (Gk "free from sorrow") mentioned in the *Odyssey* probably contained opium. Opium smoking was widely practiced in China and the Near East until recently. Isolation of active opium alkaloids and the introduction of the hypodermic needle, allowing parenteral use of morphine, increased opioid use in the West. The first of several "epidemics" of opioid use in the USA followed the Civil War. About 4% of adults in the USA used opiates regularly during the postbellum period. By the 1900s, the number had dropped to about 1 in 400 people in the USA, but the problem was still considered serious enough to justify passage of the Harrison Narcotic Act just before World War I. A new epidemic of opioid use started around 1964 and has continued unabated ever since. While fear of AIDS has reduced intravenous use of heroin, recent increases in its purity have led to markedly increased intranasal use. Present estimates are that the number of opioid-dependent people in the USA has stabilized at around 750,000.

Chemistry & Pharmacology

The most commonly abused drugs in this group are heroin, morphine, oxycodone, and—among health professionals—meperidine. The chemistry and general pharmacology of these agents are presented in Chapter 31: Opioid Analgesics & Antagonists.

Tolerance to the mental effects of opioids develops with long-term use. The need for ever-increasing amounts of drugs to sustain the desired euphoriant effects—as well as to avoid the discomfort of withdrawal—has the expected consequence of strongly reinforcing dependence once it has started. The role of endogenous opioid peptides in opioid dependence is uncertain.

Clinical Aspects

Intravenous administration is routine not only because it is the most efficient route but also because it produces a bolus of high concentration of drug that reaches the brain to produce a "rush," followed by euphoria, a feeling of tranquility, and sleepiness ("the nod"). Heroin produces effects that last 3–5 hours, and several doses a day are required to forestall manifestations of withdrawal in dependent persons. Symptoms of opioid withdrawal begin 8–10 hours after the last dose. Many of these symptoms resemble those of increased activity of the autonomic nervous system. Lacrimation, rhinorrhea, yawning, and sweating appear first. Restless sleep followed by weakness, chills, gooseflesh ("cold turkey"), nausea and vomiting, muscle aches, and involuntary movements ("kicking the habit"), hyperpnea, hyperthermia, and hypertension occur in later stages of the withdrawal syndrome. The acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.

Heroin users in particular tend to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants. None of these other drugs serve as substitutes for opioids, but they have desired additive effects. One needs to be sure that the person undergoing a withdrawal reaction is not also withdrawing from alcohol or other sedatives, which might be more dangerous and more difficult to manage.
Besides the ever-present risk of fatal overdose, hepatitis B and AIDS are among the many potential complications of sharing contaminated hypodermic syringes. Bacterial infections lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs. Attempts to illicitly manufacture meperidine have resulted in the highly specific neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which produces parkinsonism in users (see Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders).

Treatment

Treatment of acute overdoses of opioids can be lifesaving and is described in Chapters 31 and 59. In long-term treatment of opioid-dependent persons, pharmacologic and psychosocial approaches are often combined. Chronic users tend to prefer pharmacologic approaches; those with shorter histories of drug abuse are more amenable to detoxification and psychosocial interventions.

Pharmacologic treatment is most often used for detoxification. The principles of detoxification are the same for all drugs: to substitute a longer-acting, orally active, pharmacologically equivalent drug for the abused drug, stabilize the patient on that drug, and then gradually withdraw the substituted drug. Methadone is admirably suited for such use in opioid-dependent persons. Clonidine, a centrally acting sympatholytic agent, has also been used for detoxification. By reducing central sympathetic outflow, clonidine mitigates many of the signs of sympathetic overactivity. Clonidine has no narcotic action and is not addictive. Lofexidine, a clonidine analog with less hypotensive effect, is being developed for use.

While it is easy to detoxify patients, the recidivism rate (return to abuse of the agent) is high. Methadone maintenance therapy, which substitutes a long-acting orally active opioid for heroin, has been effective in some settings. A single dose can be given each day. Methadone saturates the opioid receptors and prevents the desired sudden onset of central nervous system effects normally produced by intravenous administration of additional opiates. An even longer-acting methadone analog, 1-acetylmethadol, allows three times a week rather than daily dosing and reduced abuse potential, but its association with sudden cardiac death due to prolonged QT arrhythmias has made its use uncommon. Another candidate drug for use in this setting is buprenorphine, a partial opioid agonist, that can be given once daily or even less often at sublingual doses of 4–32 mg daily depending on the patient. The lower doses are useful for detoxification from heroin, while the higher doses are for longer maintenance treatment. Treatment in an office-based primary care setting is a potential advantage of this agent over methadone (Kosten, 2002).

Use of a narcotic antagonist is a rational alternative to the above agonist-based therapies because blocking the action of self-administered opioids should eventually extinguish the habit, but this therapy is poorly accepted by patients. Naltrexone, a long-acting orally active pure opioid antagonist, can be given three times a week at doses of 100–150 mg and a depot form for monthly administration is being developed. Because it is an antagonist, the patient must first be detoxified from opioid dependence before starting naltrexone.

Psychosocial approaches include drug-free residential communities, which use peer group pressures, emphasizing confrontation and discussion.
History

Ethanol is the sedative-hypnotic with the longest history of both use and abuse; it is discussed in Chapter 23: The Alcohols. Barbiturates were introduced in 1903; they have been largely replaced in medical practice by newer agents, especially benzodiazepines in the 1960s (see Chapter 22: Sedative-Hypnotic Drugs). Short-acting members of the sedative-hypnotic group are widely abused and the most recent addition to this abused group is gamma-hydroxybutyric acid (GHB).

Chemistry & Pharmacology

The chemical relationships among this class of drugs are reviewed in Chapter 22: Sedative-Hypnotic Drugs. Depending on the dose, these drugs produce sedation, hypnosis, anesthesia, coma, and death. Both barbiturates and benzodiazepines can be classified pharmacokinetically into short- and long-acting compounds; GHB is relatively short-acting. Most abuse involves short-acting drugs, eg, secobarbital or pentobarbital sodium, and not long-acting ones, eg, phenobarbital. Drugs with half-lives in the range of 8–24 hours produce a rapidly evolving, severe withdrawal syndrome; those with longer half-lives, eg, 48–96 hours, produce a withdrawal syndrome that is slower in onset and less severe but longer in duration. Drugs with half-lives longer than 96 hours usually have a built-in tapering-off action that reduces the possibility of withdrawal reactions.

Clinical Aspects

Although statistics on alcoholism are extensive, no one knows how many persons are dependent on prescription sedatives. However, physiologic dependence has been relatively rare and usually occurs following long-term treatment with doses of 40 mg/d or more of diazepam or its equivalent. These abusers often are codependent on other drugs such as opioids, alcohol, or stimulants. "Therapeutic dose dependence" at doses of 15–30 mg/d of diazepam may be characterized by weight loss, changes in perception, paresthesias, and headache.

Finally, very rapid onset benzodiazepines have been widely reported as a means of "date rape," by using a small tasteless dose of the drug to make the victim incapable of protecting herself (or himself). This produces intoxication but not dependence. The drug most commonly used in this situation has been flunitrazepam (Rohypnol, "roofies," not available in the USA) and more recently GHB. The amnesia-producing effects of the benzodiazepines (see Chapter 22: Sedative-Hypnotic Drugs) make the victim unable to describe the events after she or he has recovered.

As these drugs are usually taken orally and the tablets or capsules are consistent in drug content, inadvertent fatal overdoses of single agents are rare. Tolerance may develop to the sedative effect but not to the respiratory depressant effect. Thus, if these drugs are used with other respiratory depressants, eg, large amounts of alcohol or opioids, fatalities can occur.

The withdrawal syndrome from sedatives is almost identical to that from alcohol and includes anxiety, tremors, twitching, and nausea and vomiting. In the case of long-acting drugs, symptoms may not appear for 2–3 days, and initial symptoms may suggest a recrudescence of those originally treated (nervousness, anxiety). Only by the fourth or fifth day can one be sure that a withdrawal reaction is under way. Convulsions are a late manifestation when they do occur—often not until the eighth or ninth day. Following this, the syndrome subsides. Severe cases are associated with delirium, hallucinations, and other psychosis-like manifestations.

Treatment
If short-acting drugs have been abused, chlordiazepoxide or phenobarbital is substituted as the pharmacologically equivalent agent. If long-acting drugs have been used, the same drug may be continued. The patient is stabilized on whatever dose is required to cause signs and symptoms to abate, and the drug is then gradually withdrawn. The rate of decrement may be 15–25% of the daily dose early in treatment, with later decrements of 5–10%. Complete detoxification can usually be achieved in less than 2 weeks.

No specific treatment programs have been developed for prescription sedative abusers. The problem is so often complicated by abuse of other drugs that it may be more expeditious to enroll the patient in a program designed for alcoholics or opiate-dependent persons. Patients with psychiatric disorders that can be defined, especially those with depression, may be treated with drug therapy specific for the underlying disorder.

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Stimulants

History

In this section, caffeine is discussed only briefly and the focus is on other stimulants that produce psychiatric disorders. Caffeine can lead to a withdrawal syndrome characterized by lethargy, irritability, and headache, but withdrawal appears to occur in less than 3% of regular coffee drinkers. Moreover, the morbidity associated with caffeine overdose, which can include disturbing effects on sleep and heart rhythm, is much less than the morbidity associated with other stimulants.

Nicotine is one of the most widely used licit drugs because it is heavily promoted and produces powerful psychologic and physical dependence. About 28% of adults in the USA still smoke cigarettes because they have become dependent on nicotine. The use of smokeless tobacco products (eg, snuff, chewing tobacco) has increased in adolescents. Deaths directly attributable to smoking account for 20% of all deaths and 30% of cancer deaths in the USA. It is estimated that about 90% of cases of chronic obstructive pulmonary disease in the USA are due to smoking. Cocaine is a plant product that has been used for at least 1200 years in the custom of chewing coca leaves by natives of the South American Andes. In contrast, amphetamine was synthesized in the late 1920s and has a large number of analogs including methylphenidate (Ritalin) and methylenedioxymethamphetamine (MDMA, "ecstasy"). A closely related natural alkaloid, cathinone, is found in khat, a plant that produces effects indistinguishable from those of the amphetamines.

Chemistry & Pharmacology

Despite their similar behavioral effects, caffeine, nicotine, cocaine, and amphetamine have very different structures and sites of action in the brain. Caffeine, a methylxanthine compound, appears to exert its central actions (and perhaps some of its peripheral ones as well) by blocking adenosine receptors. Because caffeine does not act on the dopaminergic brain structures related to reward and addiction, its abuse and dependence potential are quite small. As noted in the above section Neurobiology of Abused Drugs, dopamine is very important in the reward system of the brain; its increase probably accounts for the high dependence potential of cocaine. Cocaine binds to the dopamine reuptake transporter in the central nervous system, effectively inhibiting reuptake of dopamine as well as norepinephrine. Amphetamines probably act mainly by increasing release of catecholaminergic neurotransmitters, including dopamine, by reversal of the vesicular transporter.
A useful model of the action of these two drugs in the reward centers of the CNS is shown in Figure 32–1. Cocaine reduces reuptake of dopamine into the neuron by inhibiting the dopamine reuptake transporter. Amphetamine causes the intracellular release of dopamine within the terminal and reverses the transporter direction so that dopamine is released into the synapse by reverse transport rather than ordinary exocytosis. In addition, amphetamine inhibits intracellular MAO metabolism of dopamine. Note that both drugs result in an increase in the concentration of dopamine in the synapse.

Clinical Aspects

One common pattern of amphetamine or cocaine abuse is called a "run." Repeated smoked or intravenous injections are self-administered to obtain a "rush"—an orgasm-like reaction—followed by a feeling of mental alertness and marked euphoria. When free base cocaine is smoked, entry through the lungs is almost as fast as by intravenous injection, so that effects are more accentuated
than when the drug is snorted (Figure 32–2). Because the plasma half-life of cocaine is short, effects following a single dose persist only for an hour or so and repeated dosing may occur every 30 minutes. Because tolerance develops quickly, abusers may take monumental doses compared with those used medically, eg, as anorexiant. Total daily amphetamine doses as high as 4000 mg have been reported. After several days of such spree use, subjects may enter a paranoid schizophrenia-like state. Typically, delusions that bugs are crawling under their skin develop, which leads to scratching and characteristic discrete excoriations. Finally, the spree is terminated by exhaustion from lack of sleep and lack of food, followed by a withdrawal syndrome. A typical pattern of withdrawal includes a ravenous appetite, exhaustion, and mental depression. This syndrome may last for several days after the drug is withdrawn.

Besides the paranoid psychosis associated with chronic use of amphetamines, a specific lesion associated with chronic amphetamine use is necrotizing arteritis, which may involve many small and medium-sized arteries and lead to fatal brain hemorrhage or renal failure. Overdoses of amphetamines are rarely fatal; they can usually be managed by sedating the patient with benzodiazepines.

Overdoses of cocaine are often rapidly fatal, victims dying within minutes from arrhythmias, seizures, or respiratory depression. Those who survive for 3 hours usually recover fully. Intravenous administration of diazepam, propranolol, or calcium channel-blocking drugs may be the best.
treatment. The local anesthetic action of cocaine contributes to the production of seizures. The powerful vasoconstrictive action of cocaine has led to a significant number of patients with severe acute hypertensive episodes resulting in myocardial infarcts and strokes. This vasoconstrictive effect may also contribute to the multiple brain perfusion defects that have been described using single photon emission computed tomography (SPECT) blood flow imaging in cocaine abusers (Kosten, 1998). Finally, an epidemic of "cocaine babies" born to mothers who are using cocaine heavily has posed a major new challenge to health care facilities in the inner cities (Mayes, 1999). There are clear-cut deleterious effects on the pregnancy, with increased fetal morbidity and mortality as well as early childhood impairment in learning and attention.

Treatment

Subjects with residual emotional disorders, either schizophreniform psychosis or mental depression, may require treatment with antipsychotic or antidepressant drugs during weaning from stimulants. Dopamine agonists have been suggested to mitigate withdrawal from cocaine, reduce craving during abstinence, and facilitate abstinence, but neither these nor other agents have shown reliable efficacy. Depression occurs in up to 40% of stimulant-dependent patients, and antidepressants may be helpful for relapse prevention.

Nicotine dependence may respond to replacement therapy with either nicotine gum or transdermal patches, and detoxification from nicotine dependence has been described using clonidine. Bupropion, an antidepressant, also shows efficacy for smoking cessation. The nicotinic receptor blocker mecamylamine, which has good central nervous system access, has been used with limited efficacy. Overall, success rates for smoking abstinence at 1 year are about 20%, with even less success for depressed smokers.

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Hallucinogens

History

Almost every society has found some bark, skin, leaf, vine, berry, fungus, or weed that contains "hallucinogenic" materials, but neither hallucinations nor psychotic states are typically induced by these drugs. The more recent "club drugs" including MDMA have also been considered to be like hallucinogens, but club drugs are better considered as related to either stimulants (MDMA) or sedatives (GHB).

Chemistry & Pharmacology

The LSD-like group of drugs includes lysergic acid diethylamide (LSD), mescaline, psilocybin, and their related compounds. LSD is a synthetic agent related to the ergot alkaloids (see Chapter 16: Histamine, Serotonin, & the Ergot Alkaloids), while mescaline, a phenethylamine derivative, and psilocybin, an indol-ethylamine derivative, are found in nature. Representative structures are shown in Figure 32–3. These drugs also have chemical resemblances to three major neurotransmitters: norepinephrine, dopamine, and serotonin. LSD interacts with several serotonin (5-HT) receptor subtypes in the brain. The drug displays agonist activity at 5-HT1A and 5-HT1C receptors. These actions may be more relevant to LSD's hallucinogenic action than its 5-HT2 receptor antagonism, because a number of other drugs with good antagonist effects at central 5-HT2 receptors are not
Phencyclidine (PCP, "angel dust," many other names) is a synthetic phenylcyclohexylamine derivative originally used as a veterinary anesthetic. Ketamine, an analog, replaced phencyclidine as an anesthetic for use in humans (see Chapter 25: General Anesthetics). It too produces some emergent hallucinogenic effects. Since the 1970s, PCP and more recently ketamine have become widely accepted by drug abusers as desirable hallucinogenic agents. Phencyclidine may be smoked (by mixing the powder with tobacco), "snorted," taken orally, or injected intravenously.

Receptors for PCP have been identified in the brain, and PCP acts as an antagonist on the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. The drug is unique among hallucinogens in that animals will self-administer it.

The deliriant hallucinogens, exemplified by scopol-amine (see Chapter 8: Cholinoceptor-Blocking Drugs) and some synthetic centrally acting cholinoceptor-blocking agents, are different chemically as well as pharmacologically from the LSD group. Their effects seem to be entirely explainable by blockade of central muscarinic receptors. Similar mental effects may be seen during therapeutic or deliberate overdoses of commonly used medications with antimuscarinic action, such as
anticholinergic antiparkinsonism drugs, tricyclic antidepressants, and antispasmodics. Occasional instances of abuse of these therapeutic agents have occurred.

Clinical Effects

LSD produces a series of somatic, perceptual, and psychological effects that overlap each other. Dizziness, weakness, tremors, nausea, and paresthesias are prominent somatic symptoms. Blurring of vision, distortions of perspective, organized visual illusions or "hallucinations," less discriminant hearing, and a change in sense of time are common perceptual abnormalities. Impaired memory, difficulty in thinking, poor judgment, and altered mood are prominent psychological effects. Physiologically, LSD produces signs of central stimulation and overactivity of the sympathetic nervous system, manifested by dilated pupils, increased heart rate, mild elevation of blood pressure, tremor, and alertness. Virtually identical effects are produced by mescaline and psilocybin when they are given in equivalent doses. The onset of effects is fairly rapid, but the duration varies with the dose and is usually measured in hours. Phenomena may vary considerably from one user to another owing to such factors as the personality and expectations of the user and the circumstances under which the drug is taken, but the above effects occur in almost everyone. Waxing and waning of effects is typical.

Usual doses of LSD in humans are approximately 1–2 μg/kg, making it one of the most potent pharmacologic agents known. The drug is equally effective parenterally or orally and consequently is almost always taken by mouth. Psilocybin is usually taken in doses of 250 μg/kg and mescaline in doses of 5–6 mg/kg. Despite these differences in potency, the effects are virtually indistinguishable.

PCP and ketamine produce detachment, disorientation, distortions of body image, and loss of proprioception. Somatic symptoms and signs include numbness, nystagmus, sweating, rapid heart rate, and hypertension. Overdosage has been fatal, as contrasted with the absence of known human fatalities directly caused by drugs of the LSD group.

Scopolamine and other antimuscarinic drugs produce delirium with fluctuating levels of awareness, disorientation, marked difficulty in thinking, marked loss of memory, and bizarre delusions. Most subjects, at least under experimental conditions, find these drugs to be unpleasant and have little desire to repeat the experience.

Use of these hallucinogens has not been associated with dependence or physiologic withdrawal symptoms. This is probably because tolerance develops rapidly, so that closely spaced dosing would be necessary to cause dependence; such frequent dosing is unusual.

Treatment

Common adverse psychologic consequences of hallucinogenic drugs include panic reactions ("bad trips") and acute psychotic reactions with PCP. Treatment includes benzodiazepines for sedation and constant monitoring by a nondrugged companion for several hours. Acidification of the urine (see Chapter 59: Management of the Poisoned Patient) may hasten PCP excretion.

Overdoses of the antimuscarinic agents can be treated with infusions of physostigmine, but supportive care is usually preferred.
Marijuana

History

Use of cannabis has been recorded for thousands of years, and about 200–300 million people use it currently, including 30–40 million persons in the USA. Recent surveys suggest its use is starting at an earlier age (sixth to eighth grade, 11–13 years). Because of proposed medical uses, it has been legalized in several states, although federal law prohibits its distribution for any purpose. Much cannabis is now grown indoors using genetically altered strains with 10-fold higher levels of Δ⁹-tetrahydrocannabinol (THC) (see below).

Chemistry & Pharmacology

With the exception of THC and its analogs, no other cannabinoids have definite psychoactivity, and the content of THC varies considerably among plants. Special genetic plant lines may produce as much as 4–6% THC content.

The preferred route of administration in Western countries is by smoking. The high lipid solubility of the drug leads to extensive sequestration in the lipid compartments of the body, and metabolites may be excreted for as long as a week after a single dose.

A G protein-coupled cannabinoid receptor (CB1) is most numerous in the outflow nuclei of the basal ganglia, the substantia nigra, pars reticulata, globus pallidus, hippocampus, and brainstem. Positron emission tomographic (PET) studies have revealed increases in metabolism following THC in the same areas in which receptors are localized, suggesting that these receptors are closely involved in the clinical actions of the drug.

THC has a variety of pharmacologic effects that resemble those of amphetamines, LSD, alcohol, sedatives, atropine, and morphine. Important opioid interactions include reduction in opioid dependence in CB1 knockout mice lacking the CB1 receptor.

Clinical Effects

The expert smoker of marijuana is usually aware of a drug effect after two or three inhalations. As smoking continues, the effects increase, reaching a maximum about 20 minutes after the smoke has been finished. Most effects of the drug usually have vanished after 3 hours, by which time plasma concentrations are low. Peak effects after oral administration may be delayed until 3–4 hours after
drug ingestion but may last for 6–8 hours.

The early stage is one of being "high" and is characterized by euphoria, uncontrollable laughter, alteration of time sense, depersonalization, and sharpened vision. Later, the user becomes relaxed and experiences introspective and dream-like states if not actual sleep. Thinking or concentrating becomes difficult, though by force of will the subject can attend.

Two characteristic physiologic signs of cannabis intoxication are increased pulse rate and reddening of the conjunctiva. The latter correlates well with the presence of detectable plasma concentrations. Pupil size is not changed. The blood pressure may fall, especially in the upright position. An antiemetic effect may be present. Muscle weakness, tremors, unsteadiness, and increased deep tendon reflexes may also be noted. Virtually any psychologic test shows impairment if the doses are large enough and the test difficult enough. No distinctive biochemical changes have been found in humans.

Tolerance has been demonstrated in virtually every animal species that has been tested. It is apparent in humans only among heavy long-term users of the drug. Different degrees of tolerance develop for different effects of the drug, with tolerance for the tachycardic effect developing fairly rapidly. A mild withdrawal syndrome has been noted following chronic use at very high doses.

Three epidemiologic studies in developing countries have failed to find definite evidence of impairment among heavy users of cannabis, but field studies may lack sensitivity. Experimental studies in which subjects have smoked heavily for varying periods have shown a lower serum testosterone level in men and airway narrowing. Reports of effects on immune mechanisms, chromosomes, and cell metabolism are often contradictory. Effects on the fetus are still uncertain.

Heavy smokers of marijuana may be subject to some of the same problems of chronic bronchitis, airway obstruction, and squamous cell metaplasia as smokers of tobacco cigarettes. Angina pectoris may be aggravated by the speeding of the heart rate, orthostatic hypotension, and increased carboxyhemoglobin. Driving ability is likely to be impaired but is not easily demonstrated with usual testing. "Amotivational syndrome," in which promising young people with obvious social advantages lose interest in school and career and enter the drug culture, is a real phenomenon, but one cannot be sure whether drug use is the cause of the problem or simply a matter of personal choice. Acute panic reactions, toxic delirium, paranoid states, and frank psychoses are rare. Brain damage has not been confirmed in humans, although some suggestion of ultrastructural damage has been found in animals.

Therapeutic THC is called dronabinol (Marinol) and has been marketed with approval by the Food and Drug Administration to reduce nausea and vomiting in patients undergoing cancer chemotherapy and to stimulate appetite in AIDS patients. It has also been shown to reduce intraocular pressure in glaucoma. Levonantradol, an analog, may be useful as an analgesic.

Few abusers seek treatment, but recent studies have suggested that behavioral treatments can stop abuse and improve cognitive functioning.

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Inhalants
Chemistry

Four types of inhalants are abused: (1) anesthetic gases; (2) industrial solvents, including a variety of hydrocarbons, such as toluene; (3) aerosol propellants, such as various fluorocarbons; and (4) organic nitrites, such as amyl or butyl nitrite. The mode of action of the inhalant anesthetics has been discussed in Chapter 25: General Anesthetics.

Clinical Aspects

Anesthetic gases such as nitrous oxide produce difficulty in concentrating, dreaminess, euphoria, numbness and tingling, unsteadiness, and visual and auditory disturbances. Nitrous oxide is usually taken as 35% N₂O mixed with oxygen; administration of 100% nitrous oxide may cause asphyxia and death. Ether and chloroform are readily available, and after an initial period of exhilaration, the person often loses consciousness.

Industrial solvents include gasoline, and various toxins such as toluene, benzene, and trichloroethylene. The clinical effects of industrial solvent inhalation are short, lasting only 5–15 minutes. Rags or "toques" are soaked in the solvent and the fumes inhaled. Aerosol propellants are usually inhaled from a plastic bag. Euphoria and a relaxed "drunk" feeling are followed by disorientation, slow passage of time, and possibly hallucinations.

Organic nitrites (amyl nitrite and isobutyl nitrite) cause dizziness, giddiness, rapid heart rate, lowered blood pressure, "speeding," and flushing of the skin. These effects last only a few minutes and can readily be repeated. The main effect of the drug on sexual performance is probably to enhance or prolong erection through the release of nitric oxide in the corpora cavernosa (see Chapter 19: Nitric Oxide, Donors, & Inhibitors).

Toxicity from chronic use of inhalants can be severe. Industrial solvents have produced liver, kidney, peripheral nerve, and possibly brain damage in animals, bone marrow suppression, and pulmonary disease. In human neuroimaging studies using magnetic resonance imaging, demyelination of white matter has been described in chronic abusers. Fluorocarbon inhalation has resulted in sudden deaths, due either to ventricular arrhythmias or to asphyxiation. Nitrites have been rather safe but might pose hazards (especially arrhythmias) for persons with preexisting cardiovascular problems. Finally, recent data have indicated that nitrate inhalants may reduce lymphocyte counts and natural killer cell activity, thereby acting as a cofactor for AIDS progression.

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Steroids

History

Anabolic steroids were first used in competitive sports during the 1940s, and by the late 1980s, use was widespread in adolescents with distribution points in gymnasiums and physical fitness centers. However, the first urine testing for anabolic steroids did not occur until 1976 at the Olympic Games because of the fairly difficult assay methods needed for detection. These drugs are discussed in Chapter 40: The Gonadal Hormones & Inhibitors.
Clinical Use & Effects

Oral and injectable formulations of different steroids are often "stacked," ie, used simultaneously. Because detection of these different steroids is difficult and expensive, the history from the patient rather than urine toxicology is more generally useful for detecting anabolic steroid abuse. Anabolic steroids were added to Schedule III of the Controlled Substances Act in 1990.

Anabolic steroids are typically abused in a cyclic fashion, with a cycle of 4–18 weeks on steroids and 1 month to 1 year off. Abuse of other psychoactive drugs may occur in up to a third of these patients, but this is low compared with other substance abusers because of concerns about health and appearance by steroid abusers. The primary effects sought by abusers are increased muscle mass and strength, not euphoria. In the context of an adequate diet and sufficient physical activity, a significant increase in muscle mass and strength can be produced by these steroids.

Among the behavioral manifestations of heavy use are increases in aggression, changes in libido and sexual functions, and mood changes with occasional psychotic features. In studies comparing doses of 40–240 mg/d of methyltestosterone in a double-blind inpatient trial, irritability, mood swings, violent feelings, and hostility were greater during the high-dose period than at baseline. This clear ability of androgenic steroids to provoke aggression and irritability has aroused concerns about violence toward family members by abusers. In two prospective controlled trials using blinded administration, mood disturbances were reported in more than 50% of bodybuilders using anabolic steroids. Both increases and decreases in libido have been reported in studies comparing anabolic steroid abusers with nonusing athletes. Cognitive impairment, including distractibility, forgetfulness, and confusion, has also been demonstrated in controlled trials. A withdrawal syndrome has been described, with common symptoms being fatigue, depressed mood, and a craving for steroids.

Clinical findings may include hypertrophied muscles, acne, oily skin, hirsutism in females, gynecomastia in males, and needle punctures. Edema and jaundice may develop in heavy users. Common laboratory abnormalities include elevated hemoglobin and hematocrit measurements, elevated low-density lipoprotein cholesterol and depressed high-density lipoprotein cholesterol levels. Liver function test results may be elevated, and luteinizing hormone levels are usually depressed.

Treatment

Controlled trials of psychosocial treatments for anabolic steroid dependence have not been reported, and these individuals rarely present to substance abuse treatment programs. Patients may come to the attention of mental health professionals as a result of excessive aggression, sexual dysfunction, or mood disturbances. Peer counseling by former bodybuilders and group support may be of particular value for these users. Nutritional counseling and consultation with a fitness expert may also be helpful. Since gymnasiums are a frequent site for acquisition of steroids, abusers need to avoid these places until recovery is firmly established.