CHAPTER 26

# Local Anesthetics

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## CASE STUDY

A 67-year-old woman is scheduled for elective total knee arthroplasty. What local anesthetic agents would be most appropriate if surgical anesthesia were to be administered using a spinal or an epidural technique, and what potential complications might arise from their use? What anesthetics would be most appropriate for providing postoperative analgesia via an indwelling epidural or peripheral nerve catheter?

Simply stated, local anesthesia refers to loss of sensation in a limited region of the body. This is accomplished by disruption of afferent neural traffic via inhibition of impulse generation or propagation. Such blockade may bring with it other physiologic changes such as muscle paralysis and suppression of somatic or visceral reflexes, and these effects might be desirable or undesirable depending on the particular circumstances. Nonetheless, in most cases, it is the loss of sensation, or at least the achievement of localized analgesia, that is the primary goal.

Although local anesthetics are often used as analgesics, it is their ability to provide complete loss of all sensory modalities that is their distinguishing characteristic. The contrast with general anesthesia should be obvious, but it is perhaps worthwhile to emphasize that with local anesthesia the drug is delivered directly to the target organ, and the systemic circulation serves only to diminish or terminate its effect. Local anesthesia can also be produced by various chemical or physical means. However, in routine clinical practice, it is achieved with a rather narrow spectrum of compounds, and recovery is normally spontaneous, predictable, and without residual effects. The development of these compounds has a rich history (see Box: Historical Development of Local Anesthesia), punctuated by serendipitous observations, delayed starts, and an evolution driven more by concerns for safety than improvements in efficacy.

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## BASIC PHARMACOLOGY OF LOCAL ANESTHETICS

### Chemistry

Most local anesthetic agents consist of a lipophilic group (eg, an aromatic ring) connected by an intermediate chain via an ester or amide to an ionizable group (eg, 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 (eg, levobupivacaine, ropivacaine). Because ester links are more prone to hydrolysis than amide links, esters usually have a shorter duration of action.

Local anesthetics are weak bases and are usually made available clinically as salts to increase solubility and stability. In the body, they exist either as the uncharged base or as a cation (see Chapter 1, Ionization of Weak Acids and Weak Bases). The relative proportions of these two forms are governed by their $pK_a$ and the pH of the body fluids according to the Henderson-Hasselbalch equation, which can be expressed as:

$$pK_a = pH - \log [base]/[conjugate\ acid]$$

If the concentration of base and conjugate acid are equal, the second portion of the right side of the equation drops out, as log 1 = 0, leaving:

$$pK_a = pH\ (where\ base = conjugate\ acid)$$

## Historical Development of Local Anesthesia

Although the numbing properties of cocaine were recognized for centuries, one might consider September 15, 1884, to mark the "birth of local anesthesia." Based on work performed by Carl Koller, cocaine's numbing effect on the cornea was demonstrated before the Ophthalmological Congress in Heidelberg, ushering in the era of surgical anesthesia. Unfortunately, with widespread use came recognition of cocaine's significant CNS and cardiac toxicity, which along with its addiction potential, tempered enthusiasm for this application. As the early investigator Mattison commented, "the risk of untoward results have robbed this peerless drug of much favor in the minds of many surgeons, and so deprived them of a most valued ally." As cocaine was known to be a benzoic acid ester, the search for alternative local anesthetics focused on this class of compounds, resulting in the identification of benzocaine shortly before the turn of the last century. However, benzocaine proved to have limited utility due to its marked hydrophobicity, and was thus relegated to topical anesthesia, a use for which it still finds limited application in current clinical practice. The first useful injectable local anesthetic, procaine, was introduced shortly thereafter by Einhorn, and its structure has served as the template for the development of the most commonly used modern local anesthetics. The three basic structural elements of these compounds can be appreciated by review of Table 26–1: an aromatic ring, conferring lipophilicity, an ionizable tertiary amine, conferring hydrophilicity, and an intermediate chain connecting these via an ester or amide linkage.

One of procaine's limitations was its short duration of action, a drawback overcome with the introduction of tetracaine in 1928. Unfortunately, tetracaine demonstrated significant toxicity when employed for high-volume peripheral blocks, ultimately reducing its common usage to spinal anesthesia. Both procaine and tetracaine shared another drawback: their ester linkage conferred instability, and particularly in the case of procaine, the free aromatic acid released during ester hydrolysis of the parent compound was believed to be the source of relatively frequent allergic reactions.

Löfgren and Lundqvist circumvented the problem of instability with the introduction of lidocaine in 1948. Lidocaine was the first in a series of amino-amide local anesthetics that would come to dominate the second half of the 20th century. Lidocaine had a more favorable duration of action than procaine, and less systemic toxicity than tetracaine. To this day, it remains one of the most versatile and widely used anesthetics. Nonetheless, some applications required more prolonged block than that afforded by lidocaine, a pharmacologic void that was filled with the introduction of bupivacaine, a more lipophilic and more potent anesthetic. Unfortunately, bupivacaine was found to have greater propensity for significant effects on cardiac conduction and function, which at times proved lethal. Recognition of this potential for cardiac toxicity led to changes in anesthetic practice, and significant toxicity became sufficiently rare for it to remain a widely used anesthetic for nearly every regional technique in modern clinical practice. Nonetheless, this inherent cardiotoxicity would drive developmental work leading to the introduction of two recent additions to the anesthetic armamentarium, levobupivacaine and ropivacaine. The former is the *S*(–) enantiomer of bupivacaine, which has less affinity for cardiac sodium channels than its *R*(+) counterpart. Ropivacaine, another *S*(–) enantiomer, shares this reduced affinity for cardiac sodium channels, while being slightly less potent than bupivacaine or levobupivacaine.

Thus, $pK_a$ can be seen as an effective way to consider the tendency for compounds to exist in a charged or uncharged form, ie, the lower the $pK_a$, the greater the percentage of uncharged species at a given pH. Because the $pK_a$ of most local anesthetics is in the range of 7.5–9.0, the charged, cationic form will constitute the larger percentage at physiologic pH. A glaring exception is benzocaine, which has a $pK_a$ around 3.5, and thus exists solely as the nonionized base under normal physiologic conditions.

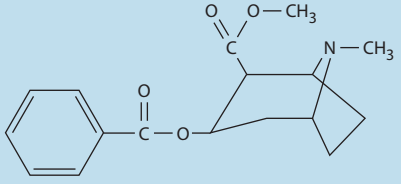
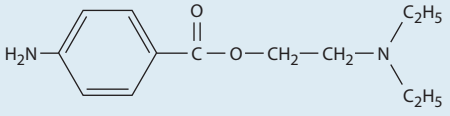
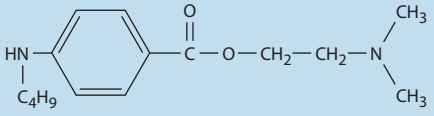
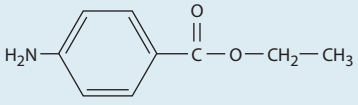
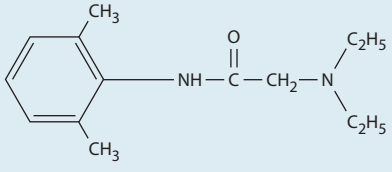
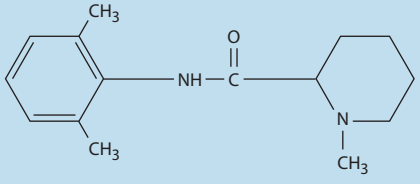
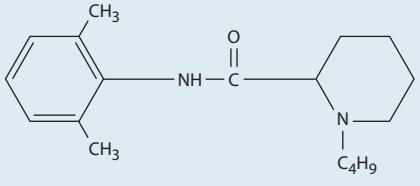
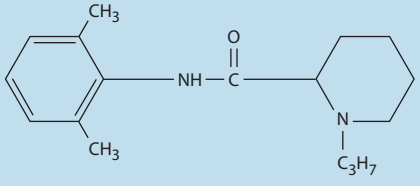
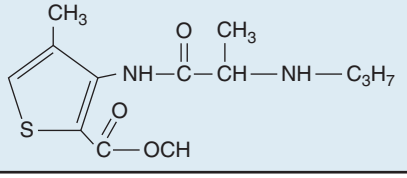
This issue of ionization is of critical importance because the cationic form is the most active at the receptor site. However, the story is a bit more complex, because the receptor site for local anesthetics is at the inner vestibule of the sodium channel, and the charged form of the anesthetic penetrates biologic membranes poorly. Thus, the uncharged form is important for cell penetration. After penetration into the cytoplasm, equilibration leads to formation and binding of the charged cation at the sodium channel, and hence the production of a clinical effect. Drug may also reach the receptor laterally through what has been termed the hydrophobic pathway (Figure 26–1). As a clinical consequence, local anesthetics are less effective when they are injected into infected tissues because the low extracellular pH favors the charged form, with less of the neutral base available for diffusion across the membrane. Conversely, adding bicarbonate to a local anesthetic—a strategy sometimes utilized in clinical practice—will raise the effective concentration of the nonionized form and thus shorten the onset time of a regional block.

## Pharmacokinetics

When local anesthetics are used for local, peripheral, and central neuraxial anesthesia—their most common clinical applications—systemic absorption, distribution, and elimination serve only to diminish or terminate their effect. Thus, classic pharmacokinetics plays a lesser role than with systemic therapeutics, yet remains important to the anesthetic's duration and critical to the potential development of adverse reactions, specifically cardiac and central nervous system (CNS) toxicity.

Some pharmacokinetic properties of the commonly used amide local anesthetics are summarized in Table 26–2. The pharmacokinetics

**TABLE 26–1 Structure and properties of some ester and amide local anesthetics.[1]**

| | Structure | Potency (Procaine = 1) | Duration of Action |
|---|---|---|---|
| **Esters** | | | |
| Cocaine |  | 2 | Medium |
| Procaine (Novocain) |  | 1 | Short |
| Tetracaine (Pontocaine) |  | 16 | Long |
| Benzocaine |  | Surface use only | |
| **Amides** | | | |
| Lidocaine (Xylocaine) |  | 4 | Medium |
| Mepivacaine (Carbocaine, Isocaine) |  | 2 | Medium |
| Bupivacaine (Marcaine), Levobupivacaine (Chirocaine) |  | 16 | Long |
| Ropivacaine (Naropin) |  | 16 | Long |
| Articaine |  | nf[2] | Medium |

[1]Other chemical types are available including ethers (pramoxine), ketones (dyclonine), and phenetidin derivatives (phenacaine).

[2]Data not found.

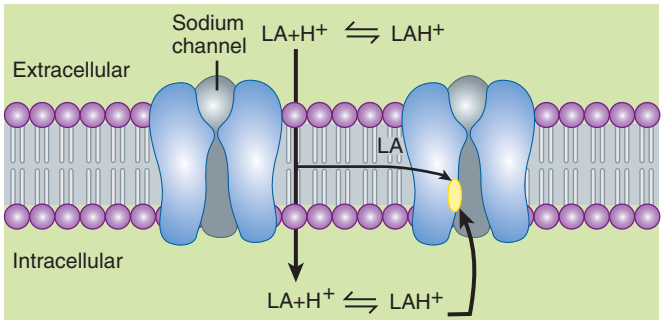



**FIGURE 26–1** Schematic diagram depicting paths of local anesthetic (LA) to receptor sites. Extracellular anesthetic exists in equilibrium between charged and uncharged forms. The charged cation penetrates lipid membranes poorly; intracellular access is thus achieved by passage of the uncharged form. Intracellular re-equilibration results in formation of the more active charged species, which binds to the receptor at the inner vestibule of the sodium channel. Anesthetic may also gain access more directly by diffusing laterally within the membrane (hydrophobic pathway).

of the ester-based local anesthetics has not been extensively studied owing to their rapid breakdown in plasma (elimination half-life < 1 minute).

## A. Absorption

Systemic absorption of injected local anesthetic from the site of administration is determined by several factors, including dosage, site of injection, drug-tissue binding, local tissue blood flow, use of a vasoconstrictor (eg, epinephrine), and the physicochemical properties of the drug itself. Anesthetics that are more lipid soluble are generally more potent, have a longer duration of action, and take longer to achieve their clinical effect. Extensive protein binding also serves to increase the duration of action.

Application of a local anesthetic to a highly vascular area such as the tracheal mucosa or the tissue surrounding intercostal nerves results in more rapid absorption and thus higher blood levels than if the local anesthetic is injected into a poorly perfused tissue such as subcutaneous fat. When used for major conduction blocks, the peak serum levels will vary as a function of the specific site of injection, with intercostal blocks among the highest, and sciatic and femoral among the lowest (Figure 26–2). When vasoconstrictors are used with local anesthetics, the resultant reduction in blood flow serves to reduce the rate of systemic absorption and thus diminishes peak serum levels. This effect is generally most evident with the shorter-acting, less potent, and less lipid-soluble anesthetics.

## B. Distribution

***1. Localized—***As local anesthetic is usually injected directly at the site of the target organ, distribution within this compartment plays an essential role with respect to achievement of clinical effect. For example, anesthetics delivered into the subarachnoid space will be diluted with cerebrospinal fluid (CSF) and the pattern of distribution will be dependent upon a host of factors, among the most critical being the specific gravity relative to that of CSF and the patient's position. Solutions are termed hyperbaric, isobaric, and hypobaric, and will respectively descend, remain relatively static, or ascend, within the subarachnoid space due to gravity when the patient sits upright. A review and analysis of relevant literature cited 25 factors that have been invoked as determinants of spread of local anesthetic in CSF, which can be broadly classified as characteristics of the anesthetic solution, CSF constituents, patient characteristics, and techniques of injection. Somewhat similar considerations apply to epidural and peripheral blocks.

***2. Systemic—***The peak blood levels achieved during major conduction anesthesia will be minimally affected by the concentration of anesthetic or the speed of injection. The disposition of these agents can be well approximated by a two-compartment model. The initial alpha phase reflects rapid distribution in blood and highly perfused organs (eg, brain, liver, heart, kidney), characterized by a steep exponential decline in concentration. This is followed by a slower declining beta phase reflecting distribution into less well perfused tissue (eg, muscle, gut), and may assume a nearly linear rate of decline. The potential toxicity of the local anesthetics is affected by the protective effect afforded by uptake by the lungs, which serve to attenuate the arterial concentration, though the time course and magnitude of this effect have not been adequately characterized.

## C. Metabolism and Excretion

The amide local anesthetics are converted to more water-soluble metabolites in the liver (amide type) or in plasma (ester type),

**TABLE 26–2 Pharmacokinetic properties of several amide local anesthetics.**

| Agent | $t_{1/2}$ Distribution (min) | $t_{1/2}$ Elimination (h) | $V_{dss}$ (L) | CL (L/min) |
|---|---|---|---|---|
| Bupivacaine | 28 | 3.5 | 72 | 0.47 |
| Lidocaine | 10 | 1.6 | 91 | 0.95 |
| Mepivacaine | 7 | 1.9 | 84 | 0.78 |
| Prilocaine | 5 | 1.5 | 261 | 2.84 |
| Ropivacaine | 23 | 4.2 | 47 | 0.44 |

CL, clearance; $V_{dss}$, volume of distribution at steady state.

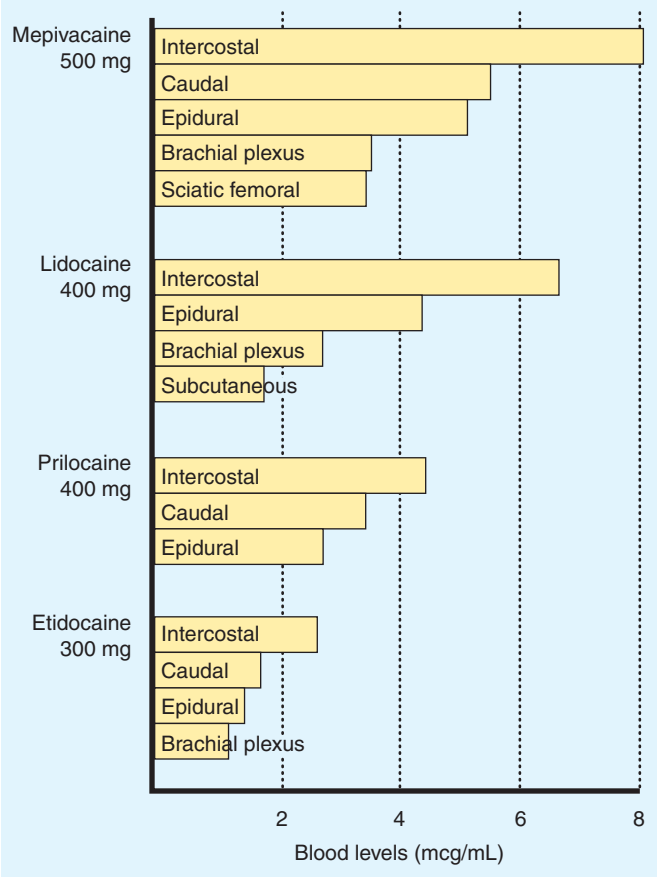



**FIGURE 26–2** Comparative peak blood levels of several local anesthetic agents following administration into various anatomic sites. (Modified, with permission, from Covino BD, Vassals HG: *Local Anesthetics: Mechanism of Action in Clinical Use.* Grune & Stratton, 1976.)

which are excreted in the urine. Since local anesthetics in the uncharged form diffuse readily through lipid membranes, little or no urinary excretion of the neutral form occurs. Acidification of urine promotes ionization of the tertiary amine base to the more water-soluble charged form, leading to more rapid elimination. Ester-type local anesthetics are hydrolyzed very rapidly in the blood by circulating butyrylcholinesterase to inactive metabolites. For example, the half-lives of procaine and chloroprocaine in plasma are less than a minute. However, excessive concentrations may accumulate in patients with reduced or absent plasma hydrolysis secondary to atypical plasma cholinesterase.

The amide local anesthetics undergo complex biotransformation in the liver, which includes hydroxylation and *N*-dealkylation by liver microsomal cytochrome P450 isozymes. There is considerable variation in the rate of liver metabolism of individual amide compounds, with prilocaine (fastest) > lidocaine > mepivacaine > ropivacaine ≈ bupivacaine and levobupivacaine (slowest). As a result, toxicity from amide-type local anesthetics is more likely to occur in patients with hepatic disease. For example, the average elimination half-life of lidocaine may be increased from 1.6 hours in normal patients ($t_{½}$, Table 26–2) to more than 6 hours in patients with severe liver disease. Many other drugs used in anesthesia are metabolized by the same P450 isozymes, and concomitant administration of these competing drugs may slow the hepatic metabolism of the local anesthetics. Decreased hepatic elimination of local anesthetics would also be anticipated in patients with reduced hepatic blood flow. For example, the hepatic elimination of lidocaine in patients anesthetized with volatile anesthetics (which reduce liver blood flow) is slower than in patients anesthetized with intravenous anesthetic techniques. Delayed metabolism due to impaired hepatic blood flow may likewise occur in patients with congestive heart failure.

## Pharmacodynamics

### A. Mechanism of Action

***1. Membrane potential*—**The primary mechanism of action of local anesthetics is blockade of voltage-gated sodium channels (Figure 26–1). The excitable membrane of nerve axons, like the membrane of cardiac muscle (see Chapter 14) and neuronal cell bodies (see Chapter 21), maintains a resting transmembrane potential of –90 to –60 mV. During excitation, the sodium channels open, and a fast, inward sodium current quickly depolarizes the membrane toward the sodium equilibrium potential (+40 mV). As a result of this depolarization process, the sodium channels close (inactivate) and potassium channels open. The outward flow of potassium repolarizes the membrane toward the potassium equilibrium potential (about –95 mV); repolarization returns the sodium channels to the rested state with a characteristic recovery time that determines the refractory period. The transmembrane ionic gradients are maintained by the sodium pump. These ionic fluxes are similar to, but simpler than, those in heart muscle, and local anesthetics have similar effects in both tissues.

***2. Sodium channel isoforms*—**Each sodium channel consists of a single alpha subunit containing a central ion-conducting pore associated with accessory beta subunits. The pore-forming alpha subunit is actually sufficient for functional expression, but the kinetics and voltage dependence of channel gating are modified by the beta subunit. A variety of different sodium channels have been characterized by electrophysiologic recording, and subsequently isolated and cloned, while mutational analysis has allowed for identification of the essential components of the local anesthetic binding site. Nine members of a mammalian family of sodium channels have been so characterized and classified as $Na_v1.1$–$Na_v1.9$, where the chemical symbol represents the primary ion, the subscript denotes the physiologic regulator (in this case voltage), the initial number denotes the gene, and the number following the period indicates the particular isoform.

***3. Channel blockade*—**Biologic toxins such as batrachotoxin, aconitine, veratridine, and some scorpion venoms bind to receptors within the channel and prevent inactivation. This results in prolonged influx of sodium through the channel and depolarization of the resting potential. The marine toxins tetrodotoxin (TTX) and saxitoxin have clinical effects that largely resemble those of local anesthetics (ie, block of conduction without a change in the resting potential). However, in contrast to the

local anesthetics, their binding site is located near the extracellular surface. The sensitivity of these channels to TTX varies, and subclassification based on this pharmacologic sensitivity has important physiologic and therapeutic implications. Six of the aforementioned channels are sensitive to nanomolar concentration of this biotoxin (TTX-S), while three are resistant (TTX-R). Of the latter, $Na_v1.8$ and $Na_v1.9$ appear to be exclusively expressed in dorsal root ganglia nociceptors, which raises the developmental possibility of targeting these specific neuronal subpopulations. Such fine-tuned analgesic therapy has the theoretical potential of providing effective analgesia, while limiting the significant adverse effects produced by nonspecific sodium channel blockers.

When progressively increasing concentrations of a local anesthetic are applied to a nerve fiber, the threshold for excitation increases, impulse conduction slows, the rate of rise of the action potential declines, action potential amplitude decreases, and, finally, the ability to generate an action potential is completely abolished. These progressive effects result from binding of the local anesthetic to more and more sodium channels. If the sodium current is blocked over a critical length of the nerve, propagation across the blocked area is no longer possible. In myelinated nerves, the critical length appears to be two to three nodes of Ranvier. At the minimum dose required to block propagation, the resting potential is not significantly altered.

The blockade of sodium channels by most local anesthetics is both voltage and time dependent: Channels in the rested state, which predominate at more negative membrane potentials, have a much lower affinity for local anesthetics than activated (open state) and inactivated channels, which predominate at more positive membrane potentials (see Figure 14–10). Therefore, the effect of a given drug concentration is more marked in rapidly firing axons than in resting fibers (Figure 26–3). Between successive action potentials, a portion of the sodium channels will recover from the local anesthetic block (see Figure 14–10). The recovery from drug-induced block is 10–1000 times slower than the recovery of channels from normal inactivation (as shown for the cardiac membrane in Figure 14–4). As a result, the refractory period is lengthened and the nerve conducts fewer action potentials.

Elevated extracellular calcium partially antagonizes the action of local anesthetics owing to the calcium-induced increase in the surface potential on the membrane (which favors the low-affinity rested state). Conversely, increases in extracellular potassium depolarize the membrane potential and favor the inactivated state, enhancing the effect of local anesthetics.

***4. Other effects—***Currently used local anesthetics bind to the sodium channel with low affinity and poor specificity, and there are multiple other sites for which their affinity is nearly the same as that for sodium channel binding. Thus, at clinically relevant concentrations, local anesthetics are potentially active at countless other channels (eg, potassium and calcium), enzymes (eg, adenylate cyclase, carnitine-acylcarnitine translocase), and receptors (eg, *N*-methyl-D-aspartate [NMDA], G protein-coupled, $5\text{-HT}_3$, neurokinin-1 [substance P receptor]).

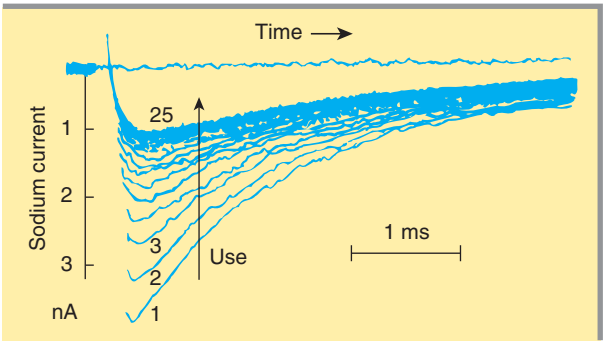



**FIGURE 26–3** Effect of repetitive activity on the block of sodium current produced by a local anesthetic in a myelinated axon. A series of 25 pulses was applied, and the resulting sodium currents (downward deflections) are superimposed. Note that the current produced by the pulses rapidly decreased from the first to the 25th pulse. A long rest period after the train resulted in recovery from block, but the block could be reinstated by a subsequent train. nA, nanoamperes. (Modified and reproduced, with permission, from Courtney KR: Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA. J Pharmacol Exp Ther 1975;195:225.)

The role that such ancillary effects play in achievement of local anesthesia appears to be important but is poorly understood. Further, interactions with these other sites are likely the basis for numerous differences between the local anesthetics with respect to anesthetic effects (eg, differential block) and toxicities that do not parallel anesthetic potency, and thus are not adequately accounted for solely by blockade of the voltage-gated sodium channel.

The actions of circulating local anesthetics at such diverse sites exert a multitude of effects, some of which go beyond pain control, including some that are also potentially beneficial. For example, there is evidence to suggest that the blunting of the stress response and improvements in perioperative outcome that may occur with epidural anesthesia derive in part from an action of the anesthetic beyond its sodium channel block. Circulating anesthetics also demonstrate antithrombotic effects having an impact on coagulation, platelet aggregation, and the microcirculation, as well as modulation of inflammation.

## B. Structure-Activity Characteristics of Local Anesthetics

The smaller and more highly lipophilic local anesthetics have a faster rate of interaction with the sodium channel receptor. As previously noted, potency is also positively correlated with lipid solubility. Lidocaine, procaine, and mepivacaine are more water soluble than tetracaine, bupivacaine, and ropivacaine. The latter agents are more potent and have longer durations of local anesthetic action. These long-acting local anesthetics also bind more extensively to proteins and can be displaced from these binding sites by other protein-bound drugs. In the case of optically active agents (eg, bupivacaine), the *R*(+) isomer can usually be shown to be slightly more potent than the *S*(–) isomer (levobupivacaine).

### C. Neuronal Factors Affecting Block

***1. Differential block***—Since local anesthetics are capable of blocking all nerves, their actions are not limited to the desired loss of sensation from sites of noxious (painful) stimuli. With central neuraxial techniques (spinal or epidural), motor paralysis may impair respiratory activity, and autonomic nerve blockade may promote hypotension. Further, while motor paralysis may be desirable during surgery, it may be disadvantageous in other settings. For example, motor weakness occurring as a consequence of epidural anesthesia during obstetrical labor may limit the ability of the patient to bear down (ie, "push") during delivery. Similarly, when used for postoperative analgesia, weakness may hamper ability to ambulate without assistance and pose a risk of falling, while residual autonomic blockade may interfere with bladder function, resulting in urinary retention and the need for bladder catheterization. These issues are particular problematic in the setting of ambulatory (same-day) surgery, which represents an ever-increasing percentage of surgical caseloads.

***2. Intrinsic susceptibility of nerve fibers***—Nerve fibers differ significantly in their susceptibility to local anesthetic blockade. It has been traditionally taught, and still often cited, that local anesthetics preferentially block smaller diameter fibers first because the distance over which such fibers can passively propagate an electrical impulse is shorter. However, a variable proportion of large fibers are blocked prior to the disappearance of the small fiber component of the compound action potential. Most notably, myelinated nerves tend to be blocked before unmyelinated nerves of the same diameter. For example, preganglionic B fibers are blocked before the smaller unmyelinated C fibers involved in pain transmission (Table 26–3).

Another important factor underlying differential block derives from the state- and use-dependent mechanism of action of local anesthetics. Blockade by these drugs is more marked at higher frequencies of depolarization. Sensory (pain) fibers have a high firing rate and relatively long action potential duration. Motor fibers fire at a slower rate and have a shorter action potential duration. As type A delta and C fibers participate in high-frequency pain transmission, this characteristic may favor blockade of these fibers earlier and with lower concentrations of local anesthetics. The potential impact of such effects mandates cautious interpretation of non-physiologic experiments evaluating intrinsic susceptibility of nerves to conduction block by local anesthetics.

***3. Anatomic arrangement***—In addition to the effect of intrinsic vulnerability to local anesthetic block, the anatomic organization of the peripheral nerve bundle may impact the onset and susceptibility of its components. As one would predict based on the necessity of having proximal sensory fibers join the nerve trunk last, the core will contain sensory fibers innervating the most distal sites. Anesthetic placed outside the nerve bundle will thus reach and anesthetize the proximal fibers located at the outer portion of the bundle first, and sensory block will occur in sequence from proximal to distal.

## CLINICAL PHARMACOLOGY OF LOCAL ANESTHETICS

Local anesthetics can provide highly effective analgesia in well-defined regions of the body. The usual routes of administration include topical application (eg, nasal mucosa, wound [incision site] margins), injection in the vicinity of peripheral nerve endings (perineural infiltration) and major nerve trunks (blocks), and injection into the epidural or subarachnoid spaces surrounding the spinal cord (Figure 26–4).

### Clinical Block Characteristics

In clinical practice, there is generally an orderly evolution of block components beginning with sympathetic transmission and

**TABLE 26–3 Relative size and susceptibility of different types of nerve fibers to local anesthetics.**

| Fiber Type | Function | Diameter (μm) | Myelination | Conduction Velocity (m/s) | Sensitivity to Block |
|---|---|---|---|---|---|
| **Type A** | | | | | |
| Alpha | Proprioception, motor | 12–20 | Heavy | 70–120 | + |
| Beta | Touch, pressure | 5–12 | Heavy | 30–70 | ++ |
| Gamma | Muscle spindles | 3–6 | Heavy | 15–30 | ++ |
| Delta | Pain, temperature | 2–5 | Heavy | 5–25 | +++ |
| **Type B** | Preganglionic autonomic | < 3 | Light | 3–15 | ++++ |
| **Type C** | | | | | |
| Dorsal root | Pain | 0.4–1.2 | None | 0.5–2.3 | ++++ |
| Sympathetic | Postganglionic | 0.3–1.3 | None | 0.7–2.3 | ++++ |

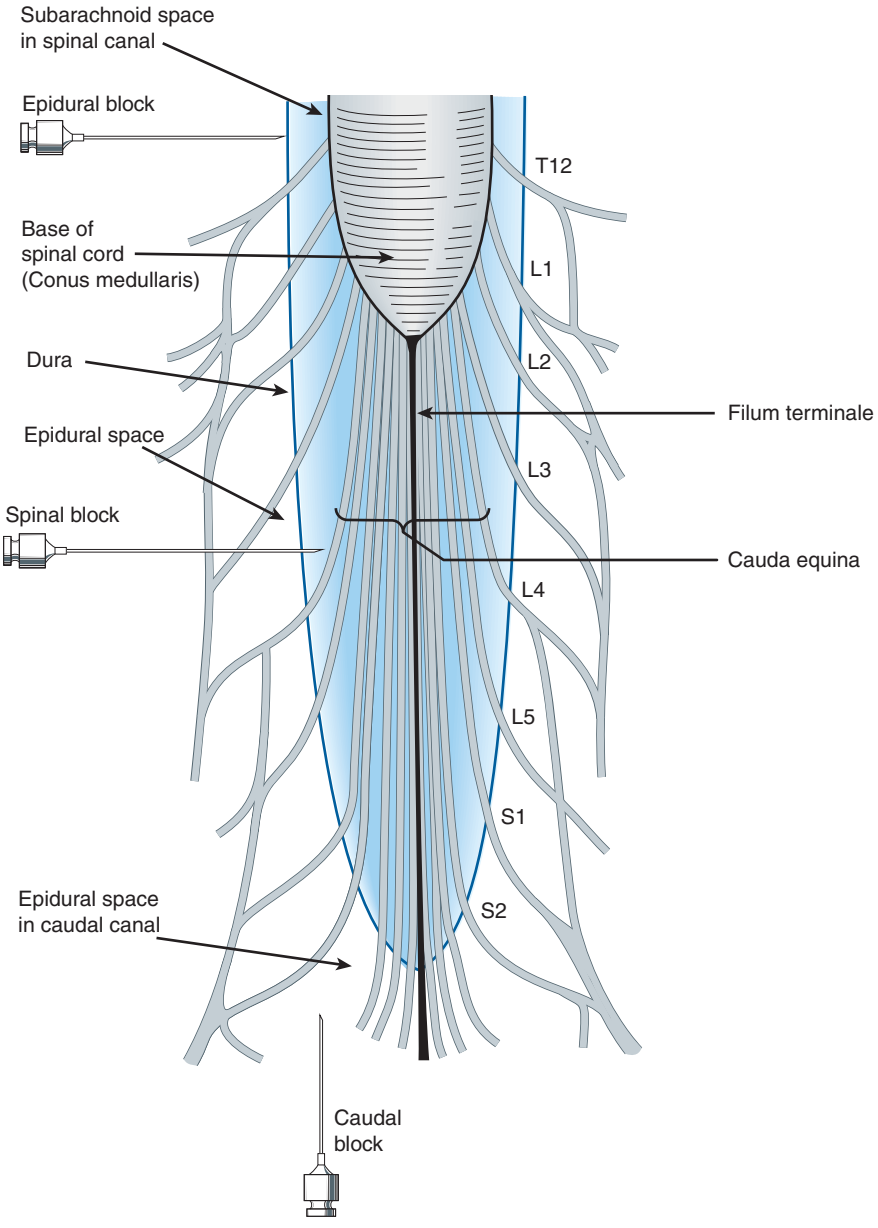



**FIGURE 26–4** Schematic diagram of the typical sites of injection of local anesthetics in and around the spinal canal. When local anesthetics are injected extradurally, it is referred to as an epidural block. A caudal block is a specific type of epidural block in which a needle is inserted into the caudal canal via the sacral hiatus. Injections around peripheral nerves are known as perineural blocks (eg, paravertebral block). Finally, injection into cerebrospinal fluid in the subarachnoid (intrathecal) space is referred to as a spinal block.

progressing to temperature, pain, light touch, and finally motor block. This is most readily appreciated during onset of spinal anesthesia, where a spatial discrepancy can be detected in modalities, the most vulnerable components achieving greater dermatomal (cephalad) spread. Thus, loss of the sensation of cold (often assessed by a wet alcohol sponge) will be roughly two segments above the analgesic level for pinprick, which in turn will be roughly two segments rostral to loss of light touch recognition. However, because of the anatomic considerations noted earlier for peripheral nerve trunks, onset with peripheral blocks is more variable, and proximal motor weakness may precede onset of more distal sensory loss. Additionally, anesthetic solution is not generally deposited evenly around a nerve bundle, and longitudinal spread and radial penetration into the nerve trunk are far from uniform.

With respect to differential block, it is worth noting that "successful" surgical anesthesia may require loss of touch, not just ablation of pain, as some patients will find even the sensation of touch distressing during surgery, often fearing that the procedure may become painful. Further, while differences may exist in modalities, it is not possible with conventional techniques to produce surgical anesthesia without some loss of motor function.

### A. Effect of Added Vasoconstrictors

Several benefits may be derived from addition of a vasoconstrictor to a local anesthetic. First, localized neuronal uptake is enhanced because of higher sustained local tissue concentrations that can translate clinically into a longer duration block. This may enable adequate anesthesia for more prolonged procedures, extended duration of postoperative pain control, and lower total anesthetic requirement. Second, peak blood levels will be lowered as absorption is more closely matched to metabolism and elimination, and the risk of systemic toxic effects is reduced. Moreover, when incorporated into a spinal anesthetic, epinephrine may not only contribute to prolongation of the local anesthetic effect via its vasoconstrictor properties, but also exert a direct analgesic effect mediated by postsynaptic $\alpha_2$ adrenoceptors within the spinal cord. Recognition of this potential has led to the clinical use of the $\alpha_2$ agonist clonidine as a local anesthetic adjuvant for spinal anesthesia.

Conversely, inclusion of epinephrine may have untoward effects. The addition of epinephrine to anesthetic solutions can potentiate the neurotoxicity of local anesthetics used for peripheral nerve blocks or spinal anesthesia. Further, the use of a vasoconstrictor agent in an area that lacks adequate collateral flow (eg, digital block) is generally avoided, though some have questioned the validity of this proscription.

### B. Intentional Use of Systemic Local Anesthetics

Although the principal use of local anesthetics is to achieve anesthesia in a restricted area, these agents are sometimes deliberately administered systemically to take advantage of suppressive effects on pain processing. In addition to documented reductions in anesthetic requirement and postoperative pain, systemic administration of local anesthetics has been used with some success in the treatment of chronic pain, and this effect may outlast the duration of anesthetic exposure. The achievement of pain control by systemic administration of local anesthetics is thought to derive, at least in part, from the suppression of abnormal ectopic discharge, an effect observed at concentrations of local anesthetic an order of magnitude lower than those required for blockade of propagation of action potentials in normal nerves. Consequently, these effects can be achieved without the adverse effects that would derive from failure of normal nerve conduction. Escalating doses of anesthetic appear to exert the following systemic actions: (1) low concentrations may preferentially suppress ectopic impulse generation in chronically injured peripheral nerves; (2) moderate concentrations may suppress central sensitization, which would explain therapeutic benefit that may extend beyond the anesthetic exposure; and (3) higher concentrations will produce general analgesic effects and may culminate in serious toxicity.

## Toxicity

Local anesthetic toxicity derives from two distinct processes: (1) systemic effects following inadvertent intravascular injection or absorption of the local anesthetic from the site of administration; and (2) neurotoxicity resulting from local effects produced by direct contact with neural elements.

### A. Systemic Toxicity

The dose of local anesthetic used for epidural anesthesia or high-volume peripheral blocks is sufficient to produce major clinical toxicity, even death. To minimize risk, maximum recommended doses for each drug for each general application have been promulgated. The concept underlying this approach is that absorption from the site of injection should appropriately match metabolism, thereby preventing toxic serum levels. However, these recommendations do not consider patient characteristics or concomitant risk factors, nor do they take into account the specific peripheral nerve block performed, which has a significant impact on the rate of systemic uptake (Figure 26–2). Most importantly, they fail to afford protection from toxicity induced by inadvertent intravascular injection (occasionally into an artery, but more commonly a vein).

***1. CNS toxicity—***All local anesthetics have the ability to produce sedation, light-headedness, visual and auditory disturbances, and restlessness when high plasma concentrations result from rapid absorption or inadvertent intravascular administration. An early symptom of local anesthetic toxicity is circumoral and tongue numbness and a metallic taste. At higher concentrations, nystagmus and muscular twitching occur, followed by tonic-clonic convulsions. Local anesthetics apparently cause depression of cortical inhibitory pathways, thereby allowing unopposed activity of excitatory neuronal pathways. This transitional stage of unbalanced excitation (ie, seizure activity) is then followed by generalized CNS depression. However, this classic pattern of evolving toxicity has been largely characterized in human volunteer studies (which are ethically constrained to low doses), and by graded administration in animal models. Deviations from such classic progression are common in clinical toxicity and will be influenced by a host of factors, including patient vulnerability, the particular anesthetic administered, concurrent drugs, and rate of rise of serum drug levels. A recent literature review of reported clinical cases of local anesthetic cardiac toxicity found prodromal signs of CNS toxicity in only 18% of cases.

When large doses of a local anesthetic are required (eg, for major peripheral nerve block or local infiltration for major plastic surgery), premedication with a parenteral benzodiazepine (eg, diazepam or midazolam) will provide some prophylaxis against local anesthetic-induced CNS toxicity. However, such premedication will have little, if any, effect on cardiovascular toxicity, potentially delaying recognition of a life-threatening overdose. Of note, administration of a propofol infusion or general anesthesia accounted for 5 of the 10 cases presenting with isolated cardiovascular toxicity in the aforementioned literature review of reported clinical cases.

If seizures do occur, it is critical to prevent hypoxemia and acidosis, which potentiate anesthetic toxicity. Rapid tracheal intubation can facilitate adequate ventilation and oxygenation, and is essential to prevent pulmonary aspiration of gastric contents in patients at risk. The effect of hyperventilation is complex, and its role in resuscitation following anesthetic overdose is somewhat controversial, but it likely offers distinct benefit if used to counteract metabolic acidosis. Seizures induced by local anesthetics

should be rapidly controlled to prevent patient harm and exacerbation of acidosis. A recent practice advisory from the American Society of Regional Anesthesia advocates benzodiazepines as first-line drugs (eg, midazolam, 0.03–0.06 mg/kg) because of their hemodynamic stability, but small doses of propofol (eg, 0.25–0.5 mg/kg) were considered acceptable alternatives, as they are often more immediately available in the setting of local anesthetic administration. The motor activity of the seizure can be effectively terminated by administration of a neuromuscular blocker, though this will not diminish the CNS manifestations, and efforts must include therapy directed at the underlying seizure activity.

***2. Cardiotoxicity—***The most feared complications associated with local anesthetic administration result from the profound effects these agents can have on cardiac conduction and function. In 1979, an editorial by Albright reviewed the circumstances of six deaths associated with the use of bupivacaine and etidocaine. This seminal piece suggested that these relatively new lipophilic and potent anesthetics had greater potential cardiotoxicity, and that cardiac arrest could occur concurrently or immediately following seizures and, most importantly, in the absence of hypoxia or acidosis. Although this suggestion was sharply criticized, subsequent clinical experience unfortunately reinforced Albright's concern—within 4 years the Food and Drug Administration (FDA) had received reports of 12 cases of cardiac arrest associated with the use of 0.75% bupivacaine for epidural anesthesia in obstetrics. Further support for enhanced cardiotoxicity of these anesthetics came from animal studies demonstrating that doses of bupivacaine and etidocaine as low as two thirds those producing convulsions could induce arrhythmias, while the margin between CNS and cardiac toxicity was less than half that for lidocaine. In response, the FDA banned the use of 0.75% bupivacaine in obstetrics. In addition, incorporation of a test dose became ingrained as a standard of anesthetic practice, along with the practice of fractionated administration of local anesthetic.

Although reduction in bupivacaine's anesthetic concentration and changes in anesthetic practice did much to reduce the risk of cardiotoxicity, the recognized differences in the toxicity of the stereoisomers comprising bupivacaine created an opportunity for the development of potentially safer anesthetics (see Chapter 1). Investigations demonstrated that the enantiomers of the racemic mixture bupivacaine were not equivalent with respect to cardiotoxicity, the *S*(–) enantiomer having better therapeutic advantage, leading to the subsequent marketing of levobupivacaine. This was followed shortly thereafter by ropivacaine, a slightly less potent anesthetic than bupivacaine. It should be noted, however, that the reduction in toxicity afforded by these compounds is only modest, and that risk of significant cardiotoxicity remains a very real concern when these anesthetics are administered for high-volume blocks.

***3. Reversal of bupivacaine toxicity—***Recently, a series of clinical events, serendipitous observations, systematic experimentation, and astute clinical decisions have identified a relatively simple, practical and apparently effective therapy for resistant bupivacaine cardiotoxicity using intravenous infusion of lipid. Furthermore, this therapy appears to have applications that extend beyond bupivacaine cardiotoxicity to the cardiac or CNS toxicity induced by an overdose of any lipid-soluble drug (see Box: Lipid Resuscitation).

## B. Localized Toxicity

***1. Neural injury—***From the early introduction of spinal anesthesia into clinical practice, sporadic reports of neurologic injury associated with this technique raised concern that local anesthetic agents were potentially neurotoxic. Following injuries associated with Durocaine—a spinal anesthetic formulation containing procaine—initial attention focused on the vehicle components. However, experimental studies found 10% procaine alone induced similar injuries in cats, whereas the vehicle did not. Concern for anesthetic neurotoxicity reemerged in the early 1980s with a series of reports of major neurologic injury occurring with the use of chloroprocaine for epidural anesthesia. In these cases, there was evidence that anesthetic intended for the epidural space was inadvertently administered intrathecally. As the dose required for spinal anesthesia is roughly an order of magnitude less than for epidural anesthesia, injury was apparently the result of excessive exposure of the more vulnerable subarachnoid neural elements.

With changes in vehicle formulation and in clinical practice, concern for toxicity again subsided, only to reemerge a decade later with reports of cauda equina syndrome associated with continuous spinal anesthesia (CSA). In contrast to the more common single-injection technique, CSA involves placing a catheter in the subarachnoid space to permit repetitive dosing to facilitate adequate anesthesia and maintenance of block for extended periods. In these cases the local anesthetic was evidently administered to a relatively restricted area of the subarachnoid space; in order to extend the block to achieve adequate surgical anesthesia, multiple repetitive doses of anesthetic were then administered. By the time the block was adequate, neurotoxic concentrations had accumulated in a restricted area of the caudal region of the subarachnoid space. Most notably, the anesthetic involved in the majority of these cases was lidocaine, a drug most clinicians considered to be the least toxic of agents. This was followed by reports of neurotoxic injury occurring with lidocaine intended for epidural administration that had inadvertently been administered intrathecally, similar to the cases involving chloroprocaine a decade earlier. The occurrence of neurotoxic injury with CSA and subarachnoid administration of epidural doses of lidocaine served to establish vulnerability whenever excessive anesthetic was administered intrathecally, regardless of the specific anesthetic used. Of even more concern, subsequent reports provided evidence for injury with spinal lidocaine administered at the high end of the recommended clinical dosage, prompting recommendations for a reduction in maximum dose. These clinical reports (as well as concurrent experimental studies) served to dispel the concept that modern local anesthetics administered at clinically relevant doses and concentrations were incapable of inducing neurotoxic injury.

The mechanism of local anesthetic neurotoxicity has been extensively investigated in cell culture, isolated axons, and in vivo models. These studies have demonstrated a myriad of deleterious effects including conduction failure, membrane damage, enzyme

## Lipid Resuscitation

Based on a case of apparent cardiotoxicity from a very low dose of bupivacaine in a patient with carnitine deficiency, Weinberg postulated that this metabolic derangement led to enhanced toxicity due to the accumulation of fatty acids within the cardiac myocyte. He hypothesized that administration of lipid would similarly potentiate bupivacaine cardiotoxicity, but experiments performed to test this hypothesis demonstrated exactly the opposite effect. Accordingly, he began systematic laboratory investigations, which clearly demonstrated the potential efficacy of an intravenous lipid emulsion (ILE) for resuscitation from bupivacaine cardiotoxicity. Clinical confirmation came 8 years later with the report of the successful resuscitation of a patient who sustained an anesthetic-induced (bupivacaine plus mepivacaine) cardiac arrest refractory to standard advanced cardiac life support procedures (ACLS). Numerous similar reports of successful resuscitations soon followed, extending this clinical experience to other anesthetics including levobupivacaine and ropivacaine, anesthetic-induced CNS toxicity, as well as toxicity induced by other classes of compounds, eg, bupropion-induced cardiovascular collapse and multiform ventricular tachycardia provoked by haloperidol. Laboratory investigations have likewise provided evidence of efficacy for treatment of diverse toxic challenges (eg, verapamil, clomipramine, and propranolol).

The mechanism by which lipid is effective is incompletely understood, but its predominant effect appears to stem from its ability to extract a lipophilic drug from aqueous plasma and tissue targets, a mechanism termed lipid sink. With respect to bupivacaine cardiotoxicity, there may be an additive effect of restoring energy to the myocardium by overcoming bupivacaine-induced inhibition of fatty acid transport. Although numerous questions remain, the evolving evidence is sufficient to warrant administration of lipid in cases of systemic anesthetic toxicity. Its use has been promulgated by a task force of the American Society of Regional Anesthesia, and administration of lipid has been incorporated into the most recent revision of ACLS guidelines for Cardiac Arrest in Special Situations. Importantly, propofol cannot be administered for this purpose, as the relatively enormous volume of this solution required for lipid therapy would deliver lethal quantities of propofol.

leakage, cytoskeletal disruption, accumulation of intracellular calcium, disruption of axonal transport, growth cone collapse, and apoptosis. It is not clear what role these factors or others play in clinical injury. It is clear, however, that injury does not result from blockade of the voltage-gated sodium channel per se, and thus clinical effect and toxicity are not tightly linked.

***2. Transient neurologic symptoms (TNS)—***In addition to the very rare but devastating neural complications that can occur with neuraxial (spinal and epidural) administration of local anesthetics, a syndrome of transient pain or dysesthesia, or both, has been recently linked to use of lidocaine for spinal anesthesia. Although these symptoms are not associated with sensory loss, motor weakness, or bowel and bladder dysfunction, the pain can be quite severe, often exceeding that induced by the surgical procedure. TNS occurs even at modest doses of anesthetic, and has been documented in as many as one third of patients receiving lidocaine, with increased risk associated with certain patient positions during surgery (eg, lithotomy), and with ambulatory anesthesia. Risk with other anesthetics varies considerably. For example, the incidence is only slightly reduced with procaine or mepivacaine but appears to be negligible with bupivacaine, prilocaine, and chloroprocaine. The etiology and significance of TNS remain to be established, but differences between factors affecting TNS and experimental animal toxicity argue strongly against a common mechanism mediating these symptoms and persistent or permanent neurologic deficits. Nonetheless, the high incidence of TNS has greatly contributed to dissatisfaction with lidocaine as a spinal anesthetic, leading to its near abandonment for this technique (although it remains a popular and appropriate anesthetic for all other applications, including epidural anesthesia). Chloroprocaine, once considered a more toxic anesthetic, is now being explored for short-duration spinal anesthesia as an alternative to lidocaine, a compound that has been used for well over 50 million spinal anesthetic procedures.

# ■ COMMONLY USED LOCAL ANESTHETICS & THEIR APPLICATIONS

## ARTICAINE

Approved for use in the USA as a dental anesthetic in April 2000, articaine is unique among the amino-amide anesthetics in having a thiophene, rather than a benzene ring, as well as an additional ester group that is subject to metabolism by plasma esterases (Table 26–1). The modification of the ring serves to enhance lipophilicity, and thus improve tissue penetration, while inclusion of the ester leads to a shorter plasma half-life (approximately 20 minutes) potentially imparting a better therapeutic index with respect to systemic toxicity. These characteristics have led to widespread popularity in dental anesthesia, where it is generally considered to be more effective, and possibly safer, than lidocaine, the prior standard. Balanced against these positive attributes are concerns that development of persistent paresthesias, while rare, may be three times more common with articaine. However, prilocaine has been associated with an even higher relative incidence (twice that of articaine). Importantly, these are the only two dental anesthetics that are formulated as 4% solutions; the others are all marketed at lower concentrations

(eg, the maximum concentration of lidocaine used for dental anesthesia is 2%), and it is well established that anesthetic neurotoxicity is, to some extent, concentration-dependent. Thus, it is quite possible that enhanced risk derives from the formulation rather than from an intrinsic property of the anesthetic. In a recent survey of US and Canadian Dental Schools, over half of respondents indicated that 4% articaine is no longer used for mandibular nerve block.

## BENZOCAINE

As previously noted, benzocaine's pronounced lipophilicity has relegated its application to topical anesthesia. However, despite over a century of use for this purpose, its popularity has recently diminished owing to increasing concerns regarding its potential to induce methemoglobinemia. Elevated levels can be due to inborn errors, or can occur with exposure to an oxidizing agent, and such is the case with significant exposure to benzocaine (or nitrites, see Chapter 12). Because methemoglobin does not transport oxygen, elevated levels pose serious risk, with severity obviously paralleling blood levels.

## BUPIVACAINE

Based on concerns for cardiotoxicity, bupivacaine is often avoided for techniques that demand high volumes of concentrated anesthetic, such as epidural or peripheral nerve blocks performed for surgical anesthesia. In contrast, relatively low concentrations (≤ 0.25%) are frequently used to achieve prolonged peripheral anesthesia and analgesia for postoperative pain control, and the drug enjoys similar popularity where anesthetic infiltration is used to control pain from a surgical incision. It is often the agent of choice for epidural infusions used for postoperative pain control and for labor analgesia. Finally, it has a comparatively unblemished record as a spinal anesthetic, with a relatively favorable therapeutic index with respect to neurotoxicity, and little, if any, risk of TNS. However, spinal bupivacaine is not well suited for outpatient or ambulatory surgery, because its relatively long duration of action can delay recovery, resulting in a longer stay prior to discharge to home.

## CHLOROPROCAINE

The introduction of chloroprocaine into clinical practice in 1951 represented a reversion to the earlier amino-ester template. Chloroprocaine gained widespread use as an epidural agent in obstetric anesthesia, where its rapid hydrolysis served to minimize risk of systemic toxicity or fetal exposure. Subsequent reports of neurologic injury associated with apparent intrathecal misplacement of large doses intended for the epidural space led to its near abandonment. However, the frequent occurrence of TNS when lidocaine is administered as a spinal anesthetic has created an anesthetic void that chloroprocaine appears well suited to fill. Its onset and duration of action are even shorter than those of lidocaine, while presenting little, if any, risk of TNS. Although chloroprocaine was never exonerated with respect to the early neurologic injuries associated with epidural anesthesia, it is now well appreciated that high doses of any local anesthetic, which are not required to achieve spinal anesthesia, are capable of inducing neurotoxic injury. In addition to chloroprocaine's emerging use as a spinal anesthetic, the drug finds some current use as an epidural anesthetic, particularly in circumstances where there is an indwelling catheter and the need for quick attainment of surgical anesthesia, such as cesarean section in a laboring parturient with a compromised fetus.

## COCAINE

Current clinical use of cocaine is largely restricted to topical anesthesia for ear, nose, and throat procedures, where its intense vasoconstriction can serve to reduce bleeding. Even here, use has diminished in favor of other anesthetics combined with vasoconstrictors because of concerns about systemic toxicity, as well as the inconvenience of dispensing and handling this controlled substance.

## ETIDOCAINE

Introduced along with bupivacaine, etidocaine has had limited application due to its poor block characteristics. It has a tendency to produce an inverse differential block (ie, compared with other anesthetics such as bupivacaine, it produces excessive motor relative to sensory block), which is rarely a favorable attribute.

## LEVOBUPIVACAINE

As previously discussed, this *S*(–) enantiomer of bupivacaine is somewhat less cardiotoxic than the racemic mixture. It is also less potent, and tends to have a longer duration of action, though the magnitude of these effects is too small to have any substantial clinical significance. Interestingly, recent work with lipid resuscitation suggests a potential advantage of levobupivacaine over ropivacaine, as the former is more effectively sequestered into a so-called lipid sink, implying greater ability to reverse toxic effects should they occur.

## LIDOCAINE

Aside from the issue of a high incidence of TNS with spinal administration, lidocaine has had an excellent record as an intermediate duration anesthetic, and remains the reference standard against which most anesthetics are compared.

## MEPIVACAINE

Although structurally similar to bupivacaine and ropivacaine (Table 26–1), mepivacaine displays clinical properties that are comparable to

lidocaine. However, it differs from lidocaine with respect to vasoactivity, as it has a tendency toward vasoconstriction rather than vasodilation. This characteristic likely accounts for its slightly longer duration of action, which has made it a popular choice for major peripheral blocks. Lidocaine has retained its dominance over mepivacaine for epidural anesthesia, where the routine placement of a catheter negates the importance of a longer duration. More importantly, mepivacaine is slowly metabolized by the fetus, making it a poor choice for epidural anesthesia in the parturient. When used for spinal anesthesia, mepivacaine has a slightly lower incidence of TNS than lidocaine.

## PRILOCAINE

Prilocaine has the highest clearance of the amino-amide anesthetics, imparting reduced risk of systemic toxicity. Unfortunately, this is somewhat offset by its propensity to induce methemoglobinemia, which results from accumulation of one its metabolites, ortho-toluidine, an oxidizing agent. As a spinal anesthetic, prilocaine's duration of action is slightly longer than that of lidocaine, and the limited data suggest it carries a low risk of TNS. It is gaining increasing use for spinal anesthesia in Europe, where it has been marketed specifically for this purpose. No approved formulation exists in the USA, nor is there any formulation that would be appropriate to use for spinal anesthesia as an off-label indication.

## ROPIVACAINE

Ropivacaine is an *S*(–) enantiomer in a homologous series that includes bupivacaine and mepivacaine, distinguished by its chirality, and the propyl group off the piperidine ring (Table 26–1). Its perceived reduced cardiotoxicity has led to widespread use for high-volume peripheral blocks. It is also a popular choice for epidural infusions for control of labor and postoperative pain. Although there is some evidence to suggest that ropivacaine might produce a more favorable differential block than bupivacaine, the lack of equivalent clinical potency adds complexity to such comparisons.

## EMLA

The term eutectic is applied to mixtures in which the combination of elements has a lower melting temperature than its component elements. Lidocaine and prilocaine can combine to form such a mixture, which is marketed as EMLA (**E**utectic **M**ixture of **L**ocal **Anesthetics**). This formulation, containing 2.5% of lidocaine and 2.5% prilocaine, permits anesthetic penetration of the keratinized layer of skin, producing localized numbness. It is commonly used in pediatrics to anesthetize the skin prior to venipuncture for intravenous catheter placement.

## FUTURE DEVELOPMENTS

### Sustained-Release Formulations

The provision of prolonged analgesia or anesthesia, as in the case of postoperative pain management, has traditionally been accomplished by placement of a catheter to permit continuous administration of anesthetic. More recently, efforts have focused on drug delivery systems that can slowly release anesthetic, thereby providing extended duration without the drawbacks of a catheter. Sustained-release delivery has the potential added advantage of reducing risk of systemic toxicity. Preliminary work encapsulating local anesthetic into microspheres, liposomes, and other microparticles has established proof of concept, although significant developmental problems, as well as questions regarding potential tissue toxicity, remain to be resolved.

### Less Toxic Agents; More Selective Agents

It has been clearly demonstrated that anesthetic neurotoxicity does not result from blockade of the voltage-gated sodium channel. Thus, effect and tissue toxicity are not mediated by a common mechanism, establishing the possibility of developing compounds with considerably better therapeutic indexes.

As previously discussed, the identification and subclassification of families of neuronal sodium channels has spurred research aimed at development of more selective sodium channel blockers. The variable neuronal distribution of these isoforms and the unique role that some play in pain signaling suggests that selective blockade of these channels is feasible, and may greatly improve the therapeutic index of sodium channel modulators.

## SUMMARY Drugs Used for Local Anesthesia

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities |
|---|---|---|---|---|
| **AMIDES** | | | | |
| • Lidocaine | Blockade of sodium channels | Slows, then blocks, action potential propagation | Short-duration procedures • topical (mucosal), intravenous, infiltration, spinal, epidural, minor and major peripheral blocks | Parenteral (eg, peripheral block, but varies significantly based on specific site) • duration 1–2 h • 2–4 h with epinephrine • *Toxicity:* Central nervous system (CNS) excitation (high-volume blocks) and local neurotoxicity |
| • Bupivacaine | Same as lidocaine | Same as lidocaine | Longer-duration procedures (but not used topically or intravenously) | Parenteral • duration 3–6 h • *Toxicity:* CNS excitation • cardiovascular collapse (high-volume blocks) |
| • *Prilocaine, mepivacaine: Like lidocaine (but also risk of methemoglobinemia with prilocaine)* | | | | |
| • *Ropivacaine, levobupivacaine: Like bupivacaine* | | | | |
| **ESTERS** | | | | |
| • Chloroprocaine | Like lidocaine | Like lidocaine | Very short procedures (not generally used topically or intravenously) | Parenteral • duration 30–60 min • 60–90 min with epinephrine • *Toxicity:* Like lidocaine |
| • Cocaine | Same as above • also has sympathomimetic effects | Same as above | Procedures requiring high surface activity and vasoconstriction | Topical or parenteral • duration 1–2 h • *Toxicity:* CNS excitation, convulsions, cardiac arrhythmias, hypertension, stroke |
| • *Procaine: Like chloroprocaine (but not used epidurally)* | | | | |
| • *Tetracaine: Used primarily for spinal anesthesia; duration 2–3 h* | | | | |

## PREPARATIONS AVAILABLE

**Articaine (Septocaine)**
Parenteral: 4% with 1:100,000 epinephrine

**Benzocaine (generic)**
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

**Chloroprocaine (generic, Nesacaine)**
Parenteral: 1, 2, 3% for injection

**Cocaine (generic)**
Topical: 40, 100 mg/mL regular and viscous solutions; 5, 25 g powder

**Dibucaine (generic, Nupercainal)**
Topical: 1% ointment

**Dyclonine (Dyclone)**
Topical: 0.5, 1% solution

**Levobupivacaine (Chirocaine)**
Parenteral: 2.5, 5, 7.5 mg/mL

**Lidocaine (generic, Xylocaine)**
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 $cm^2$ patch

**Lidocaine and hydrocortisone**
Patch: 3% lidocaine plus 0.5% hydrocortisone

**Lidocaine and bupivacaine mixture (Duocaine)**
Parenteral: 10 mg/mL lidocaine plus 3.75 mg/mL bupivacaine for injection

**Lidocaine and prilocaine eutectic mixture (EMLA cream)**
Topical: lidocaine 2.5% plus prilocaine 2.5%

**Mepivacaine (generic, Carbocaine)**
Parenteral: 1, 1.5, 2, 3% for injection; 2% with 1:20,000 levonordefrin

**Pramoxine (generic, Tronothane)**
Topical: 1% cream, lotion, spray, and gel

**Prilocaine (Citanest)**
Parenteral: 4%; 4% with epinephrine

**Procaine (generic, Novocain)**
Parenteral: 1, 2, 10% for injection

**Proparacaine (generic, Alcaine, others)**
0.5% solution for ophthalmic use

**Ropivacaine (Naropin)**
Parenteral: 0.2, 0.5, 0.75, 1.0% solution for injection

**Tetracaine (generic, 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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## CASE STUDY ANSWER

If a spinal anesthetic technique were selected, bupivacaine would be an excellent choice. It has an adequately long duration of action and a relatively unblemished record with respect to neurotoxic injury and transient neurologic symptoms, which are the complications of most concern with spinal anesthetic technique. Although bupivacaine has greater potential for cardiotoxicity, this is not a concern when the drug is used for spinal anesthesia because of the extremely low doses required for intrathecal administration. If an epidural technique were chosen for the surgical procedure, the potential for systemic toxicity would need to be considered, making lidocaine or mepivacaine (generally with epinephrine) preferable to bupivacaine (or even ropivacaine or levobupivacaine) because of their better therapeutic indexes with respect to cardiotoxicity. However, this does not apply to epidural administration for postoperative pain control, which involves administration of more dilute anesthetic at a slower rate. The most common agents used for this indication are bupivacaine, ropivacaine, and levobupivacaine.

CHAPTER 27

# Skeletal Muscle Relaxants

Marieke Kruidering-Hall, PhD, &
Lundy Campbell, MD*

## CASE STUDY

A 30-year-old woman is rushed to the emergency department at a major trauma center after a motor vehicle accident. Although in significant pain, she is awake, alert, and able to give a brief history. She states that she was the driver and was wearing a seatbelt. There were no passengers in the car. Her past medical history is significant only for asthma, for which she has been intubated once in the past. She has no allergies to medications. There are multiple lacerations on her face and extremities and a large open fracture of her right femur. An orthopedic surgeon has scheduled immediate operative repair of the femur fracture, and the plastic surgeon wants to suture the facial lacerations at the same time. You decide to intubate the patient for the procedure. What muscle relaxant would you choose? Would you choose the same agent if she had experienced a 30% total body burn in a fire at the time of the accident? What if the past medical history included right-sided hemiparesis of 10 years' duration?

Drugs that affect skeletal muscle function include two different therapeutic groups: those used during surgical procedures and in the intensive care unit (ICU) to produce muscle paralysis (ie, **neuromuscular blockers**), and those used to reduce spasticity in a variety of painful 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 during general anesthesia to facilitate endotracheal intubation and optimize surgical conditions while ensuring adequate ventilation. Drugs in the spasmolytic group have traditionally been called "centrally acting" muscle relaxants and are used primarily to treat chronic back pain and painful fibromyalgic conditions. Dantrolene, a spasmolytic agent that has no significant central effects and is used primarily to treat a rare anesthetic-related complication, malignant hyperthermia, is also discussed in this chapter.

*The authors thank Paul F. White, PhD, MD, and Bertram G. Katzung, MD, PhD, for contributions to this chapter in previous editions.

## NEUROMUSCULAR BLOCKING DRUGS

### History

During the 16th century, European explorers found that natives in the Amazon Basin of South America were using curare, an arrow poison that produced skeletal muscle paralysis, to kill animals. The active compound, *d*-tubocurarine, and its modern synthetic derivatives have had a major influence on the practice of anesthesia and surgery and have proved useful in understanding the basic mechanisms involved in neuromuscular transmission.

### Normal Neuromuscular Function

The mechanism of neuromuscular transmission at the motor end plate is similar to that described for preganglionic cholinergic nerves in Chapter 6. The arrival of an action potential at the motor nerve terminal causes an influx of calcium and release of the neurotransmitter acetylcholine. Acetylcholine then diffuses across the synaptic cleft to activate the nicotinic receptors located on the motor end plate. As noted in Chapter 7, the adult $N_M$ receptor is composed of five peptides: two alpha peptides, one beta, one gamma, and one delta peptide (Figure 27–1). The binding of two acetylcholine

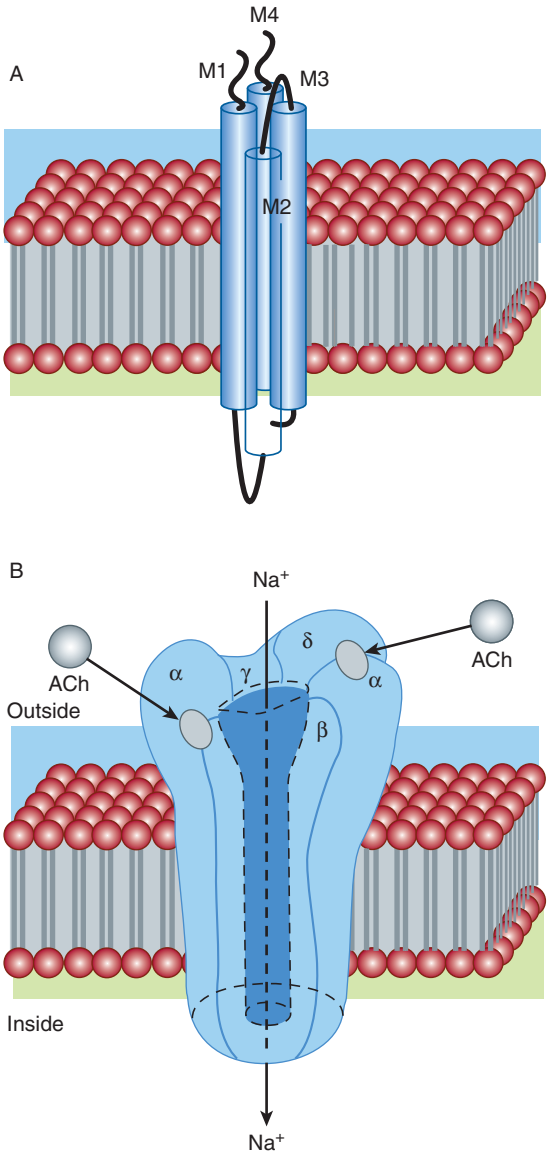



**FIGURE 27–1** The adult nicotinic acetylcholine receptor (nAChR) is an intrinsic membrane protein with five distinct subunits ($\alpha_2\beta\delta\gamma$). **A:** Cartoon of the one of five subunits of the AChR in the end plate surface of adult mammalian muscle. Each subunit contains four helical domains labeled M1 to M4. The M2 domains line the channel pore. **B:** Cartoon of the full nAChR. The N termini of two subunits cooperate to form two distinct binding pockets for acetylcholine (ACh). These pockets occur at the α-β and the δ-α subunit interfaces.

molecules to receptors on the α-β and δ-α subunits causes opening of the channel. The subsequent movement of sodium and potassium through the channel is associated with a graded depolarization of the end plate membrane (Figure 27–2). 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.

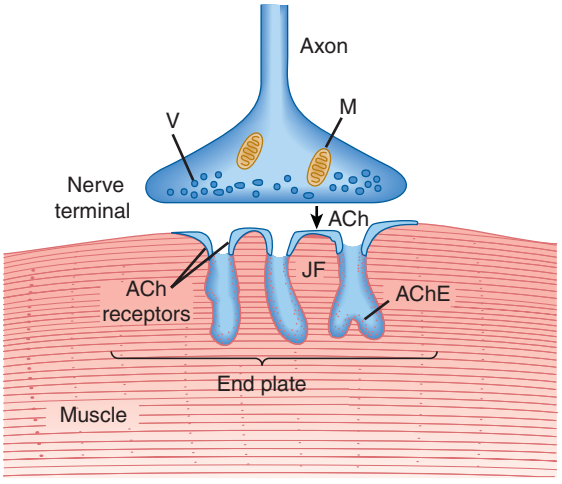



**FIGURE 27–2** Schematic representation of the neuromuscular junction. ACh, acetylcholine; AChE, acetylcholinesterase; JF, junctional folds; M, mitochondrion; V, transmitter vesicle. (Reproduced, with permission, from Drachman DB: Myasthenia gravis. N Engl J Med 1978;298:135.)

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 both diffusion and enzymatic destruction by the local acetylcholinesterase enzyme.

At least two additional types of acetylcholine receptors are found within the neuromuscular apparatus. One type is located on the presynaptic motor axon terminal, and activation of these receptors mobilizes additional transmitter for subsequent release by moving more acetylcholine vesicles toward the synaptic membrane. 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, thermal burns), these receptors may proliferate sufficiently to affect subsequent neuromuscular transmission.

Skeletal muscle relaxation and paralysis can occur from interruption of function at several sites along the pathway from the central nervous system (CNS) to myelinated somatic nerves, unmyelinated motor nerve terminals, nicotinic acetylcholine receptors, the motor end plate, the muscle membrane, and the intracellular muscular contractile apparatus itself.

Blockade of end plate function can be accomplished by two basic mechanisms. Pharmacologic blockade of the physiologic agonist acetylcholine is characteristic of the antagonist neuromuscular blocking drugs (ie, nondepolarizing neuromuscular blocking drugs). These drugs prevent access of the transmitter to its receptor and thereby prevent depolarization. The prototype of this nondepolarizing subgroup is ***d*-tubocurarine.** The second type of blockade can be produced by an excess of a depolarizing agonist, such as acetylcholine. This seemingly paradoxical effect of acetylcholine also occurs at the ganglionic nicotinic acetylcholine receptor. The prototypical depolarizing blocking drug is **succinylcholine.** A similar depolarizing block can be produced by acetylcholine itself when high local concentrations are achieved in the synaptic

cleft (eg, by cholinesterase inhibitor intoxication) and by nicotine and other nicotinic agonists. However, the neuromuscular block produced by depolarizing drugs other than succinylcholine cannot be precisely controlled and is of no clinical value.

# BASIC PHARMACOLOGY OF NEUROMUSCULAR BLOCKING DRUGS

## Chemistry

All of the available neuromuscular blocking drugs bear a structural resemblance to acetylcholine. For example, succinylcholine is two acetylcholine molecules linked end-to-end (Figure 27–3). 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, semirigid ring systems (Figure 27–3). Examples of the two major families of nondepolarizing blocking drugs—the isoquinoline and steroid derivatives—are shown in Figures 27–4 and 27–5. 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 CNS.

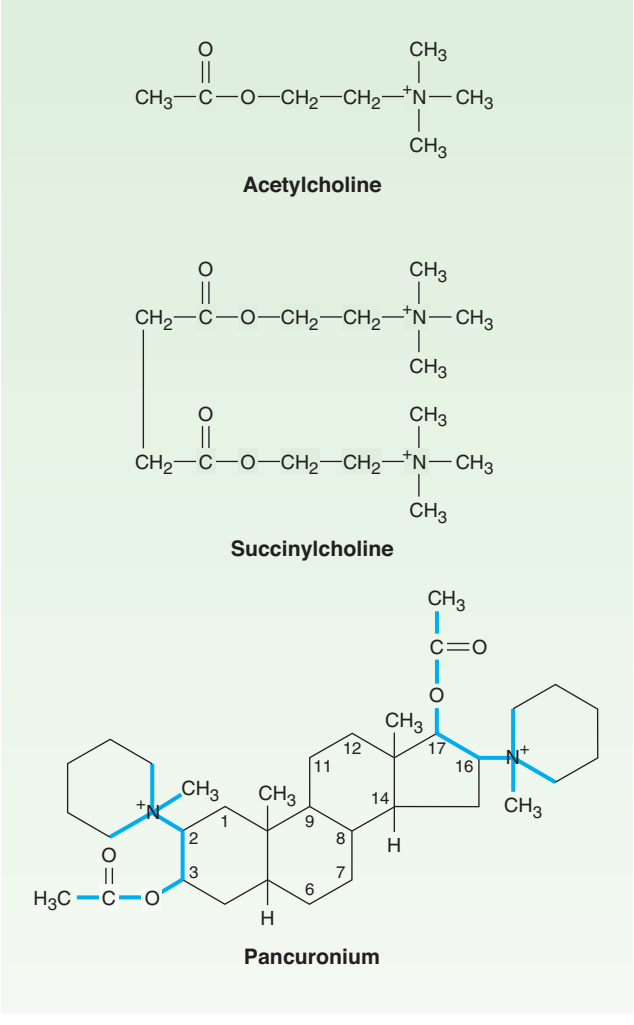



**FIGURE 27–3** Structural relationship of succinylcholine, a depolarizing agent, and pancuronium, a nondepolarizing agent, to acetylcholine, the neuromuscular transmitter. Succinylcholine, originally called diacetylcholine, is simply two molecules of acetylcholine linked through the acetate methyl groups. Pancuronium may be viewed as two acetylcholine-like fragments (outlined in color) oriented on a steroid nucleus.

## Pharmacokinetics of Neuromuscular Blocking Drugs

All of the neuromuscular blocking drugs are highly polar compounds and inactive orally; they must be administered parenterally.

### A. Nondepolarizing Relaxant Drugs

The rate of disappearance of a nondepolarizing neuromuscular blocking drug from the blood is characterized by a rapid initial distribution phase followed by a slower elimination phase. Neuromuscular blocking drugs are highly ionized, do not readily cross cell membranes, and are not strongly bound in peripheral tissues. Therefore, their volume of distribution (80–140 mL/kg) is only slightly larger than the blood volume.

The duration of neuromuscular blockade produced by nondepolarizing relaxants is strongly correlated with the elimination half-life. Drugs that are excreted by the kidney typically have longer half-lives, leading to longer durations of action (> 35 minutes). Drugs eliminated by the liver tend to have shorter half-lives and durations of action (Table 27–1). All steroidal muscle relaxants are metabolized to their 3-hydroxy, 17-hydroxy, or 3,17-dihydroxy products in the liver. The 3-hydroxy metabolites are usually 40–80% as potent as the parent drug. Under normal circumstances, metabolites are not formed in sufficient quantities to produce a significant degree of neuromuscular blockade during or after anesthesia. However, if the parent compound is administered for several days in the ICU setting, the 3-hydroxy metabolite may accumulate and cause prolonged paralysis because it has a longer half-life than the parent compound. The remaining metabolites possess minimal neuromuscular blocking properties.

The intermediate-acting steroid muscle relaxants (eg, **vecuronium** and **rocuronium**) tend to be more dependent on biliary excretion or hepatic metabolism for their elimination. These muscle relaxants are more commonly used clinically than the long-acting steroid-based drugs (eg, pancuronium).

**Atracurium** (Figure 27–4) is an intermediate-acting isoquinoline nondepolarizing muscle relaxant. In addition to hepatic metabolism, atracurium is inactivated by a form of spontaneous breakdown known as Hofmann elimination. The main breakdown products are laudanosine and a related quaternary acid, neither of which possesses neuromuscular blocking properties. Laudanosine is slowly metabolized by the liver and has a longer elimination half-life (ie, 150 minutes). It readily crosses the blood-brain barrier, and high blood concentrations may cause seizures and an increase in the volatile anesthetic requirement. During surgical anesthesia, blood levels of laudanosine typically range from 0.2 to 1 mcg/mL;

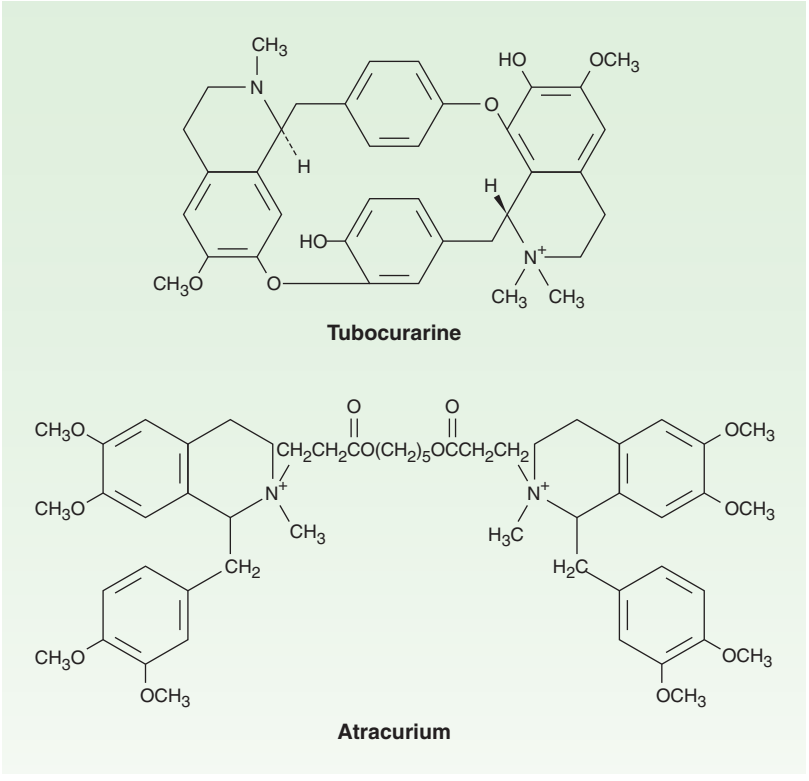



**FIGURE 27–4** Structures of two isoquinoline neuromuscular blocking drugs. These agents are nondepolarizing muscle relaxants.

however, with prolonged infusions of atracurium in the ICU, laudanosine blood levels may exceed 5 mcg/mL.

Atracurium has several stereoisomers, and the potent isomer **cisatracurium** has become one of the most commonly used muscle relaxants in clinical practice. Although cisatracurium resembles atracurium, it has less dependence on hepatic inactivation, produces less laudanosine, and is less likely to release histamine. From the clinical perspective, cisatracurium has all the advantages of atracurium with fewer side effects. Therefore, cisatracurium has largely replaced atracurium in clinical practice.

**Mivacurium,** another isoquinoline compound, has the shortest duration of action of all nondepolarizing muscle relaxants (Table 27–1). However, its onset of action is significantly slower than that of succinylcholine. In addition, the use of a larger dose to speed the onset can be associated with profound histamine release leading to hypotension, flushing, and bronchospasm. Clearance of mivacurium by plasma cholinesterase is rapid and independent of the liver or kidney (Table 27–1). However, because patients with renal failure often have decreased levels of plasma cholinesterase, the short duration of action of mivacurium may be prolonged in patients with impaired renal function. Although mivacurium is no longer in widespread clinical use, an investigational ultra-short-acting isoquinoline nondepolarizing muscle relaxant, gantacurium, is currently in phase 3 clinical testing.

**Gantacurium** represents a new class of nondepolarizing neuromuscular blockers, called asymmetric mixed-onium chlorofumarates. It is degraded nonenzymatically by adduction of the amino acid cysteine and ester bond hydrolysis. Preclinical and clinical data indicate gantacurium has a rapid onset of effect and predictable duration of action (very short, similar to succinylcholine) that can be reversed with edrophonium or administration of cysteine. At doses above three times the $ED_{95}$, cardiovascular adverse effects have occurred, probably due to histamine release. No bronchospasm or pulmonary vasoconstriction has been reported at these higher doses.

### B. Depolarizing Relaxant Drugs

The extremely short duration of action of succinylcholine (5–10 minutes) is due to its rapid hydrolysis by butyrylcholinesterase and pseudocholinesterase in the liver and plasma, respectively. Plasma cholinesterase metabolism is the predominant pathway for succinylcholine elimination. Since succinylcholine is more rapidly metabolized than mivacurium, its duration of action is shorter than that of mivacurium (Table 27–1). The primary metabolite of succinylcholine, succinylmonocholine, is rapidly broken down to succinic acid and choline. Because plasma cholinesterase has an enormous capacity to hydrolyze succinylcholine, only a small percentage of the original intravenous dose ever reaches the neuromuscular junction. In addition, because there is little if any plasma cholinesterase at the motor end plate, a succinylcholine-induced blockade is terminated by its diffusion away from the end plate into extracellular fluid. Therefore, the circulating levels of plasma cholinesterase influence the duration of action of succinylcholine by determining the amount of the drug that reaches the motor end plate.

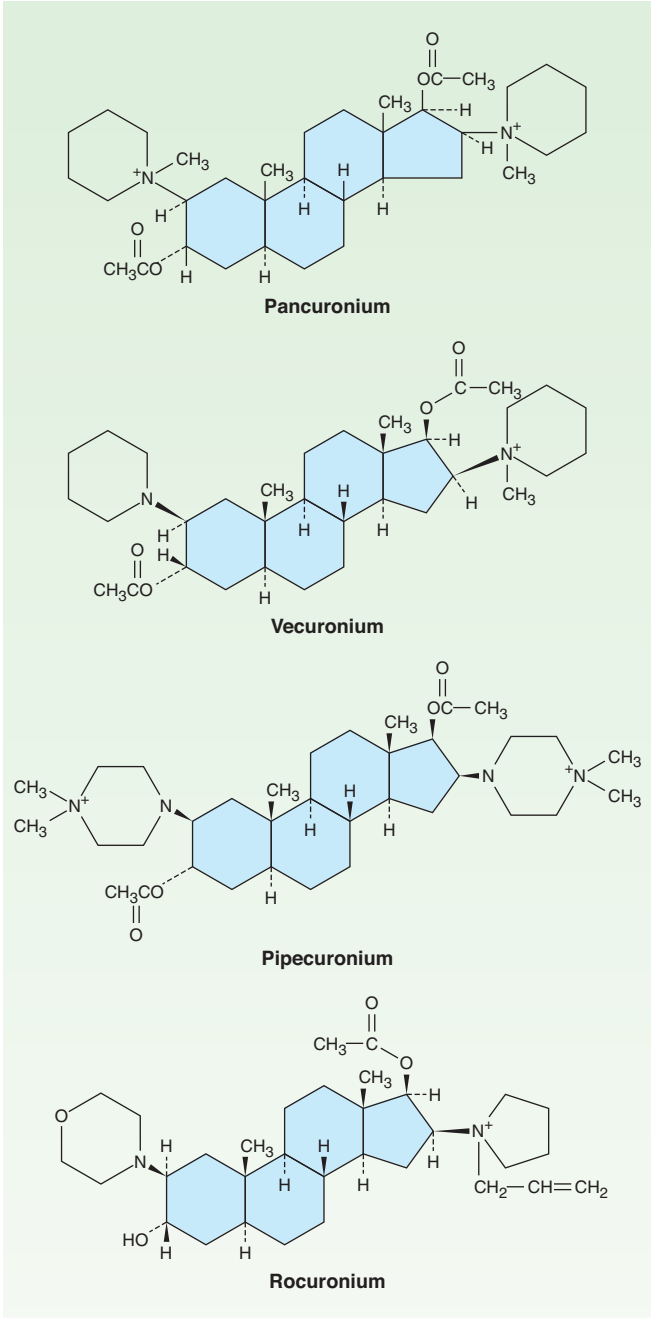



**FIGURE 27–5** Structures of steroid neuromuscular blocking drugs (steroid nucleus in color). These agents are all nondepolarizing muscle relaxants.

Neuromuscular blockade produced by succinylcholine and mivacurium can be prolonged in patients with an abnormal genetic variant of plasma cholinesterase. The *dibucaine number* is a measure of the ability of a patient to metabolize succinylcholine and can be used to identify at-risk patients. Under standardized test conditions, dibucaine inhibits the normal enzyme by 80% and the abnormal enzyme by only 20%. Many genetic variants of plasma cholinesterase have been identified, although the dibucaine-related variants are the most important. Given the rarity of these genetic variants, plasma cholinesterase testing is not a routine clinical procedure.

## Mechanism of Action

The interactions of drugs with the acetylcholine receptor-end plate channel have been described at the molecular level. Several modes of action of drugs on the receptor are illustrated in Figure 27–6.

### A. Nondepolarizing Relaxant Drugs

All the neuromuscular blocking drugs in current use in the USA except succinylcholine are classified as nondepolarizing agents. Although it is no longer in widespread clinical use, ***d*-tubocurarine** is considered the prototype neuromuscular blocker. When small doses of nondepolarizing muscle relaxants are administered, they act predominantly at the nicotinic receptor site by competing with acetylcholine. The least potent nondepolarizing relaxants (eg, rocuronium) have the fastest onset and the shortest duration of action. In larger doses, nondepolarizing drugs can enter the pore of the ion channel (Figure 27–1) to produce a more intense motor blockade. This action further weakens neuromuscular transmission and diminishes the ability of the acetylcholinesterase inhibitors (eg, neostigmine, edrophonium, pyridostigmine) to antagonize the effect of nondepolarizing muscle relaxants.

Nondepolarizing relaxants can also block prejunctional sodium channels. As a result of this action, muscle relaxants interfere with the mobilization of acetylcholine at the nerve ending and cause fade (Figure 27-7). One consequence of the surmountable nature of the postsynaptic blockade produced by nondepolarizing muscle relaxants is the fact that tetanic stimulation, by releasing a large quantity of acetylcholine, is followed by transient posttetanic facilitation of the twitch strength (ie, relief of blockade). An important clinical consequence of this principle is the reversal of residual blockade by cholinesterase inhibitors. The characteristics of a nondepolarizing neuromuscular blockade are summarized in Table 27–2 and Figure 27–7.

### B. Depolarizing Relaxant Drugs

***1. Phase I block (depolarizing)*—**Succinylcholine is the only clinically useful depolarizing blocking drug. Its neuromuscular effects are like those of acetylcholine except that succinylcholine produces a longer effect at the myoneural junction. Succinylcholine reacts with the nicotinic receptor to open the channel and cause depolarization of the motor end plate, and this in turn spreads to the adjacent membranes, causing contractions of muscle motor units. Data from single-channel recordings indicate that depolarizing blockers can enter the channel to produce a prolonged "flickering" of the ion conductance (Figure 27–8). Because succinylcholine is not metabolized effectively at the synapse, the depolarized membranes remain depolarized and unresponsive to subsequent impulses (ie, a state of depolarizing blockade). Furthermore, because excitation-contraction coupling requires end plate repolarization ("repriming") and repetitive firing to maintain muscle tension, a flaccid paralysis results. In contrast to the nondepolarizing drugs, this so-called phase I (depolarizing) block is augmented, not reversed, by cholinesterase inhibitors.

The characteristics of a depolarizing neuromuscular blockade are summarized in Table 27–2 and Figure 27–7.

**TABLE 27–1 Pharmacokinetic and dynamic properties of neuromuscular blocking drugs.**

| Drug | Elimination | Clearance (mL/kg/min) | Approximate Duration of Action (minutes) | Approximate Potency Relative to Tubocurarine |
|---|---|---|---|---|
| **Isoquinoline derivatives** | | | | |
| Atracurium | Spontaneous[1] | 6.6 | 20–35 | 1.5 |
| Cisatracurium | Mostly spontaneous | 5–6 | 25–44 | 1.5 |
| Mivacurium | Plasma ChE[2] | 70–95 | 10–20 | 4 |
| Tubocurarine | Kidney (40%) | 2.3–2.4 | > 50 | 1 |
| **Steroid derivatives** | | | | |
| Pancuronium | Kidney (80%) | 1.7–1.8 | > 35 | 6 |
| Rocuronium | Liver (75–90%) and kidney | 2.9 | 20–35 | 0.8 |
| Vecuronium | Liver (75–90%) and kidney | 3–5.3 | 20–35 | 6 |
| **Depolarizing agent** | | | | |
| Succinylcholine | Plasma ChE[2] (100%) | > 100 | < 8 | 0.4 |

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.

[2]Butyrylcholinesterase (pseudocholinesterase).

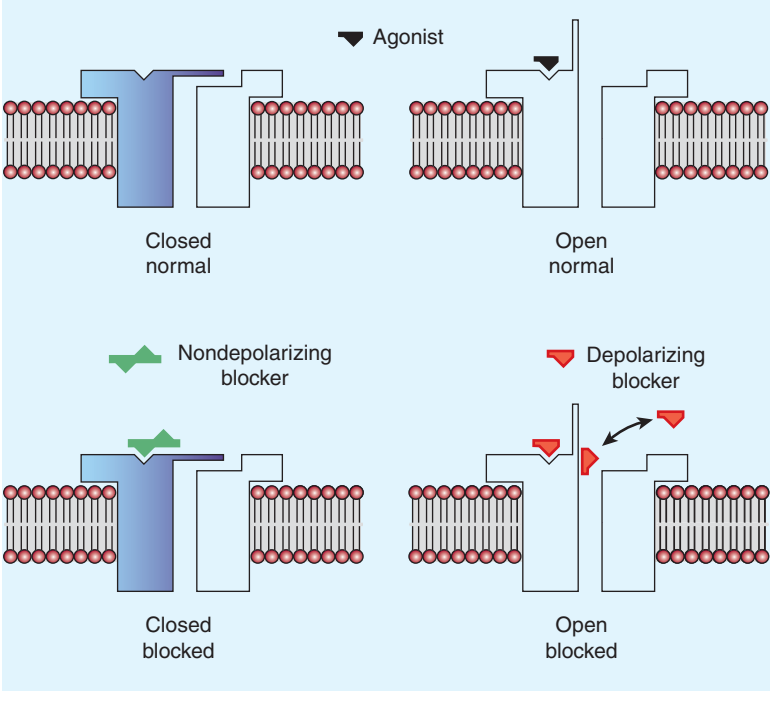



**FIGURE 27–6** Schematic diagram of the interactions of drugs with the acetylcholine receptor on the end plate channel (structures are purely symbolic). **Top:** The action of the normal agonist, acetylcholine, in opening the channel. **Bottom, left:** A nondepolarizing blocker, eg, rocuronium, is shown as preventing the opening of the channel when it binds to the receptor. **Bottom, right:** A depolarizing blocker, eg, succinylcholine, both occupying the receptor and blocking the channel. Normal closure of the channel gate is prevented and the blocker may move rapidly in and out of the pore. Depolarizing blockers may desensitize the end plate by occupying the receptor and causing persistent depolarization. An additional effect of drugs on the end plate channel may occur through changes in the lipid environment surrounding the channel (not shown). General anesthetics and alcohols may impair neuromuscular transmission by this mechanism.

**TABLE 27–2 Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).**

| | | Succinylcholine | |
|---|---|---|---|
| | **Rocuronium** | **Phase I** | **Phase II** |
| Administration of tubocurarine | Additive | Antagonistic | Augmented[1] |
| Administration of succinylcholine | Antagonistic | Additive | Augmented[1] |
| Effect of neostigmine | Antagonistic | Augmented[1] | Antagonistic |
| Initial excitatory effect on skeletal muscle | None | Fasciculations | None |
| Response to a tetanic stimulus | Unsustained (fade) | Sustained[2] (no fade) | Unsustained (fade) |
| Posttetanic facilitation | Yes | No | Yes |
| Rate of recovery | 30–60 min[3] | 4–8 min | > 20 min[3] |

[1]It is not known whether this interaction is additive or synergistic (superadditive).

[2]The amplitude is decreased, but the response is sustained.

[3]The rate depends on the dose and on the completeness of neuromuscular blockade.

***2. Phase II block (desensitizing)—***With prolonged exposure to succinylcholine, the initial end plate depolarization decreases and the membrane becomes repolarized. Despite this repolarization, the membrane cannot easily be depolarized again because it is *desensitized*. The mechanism for this desensitizing phase is unclear, but some evidence indicates that channel block may become more important than agonist action at the receptor in phase II of succinylcholine's neuromuscular blocking action. Regardless of the mechanism, the channels behave as if they are in a prolonged closed state (Figure 27–7). Later in phase II, the characteristics of the blockade are nearly identical to those of a nondepolarizing block (ie, a nonsustained twitch response to a tetanic stimulus) (Figure 27–7), with possible reversal by acetylcholinesterase inhibitors.

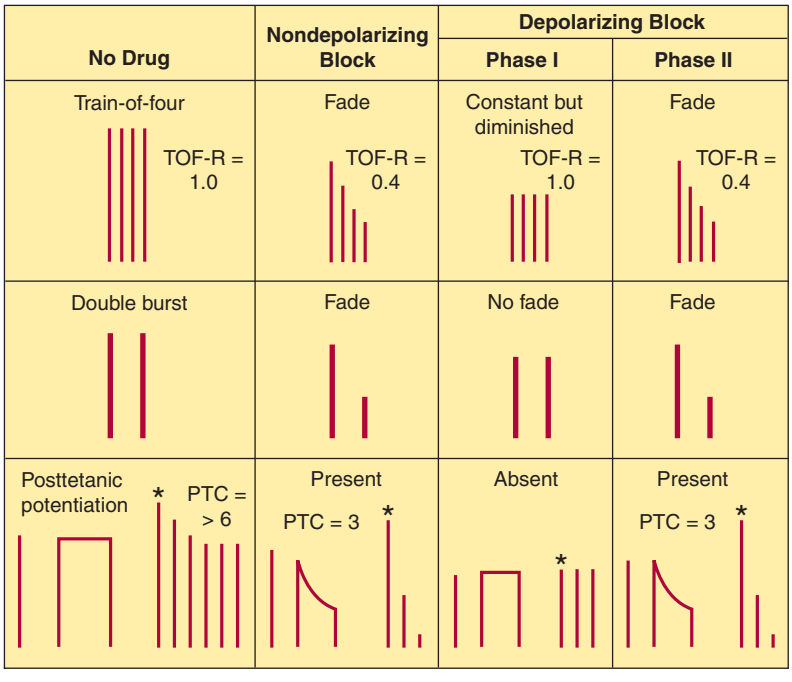



**FIGURE 27–7** Muscle contraction responses to different patterns of nerve stimulation used in monitoring skeletal muscle relaxation. The alterations produced by a nondepolarizing blocker and depolarizing and desensitizing blockade by succinylcholine are shown. In the train-of-four (TOF) pattern, four stimuli are applied at 2 Hz. The TOF ratio (TOF-R) is calculated from the strength of the fourth contraction divided by that of the first. In the double-burst pattern, three stimuli are applied at 50 Hz, followed by a 700 ms rest period and then repeated. In the posttetanic potentiation pattern, several seconds of 50 Hz stimulation are applied, followed by several seconds of rest and then by single stimuli at a slow rate (eg, 0.5 Hz). The number of detectable posttetanic twitches is the posttetanic count (PTC). *, first posttetanic contraction.

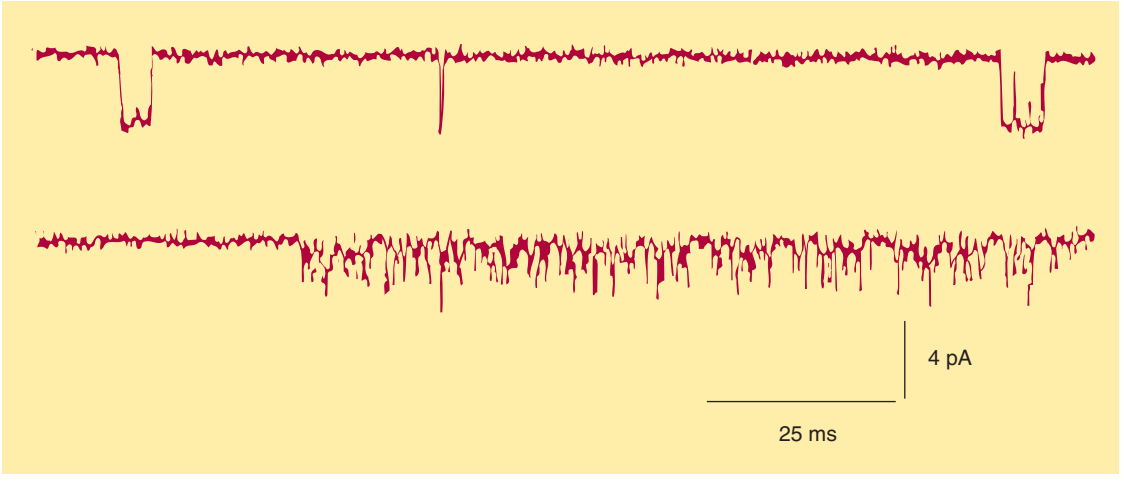



**FIGURE 27–8** Action of succinylcholine on single-channel end plate receptor currents in frog muscle. Currents through a single AChR channel were recorded using the patch clamp technique. The upper trace was recorded in the presence of a low concentration of succinylcholine; the downward deflections represent openings of the channel and passage of inward (depolarizing) current. The lower trace was recorded in the presence of a much higher concentration of succinylcholine and shows prolonged "flickering" of the channel as it repetitively opens and closes or is "plugged" by the drug. (Reproduced, with permission, from Marshall CG, Ogden DC, Colquhoun D: The actions of suxamethonium (succinyldicholine) as an agonist and channel blocker at the nicotinic receptor of frog muscle. J Physiol [Lond] 1990;428:155.)

# 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 levels of volatile (inhaled) anesthesia deep enough to produce 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 produced by deep anesthesia.

## Assessment of Neuromuscular Transmission

Monitoring the effect of muscle relaxants during surgery (and recovery following the administration of cholinesterase inhibitors) typically involves the use of a device that produces transdermal electrical stimulation of one of the peripheral nerves to the hand or facial muscles and recording of the evoked contractions (ie, twitch responses). The motor responses to different patterns of peripheral nerve stimulation can be recorded in the operating room during the procedure (Figure 27–7). The three most commonly used patterns 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 with 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 proportional to the degree of blockade. During recovery from nondepolarizing block, the amount of fade decreases and the TOF ratio approaches 1.0. Recovery to a TOF ratio greater than 0.7 is typically necessary for resumption of spontaneous ventilation. However, complete clinical recovery from a nondepolarizing block is considered to require a TOF greater than 0.9. Fade in the TOF response after administration of succinylcholine signifies the development of a phase II block.

Tetanic stimulation consists of a very rapid (30–100 Hz) delivery of electrical stimuli for several seconds. During a nondepolarizing neuromuscular block (and a phase II block after succinylcholine), the response is not sustained and fade of the twitch responses 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 an increase in the posttetanic twitch response, so-called posttetanic facilitation of neuromuscular transmission. During 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 and reflects the duration of profound (clinical) neuromuscular blockade. To determine the posttetanic count, 5 seconds of 50 Hz

tetany is applied, followed by 3 seconds of rest, followed by 1 Hz pulses for about 10 seconds (10 pulses). The counted number of muscle twitches provides an estimation of the depth of blockade. For instance, a posttetanic count of 2 suggests no twitch response (by TOF) for about 20–30 minutes, and a posttetanic count of 5 correlates to a no-twitch response (by TOF) of about 10–15 minutes (Figure 27–7, bottom panel).

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 to TOF stimulation. The absence of fade in response to double-burst stimulation implies that clinically significant residual neuromuscular blockade does not exist.

The standard approach used for monitoring the clinical effects of muscle relaxants during surgery is to use a peripheral nerve stimulating device to elicit motor responses, which are visually observed by the anesthesiologist. A more quantitative approach to neuromuscular monitoring involves the use of acceleromyography or force-transduction for measuring the evoked response (ie, movement) of the thumb to TOF stimulation over the ulnar nerve at the wrist.

### A. Nondepolarizing Relaxant Drugs

During anesthesia, administration of tubocurarine, 0.1–0.4 mg/kg IV, initially causes motor weakness, followed by the skeletal muscles becoming flaccid and inexcitable to electrical stimulation (Figure 27–9). In general, larger muscles (eg, abdominal, trunk, paraspinous, diaphragm) are more resistant to neuromuscular 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. 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, increasing the likelihood of adverse outcomes, eg, aspiration and decreased hypoxic drive. 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 the blocking effect, which determines how rapidly the patient's trachea can be intubated. Of the currently available nondepolarizing drugs, rocuronium has the most rapid onset time (60–120 seconds).

### B. Depolarizing Relaxant Drugs

Following the administration of succinylcholine, 0.75–1.5 mg/kg IV, transient muscle fasciculations occur over the chest and abdomen within 30 seconds, although general anesthesia and the prior administration of a small dose of a nondepolarizing muscle relaxant tends to attenuate them. As paralysis develops rapidly (< 90 seconds), the arm, neck, and leg muscles are initially relaxed followed by the respiratory muscles. As a result of succinylcholine's rapid hydrolysis by cholinesterase in the plasma (and liver), the duration of neuromuscular block typically lasts less than 10 minutes (Table 27–1).

## Cardiovascular Effects

Vecuronium, cisatracurium, and rocuronium have minimal, if any, cardiovascular effects. The other nondepolarizing muscle relaxants (ie, pancuronium, atracurium, mivacurium) produce cardiovascular effects that are mediated by either autonomic or

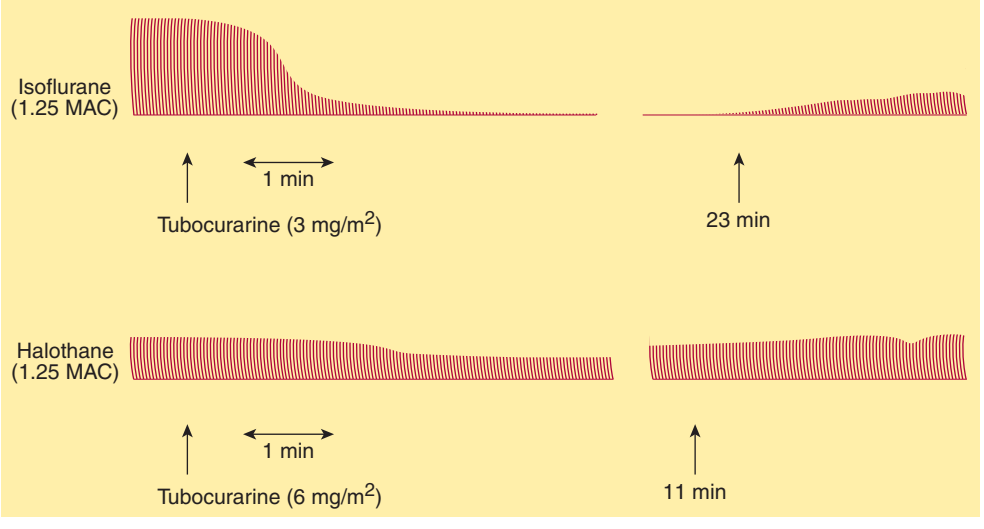



**FIGURE 27–9** Neuromuscular blockade from tubocurarine during equivalent levels of isoflurane and halothane anesthesia in patients. Note that isoflurane augments the block far more than does halothane.

histamine receptors (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 antihistaminic compound attenuates 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 may be secondary mechanisms. Bronchospasm may be produced by neuromuscular blockers that release histamine (eg, mivacurium), but insertion of a endotracheal tube is the most common reason for bronchospasm after induction of general anesthesia.

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

## Other Adverse Effects of Depolarizing Blockade

### A. Hyperkalemia

Patients with burns, nerve damage or neuromuscular disease, closed head injury, and other trauma can respond to succinylcholine by releasing potassium into the blood, which, on rare occasions, results in cardiac arrest.

### B. Increased Intraocular Pressure

Administration of succinylcholine may be associated with the rapid onset of an increase in intraocular pressure (< 60 seconds), peaking at 2–4 minutes, and declining after 5 minutes. The mechanism may involve tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels. Despite the increase in intraocular pressure, the use of succinylcholine for ophthalmologic operations is not contraindicated unless the anterior chamber is open ("open globe") due to trauma.

### C. Increased Intragastric Pressure

In heavily muscled patients, the fasciculations associated with succinylcholine may cause an increase in intragastric pressure ranging from 5 to 40 cm $H_2O$, increasing the risk for regurgitation and aspiration of gastric contents. This complication is more likely to occur in patients with delayed gastric emptying (eg, those with diabetes), traumatic injury (eg, an emergency case), esophageal dysfunction, and morbid obesity.

### D. Muscle Pain

Myalgias are a common postoperative complaint of heavily muscled patients and those who receive large doses (> 1.5 mg/kg) of succinylcholine. The true incidence of myalgias related to muscle fasciculations is difficult to establish because of confounding

**TABLE 27–3 Effects of neuromuscular blocking drugs on other tissues.**

| Drug | Effect on Autonomic Ganglia | Effect on Cardiac Muscarinic Receptors | Tendency to Cause Histamine Release |
|---|---|---|---|
| **Isoquinoline derivatives** | | | |
| Atracurium | None | None | Slight |
| Cisatracurium | None | None | None |
| Mivacurium | None | None | Moderate |
| Tubocurarine | Weak block | None | Moderate |
| **Steroid derivatives** | | | |
| Pancuronium | None | Moderate block | None |
| Rocuronium[1] | None | Slight | None |
| Vecuronium | None | None | None |
| **Other agents** | | | |
| Gallamine | None | Strong block | None |
| Succinylcholine | Stimulation | Stimulation | Slight |

[1]Allergic reactions have been reported.

factors, including the anesthetic technique, type of surgery, and positioning during the operation. However, the incidence of myalgias has been reported to vary from less than 1% to 20%. 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 actually higher than with nondepolarizing muscle relaxants when other potentially confounding factors are taken into consideration.

## Interactions with Other Drugs

### A. Anesthetics

Inhaled (volatile) anesthetics potentiate the neuromuscular blockade produced by nondepolarizing muscle relaxants in a dose-dependent fashion. Of the general anesthetics that have been studied, inhaled anesthetics augment the effects of muscle relaxants in the following order: isoflurane (most); sevoflurane, desflurane, enflurane, and halothane; and nitrous oxide (least) (Figure 27–9). 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 produced by volatile anesthetics), 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.

A rare interaction of succinylcholine with volatile anesthetics results in **malignant hyperthermia**, a condition caused by abnormal release of calcium from stores in skeletal muscle. This condition is treated with dantrolene and is discussed below under Spasmolytic Drugs and in Chapter 16.

### B. Antibiotics

Numerous reports have described enhancement of neuromuscular blockade by antibiotics (eg, aminoglycosides). Many of the antibiotics have been shown to cause a depression of evoked release of acetylcholine similar to that caused by administering magnesium. The mechanism of this prejunctional effect appears to be blockade of specific P-type calcium channels in the motor nerve terminal.

### C. Local Anesthetics and Antiarrhythmic Drugs

In small doses, local anesthetics can depress posttetanic potentiation via a prejunctional neural effect. In large doses, local anesthetics can block neuromuscular transmission. With higher doses, local anesthetics block acetylcholine-induced muscle contractions as a 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.

### D. 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 nondepolarizing drug can be given before succinylcholine (eg, *d*-tubocurarine, 2 mg IV, or pancuronium, 0.5 mg IV). Although this dose usually reduces fasciculations and postoperative myalgias, it can increase the amount of succinylcholine required for relaxation by 50–90% and can produce a feeling of weakness in awake patients. Therefore, "pre-curarization" before 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 enhances the neuromuscular blockade produced by these drugs. Advanced age 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 dosage of neuromuscular blocking drugs should be reduced in older patients (> 70 years).

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. **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 the release of this transmitter from the motor nerve terminal. In contrast, **edrophonium** antagonizes neuromuscular blockade purely by inhibiting acetylcholinesterase activity. Edrophonium has a more rapid onset of action but may be less effective than neostigmine in reversing the effects of nondepolarizing blockers in the presence of a 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 hypoventilation, leading to hypoxia and even apnea, especially if patients have received central depressant medications in the early recovery period.

Since mivacurium is metabolized by plasma cholinesterase, its interaction with the anticholinesterase reversal drugs is less predictable. On the 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 itself.

Sugammadex is a novel reversal agent approved in Europe but not yet approved for use in the USA. It is a modified γ-cyclodextran that binds tightly to rocuronium in a 1:1 ratio. By binding to plasma rocuronium, sugammadex decreases the free plasma rocuronium concentration and establishes a concentration gradient for rocuronium to diffuse away from the neuromuscular junction back into the circulation, where it is quickly bound by free sugammadex.

The optimum dose of sugammadex required to achieve adequate reversal of the neuromuscular blocking agent has yet to be definitively established. Clinical trials studying safety and efficacy have used doses ranging from 0.5 to 16 mg/kg. From 2 mg/kg upward, sugammadex dose-dependently reverses rocuronium with increasing speed and efficacy. These trials reported no difference in prevalence of untoward effects among sugammadex, placebo, and neostigmine. The data need to be confirmed in larger trials, especially the drug's potential to elicit allergic or hypersensitivity reactions.

The sugammadex-rocuronium complex is typically excreted unchanged in the urine within 24 hours in patients with normal renal function. In patients with renal insufficiency, complete urinary elimination may take much longer. However, due to the strong complex formation with rocuronium, no signs of recurrence of neuromuscular blockade have been noted up to 48 hours after use in such patients.

Further large-scale studies will be needed to evaluate the efficacy, safety, and clearance of sugammadex in patient populations with various levels of renal failure.

## Uses of Neuromuscular Blocking Drugs

### A. Surgical Relaxation

One of the most important applications of the neuromuscular blockers is in facilitating intracavitary surgery, especially in intra-abdominal and intrathoracic procedures.

### B. Endotracheal Intubation

By relaxing the pharyngeal and laryngeal muscles, neuromuscular blocking drugs facilitate laryngoscopy and placement of the endotracheal tube. Placement of a endotracheal tube ensures an adequate airway and minimizes the risk of pulmonary aspiration during general anesthesia.

### C. 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. In the ICU, neuromuscular blocking drugs are frequently administered to reduce chest wall resistance (ie, improve thoracic compliance) and ineffective spontaneous ventilation in intubated patients.

### D. Treatment of Convulsions

Neuromuscular blocking drugs (ie, succinylcholine) are occasionally used to attenuate the peripheral (motor) manifestations of convulsions associated with status epilepticus 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 because neuromuscular blocking drugs do not cross the blood-brain barrier.

# SPASMOLYTIC 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 spinal injury, 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 CNS (ie, upper motor neuron lesion), with damage to descending pathways in the spinal cord resulting in hyperexcitability of the alpha motoneurons in the cord. 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.

Drugs that modify this reflex arc may modulate excitatory or inhibitory synapses (see Chapter 21). Thus, to reduce the hyperactive stretch reflex, it is desirable to reduce the activity of the Ia 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 muscle tone. However, as illustrated in Figure 27–11, nonspecific depression of synapses involved in the stretch reflex could reduce the desired GABAergic inhibitory activity, as well as the excitatory glutamatergic transmission. Currently available drugs can provide significant relief from painful muscle spasms, but they are less effective in improving meaningful function (eg, mobility and return to work).

## DIAZEPAM

As described in Chapter 22, benzodiazepines facilitate the action of GABA in the central nervous system. Diazepam acts at $GABA_A$ synapses, and its action in reducing spasticity is at least partly mediated in the spinal cord because it is somewhat effective in patients with cord transection. Although diazepam can be used in patients with muscle spasm of almost any origin (including local muscle trauma), it also produces sedation at the doses required to reduce muscle tone. The initial dosage is 4 mg/d, and it is gradually increased to a maximum of 60 mg/d. Other benzodiazepines have been used as spasmolytics (eg, midazolam), but clinical experience with them is limited.

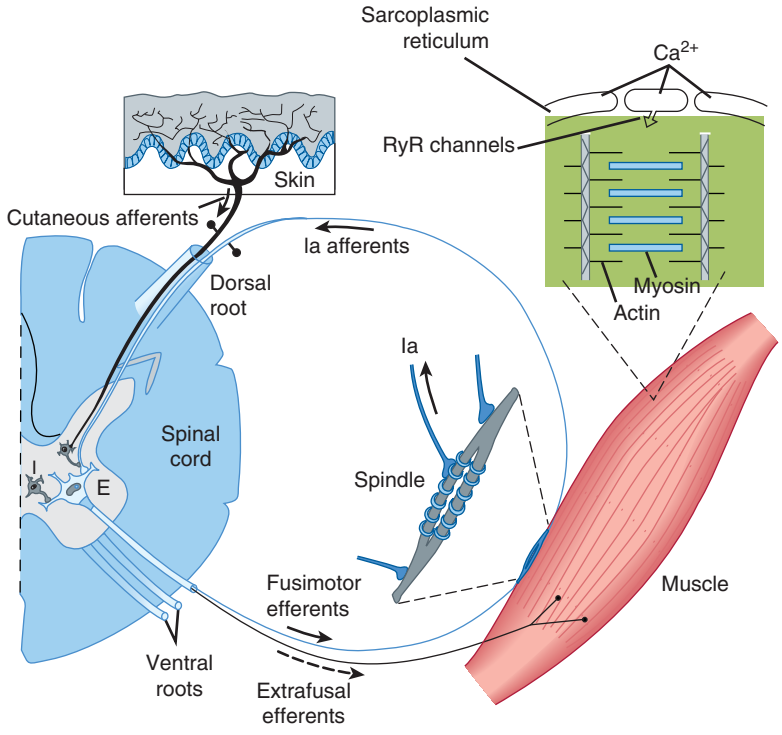
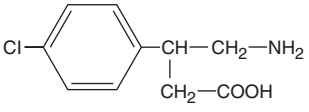



**FIGURE 27–10** Diagram of the structures involved in the stretch reflex arc. *I* is an inhibitory interneuron; *E* indicates an excitatory presynaptic terminal; Ia is a primary intrafusal afferent fiber; $Ca^{2+}$ denotes activator calcium stored in the sarcoplasmic reticulum of skeletal muscle; RyR channels indicates the $Ca^{2+}$ release channels. (Reproduced, with permission, from Young RR, Delwaide PJ: Drug therapy: Spasticity. N Engl J Med 1981;304:28.)

## BACLOFEN

Baclofen (*p*-chlorophenyl-GABA) was designed to be an orally active GABA-mimetic agent and is an agonist at $GABA_B$ receptors. Activation of these receptors by baclofen results in hyperpolarization, probably by increased $K^+$ conductance (see Figure 24–2). It has been suggested that hyperpolarization 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 (neurokinin-1) in the spinal cord.




**Baclofen**

Baclofen is at least as effective as diazepam in reducing spasticity and causes 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; however, patients become tolerant to the sedative effect with chronic administration. Increased seizure activity has been reported in epileptic patients. Therefore, withdrawal from 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. Excessive somnolence, respiratory depression, and even coma have been described. Although a major disadvantage of this therapeutic approach is the difficulty of maintaining the drug delivery catheter in the subarachnoid space, risking an acute withdrawal syndrome upon treatment interruption, 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, including patients with intractable low back pain. Preliminary studies suggest that it may also be effective in reducing craving in recovering alcoholics (see Chapter 32). Finally, it has been alleged to be effective in preventing migraine headaches in some patients.

## TIZANIDINE

As noted in Chapter 11, $\alpha_2$ agonists such as clonidine and other imidazoline compounds have a variety of effects on the CNS that are not fully understood. Among these effects is the ability to reduce muscle spasm. Tizanidine is a congener of clonidine that

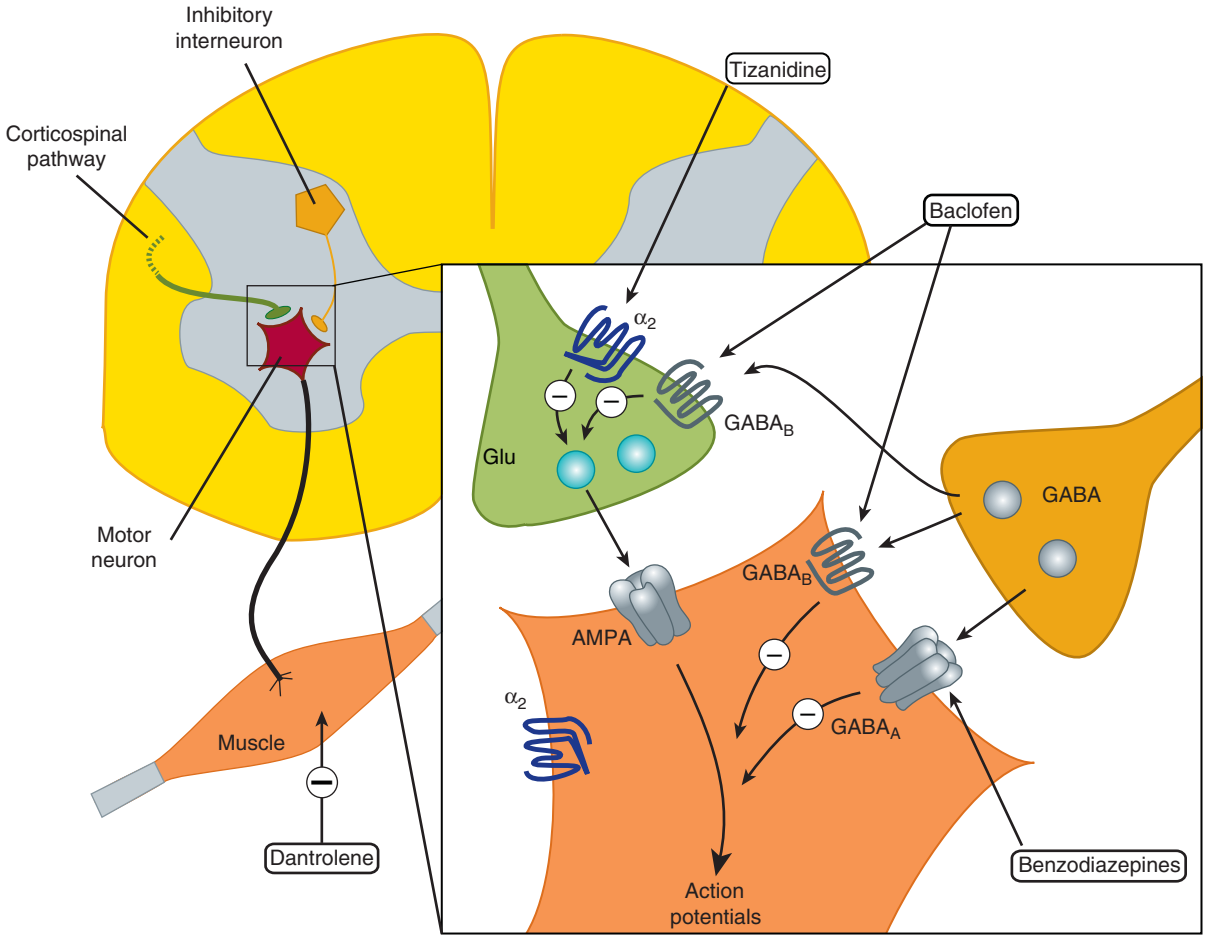



**FIGURE 27–11** Postulated sites of spasmolytic action of tizanidine ($\alpha_2$), benzodiazepines ($GABA_A$), and baclofen ($GABA_B$) in the spinal cord. Tizanidine may also have a postsynaptic inhibitory effect. Dantrolene acts on the sarcoplasmic reticulum in skeletal muscle. Glu, glutamatergic neuron.

has been studied for its spasmolytic actions. Tizanidine has significant $\alpha_2$-adrenoceptor agonist effects, but it reduces spasticity in experimental models at doses that cause fewer cardiovascular effects than clonidine or dexmedetomidine. Tizanidine has approximately one tenth to one fifteenth of the blood pressure-lowering effects of 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. Tizanidine's actions are believed to be mediated via restoration of inhibitory suppression of the group II spinal interneurons without inducing any changes in intrinsic muscle properties.

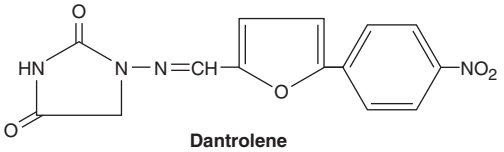
Clinical trials with oral tizanidine report comparable efficacy in relieving muscle spasm to diazepam, baclofen, and dantrolene. Tizanidine causes markedly less muscle weakness but produces a different spectrum of adverse effects, including drowsiness, hypotension, dizziness, dry mouth, asthenia, and hepatotoxicity. The drowsiness can be managed by taking the drug at night. Tizanidine displays linear pharmacokinetics, and dosage requirements vary considerably among patients. Dosage must be adjusted in patients with hepatic or renal impairment. In addition to its effectiveness in spastic conditions, tizanidine also appears to be effective for management of chronic migraine.

## OTHER CENTRALLY ACTING SPASMOLYTIC DRUGS

**Gabapentin** is an antiepileptic drug (see Chapter 24) that has shown considerable promise as a spasmolytic agent in several studies involving patients with multiple sclerosis. Pregabalin is a newer analog of gabapentin that may also prove useful in relieving painful disorders that involve a muscle spasm component. **Progabide** and **glycine** have also been found in preliminary studies to reduce spasticity. Progabide is a $GABA_A$ and $GABA_B$ agonist and has active metabolites, including GABA itself. Glycine is another inhibitory amino acid neurotransmitter (see Chapter 21) that 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 (ALS) 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 spasmolytic activity. In contrast to the centrally acting 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, called the **ryanodine receptor (RyR) channel** because the plant alkaloid ryanodine combines with a receptor on the channel protein. In the case of the skeletal muscle RyR1 channel, ryanodine facilitates the open configuration.




**Dantrolene**

Dantrolene interferes with the release of activator calcium through this sarcoplasmic reticulum calcium channel by binding to the RyR1 and blocking the opening of the channel. Motor units that contract rapidly are more sensitive to the drug's effects than are slower-responding units. Cardiac muscle and smooth muscle are minimally depressed because the release of calcium from their sarcoplasmic reticulum involves a different RyR channel (RyR2).

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 approximately 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; see also Chapter 16). Patients at risk for this condition have a hereditary alteration in $Ca^{2+}$-induced $Ca^{2+}$ release via the RyR1 channel or impairment in the ability of the sarcoplasmic reticulum to sequester calcium via the $Ca^{2+}$ transporter (Figure 27–10). Several mutations associated with this risk have been identified. After 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 by administering intravenous dantrolene, starting with a dose of 1 mg/kg IV, 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. Local facial injections of botulinum toxin are widely used for the short-term treatment (1–3 months per treatment) of wrinkles associated with aging around the eyes and mouth. Local injection of botulinum toxin has also become a useful treatment for 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 have used type A botulinum toxin, but type B is also available.

## DRUGS USED TO TREAT ACUTE LOCAL MUSCLE SPASM

A large number of less well-studied, centrally active 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 muscle strains. It has been suggested that these drugs act primarily at the level of the brainstem. Cyclobenzaprine may be regarded as the prototype of the group. Cyclobenzaprine is structurally related to the tricyclic antidepressants and produces antimuscarinic side effects. It is ineffective in treating muscle spasm due to cerebral palsy or spinal cord injury. As a result of its strong antimuscarinic actions, cyclobenzaprine 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 orally in divided doses.

## SUMMARY Skeletal Muscle Relaxants

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities, Interactions |
|---|---|---|---|---|
| **DEPOLARIZING NEUROMUSCULAR BLOCKING AGENT** | | | | |
| • Succinylcholine | Agonist at nicotinic acetylcholine (ACh) receptors, especially at neuromuscular junctions • depolarizes • may stimulate ganglionic nicotinic ACh and cardiac muscarinic ACh receptors | Initial depolarization causes transient contractions, followed by prolonged flaccid paralysis • depolarization is then followed by repolarization that is also accompanied by paralysis | Placement of endotracheal tube at start of anesthetic procedure • rarely, control of muscle contractions in status epilepticus | Rapid metabolism by plasma cholinesterase • normal duration, ~5 min • *Toxicities:* Arrhythmias • hyperkalemia • transient increased intra-abdominal, intraocular pressure • postoperative muscle pain |
| **NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS** | | | | |
| • *d*-Tubocurarine | Competitive antagonist at nACh receptors, especially at neuromuscular junctions | Prevents depolarization by ACh, causes flaccid paralysis • can cause histamine release with hypotension • weak block of cardiac muscarinic ACh receptors | Prolonged relaxation for surgical procedures • superseded by newer nondepolarizing agents | Renal excretion • duration, ~40–60 min • *Toxicities:* Histamine release • hypotension • prolonged apnea |
| • Cisatracurium | Similar to tubocurarine | Like tubocurarine but lacks histamine release and antimuscarinic effects | Prolonged relaxation for surgical procedures • relaxation of respiratory muscles to facilitate mechanical ventilation in intensive care unit | Not dependent on renal or hepatic function • duration, ~25–45 min • *Toxicities:* Prolonged apnea but less toxic than atracurium |
| • Rocuronium | Similar to cisatracurium | Like cisatracurium but slight antimuscarinic effect | Like cisatracurium • useful in patients with renal impairment | Hepatic metabolism • duration, ~20–35 min • *Toxicities:* Like cisatracurium |
| • *Mivacurium: Rapid onset, short duration (10–20 min); metabolized by plasma cholinesterase* | | | | |
| • *Vecuronium: Intermediate duration; metabolized in liver* | | | | |
| **CENTRALLY ACTING SPASMOLYTIC DRUGS** | | | | |
| • Baclofen | $GABA_B$ agonist, facilitates spinal inhibition of motor neurons | Pre- and postsynaptic inhibition of motor output | Severe spasticity due to cerebral palsy, multiple sclerosis, stroke | Oral, intrathecal • *Toxicities:* Sedation, weakness |
| • Cyclobenzaprine | Poorly understood inhibition of muscle stretch reflex in spinal cord | Reduction in hyperactive muscle reflexes • antimuscarinic effects | Acute spasm due to muscle injury • inflammation | Hepatic metabolism • duration, ~4–6 h • *Toxicities:* Strong antimuscarinic effects |
| • *Chlorphenesin, methocarbamol, orphenadrine, others: Like cyclobenzaprine with varying degrees of antimuscarinic effect* | | | | |
| • Diazepam | Facilitates GABAergic transmission in central nervous system (see Chapter 22) | Increases interneuron inhibition of primary motor afferents in spinal cord • central sedation | Chronic spasm due to cerebral palsy, stroke, spinal cord injury • acute spasm due to muscle injury | Hepatic metabolism • duration, ~12–24 h • *Toxicities:* See Chapter 22 |
| • Tizanidine | $\alpha_2$-Adrenoceptor agonist in the spinal cord | Presynaptic and postsynaptic inhibition of reflex motor output | Spasm due to multiple sclerosis, stroke, amyotrophic lateral sclerosis | Renal and hepatic elimination • duration, 3–6 h • *Toxicities:* Weakness, sedation • hypotension |
| **DIRECT-ACTING MUSCLE RELAXANT** | | | | |
| • Dantrolene | Blocks RyR1 $Ca^{2+}$-release channels in the sarcoplasmic reticulum of skeletal muscle | Reduces actin-myosin interaction • weakens skeletal muscle contraction | IV: Malignant hyperthermia • Oral: Spasm due to cerebral palsy, spinal cord injury, multiple sclerosis | IV, oral • duration, 4–6 h • *Toxicities:* Muscle weakness |

## PREPARATIONS AVAILABLE

### NEUROMUSCULAR BLOCKING DRUGS

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

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

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

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

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

**Succinylcholine (generic, Anectine, Quelicin)**
Parenteral: 20, 50, 100 mg/mL for injection; 500, 1000 mg per vial powder 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, Gablofen)**
Oral: 10, 20 mg tablets
Intrathecal: 0.05, 0.5, 2 mg/mL

**Botulinum toxin type A (Botox)**
Parenteral: Powder for solution, 50, 100, 200 units/vial

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

**Carisoprodol (generic, Soma)**
Oral: 250, 350 mg tablets

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

**Cyclobenzaprine (generic, Amrix, Fexmid, Flexeril)**
Oral: 5, 7.5, 10 mg tablets; 15, 30 mg capsules

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

**Diazepam (generic, Diastat, Valium)**
Oral: 2, 5, 10 mg tablets; 5 mg/5 mL, 5 mg/mL solutions
Parenteral: 5 mg/mL for injection
Rectal: 2.5, 5, 10 mg gel

**Gabapentin (Neurontin)**
Oral: 100, 300, 400 mg capsules; 600, 800 mg tablets; 50 mg/mL oral solution
*Note:* This drug is labeled for use only in epilepsy and postherpetic neuralgia.

**Metaxalone (Skelaxin)**
Oral: 800 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: 2, 4 mg tablets, capsules; 6 mg capsules

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## CASE STUDY ANSWER

Because of trauma and associated pain, it is assumed that gastric emptying will be significantly delayed. To avoid possible aspiration at the time of intubation, a very rapid-acting muscle relaxant should be used so the airway can be secured with an endotracheal tube. Therefore, succinylcholine is the agent of choice in this case. Despite its side effects, succinylcholine has the fastest mechanism of action of any currently available skeletal muscle relaxant. An alternative to succinylcholine is high-dose (up to 1.2 mg/kg) rocuronium, a nondepolarizing muscle relaxant. At this dose, rocuronium has a very rapid onset, which approaches but does not quite equal that of succinylcholine.

Both burns and neurologic injuries result in the expression of extrajunctional acetylcholine receptors. In patients with recent burns, succinylcholine use can lead to life-threatening hyperkalemia. Although the drug would not result in dangerous hyperkalemia if given immediately after a severe neurologic injury, in a patient with a chronic paralysis, its use may lead to hyperkalemia. Therefore, succinylcholine would also be contraindicated in a patient with long-standing hemiparesis.

CHAPTER 28

# Pharmacologic Management of Parkinsonism & Other Movement Disorders

Michael J. Aminoff, MD, DSc, FRCP

## CASE STUDY

A 64-year-old architect complains of left-hand tremor at rest, which interferes with his writing and drawing. He also notes a stooped posture, a tendency to drag his left leg when walking, and slight unsteadiness on turning. He remains independent in all activities of daily living. Examination reveals hypomimia (flat facies), hypophonia, a rest tremor of the left arm and leg, mild rigidity in all limbs, and impaired rapid alternating movements in the left limbs. Neurologic and general examinations are otherwise normal. What is the likely diagnosis and prognosis, and how should his condition be managed?

Several 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 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; it 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. Various genetic loci have been reported (eg, 9q34, 8p21–q22, 18p, 1p36.32–p36.13, 14q22.1–q22.2, 19q13, Xq13) depending on the age of onset, mode of inheritance, and response to dopaminergic therapy. The 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 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. The basic circuitry of the basal ganglia involves three interacting neuronal loops that include the cortex and thalamus as well as the basal ganglia themselves (Figure 28–1). However, 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.

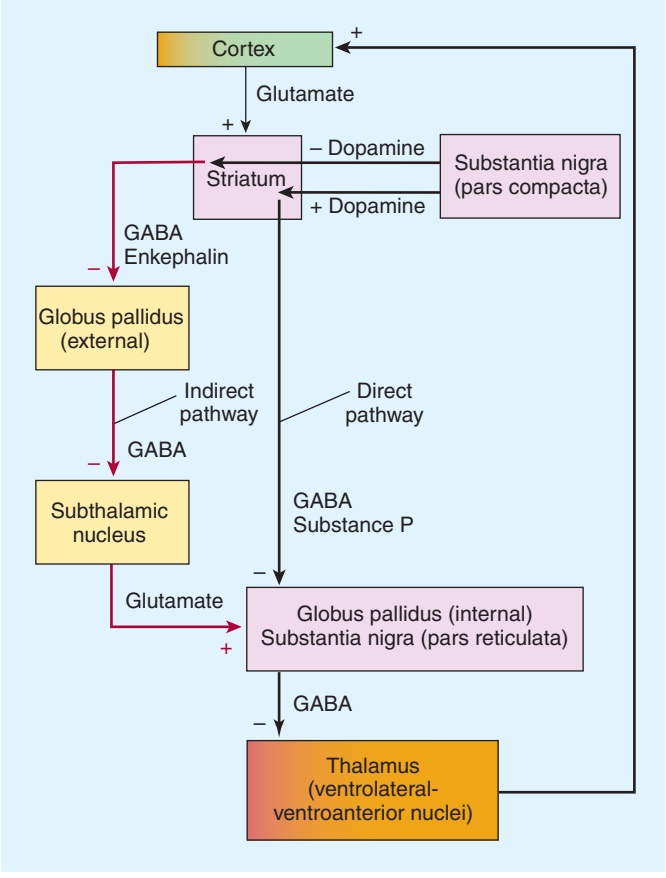



**FIGURE 28–1** Functional circuitry between the cortex, basal ganglia, and thalamus. The major neurotransmitters are indicated. In Parkinson's disease, there is degeneration of the pars compacta of the substantia nigra, leading to overactivity in the indirect pathway (red) and increased glutamatergic activity by the subthalamic nucleus.

# PARKINSONISM

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons but is usually idiopathic (Parkinson's disease or paralysis agitans). Cognitive decline occurs in many patients as the disease advances. Other nonmotor symptoms—which are receiving increasing attention—are affective disorders (anxiety or depression), personality changes, abnormalities of autonomic function (sphincter or sexual functions; choking; sweating abnormalities; and disturbances of blood pressure regulation), sleep disorders, and sensory complaints or pain. The disease is generally progressive, leading to increasing disability unless effective treatment is provided.

## Pathogenesis

The pathogenesis of parkinsonism seems to relate to a combination of impaired degradation of proteins, intracellular protein accumulation and aggregation, oxidative stress, mitochondrial damage, inflammatory cascades, and apoptosis. Studies in twins suggest that genetic factors are important, especially when the disease occurs in patients under age 50. Recognized genetic abnormalities account for 10–15% of cases. Mutations of the α-synuclein gene at 4q21 or duplication and triplication of the normal synuclein gene are associated with Parkinson's disease, which is now widely recognized as a *synucleinopathy*. Mutations of the leucine-rich repeat kinase 2 (*LRRK2*) gene at 12cen, and the *UCHL1* gene may also cause autosomal dominant parkinsonism. Mutations in the *parkin* gene (6q25.2–q27) cause early-onset, autosomal recessive, familial parkinsonism, or sporadic juvenile-onset parkinsonism. Several other genes or chromosomal regions have been associated with familial forms of the disease. Environmental or endogenous toxins may also be important in the etiology of the disease. Epidemiologic studies reveal that cigarette smoking, coffee, anti-inflammatory drug use, and high serum uric acid levels are protective, whereas the incidence of the disease is increased in those working in teaching, health care, or farming, and in those with lead or manganese exposure or with vitamin D deficiency.

The finding of Lewy bodies (intracellular inclusion bodies containing α-synuclein) in fetal dopaminergic cells transplanted into the brain of parkinsonian patients some years previously has provided some support for suggestions that Parkinson's disease may represent a prion disease.

Staining for α-synuclein has revealed that pathology is more widespread than previously recognized, developing initially in the olfactory nucleus and lower brainstem (stage 1 of Braak), then the higher brainstem (stage 2), the substantia nigra (stage 3), the mesocortex and thalamus (stage 4), and finally the entire neocortex (stage 5). The motor features of Parkinson's disease develop at stage 3 on the Braak scale.

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 alleviate many of the motor 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 28–2). Drugs that induce parkinsonian syndromes either are dopamine receptor antagonists (eg, antipsychotic agents; see Chapter 29) or lead to the destruction of the dopaminergic nigrostriatal neurons (eg, 1-methyl-4-phenyl-1-,2,3,6-tetrahydropyridine [MPTP]; see below). Various other neurotransmitters, such as norepinephrine, are also depleted in the brain in parkinsonism, but these deficiencies are of uncertain clinical relevance.

## 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 enter the brain

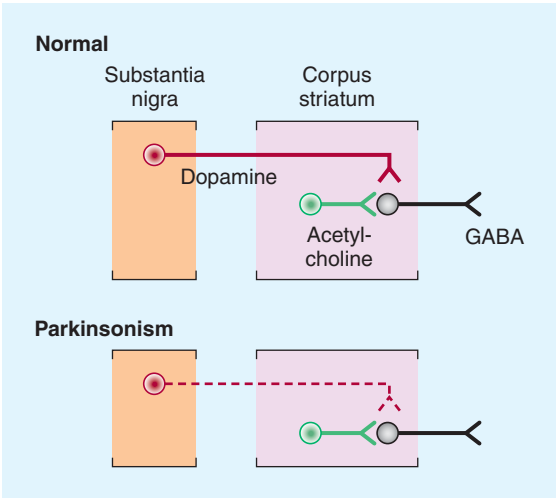



**FIGURE 28–2** Schematic representation of the sequence of neurons involved in parkinsonism. **Top:** Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect. **Bottom:** In parkinsonism, there is a selective loss of dopaminergic neurons (dashed, red).

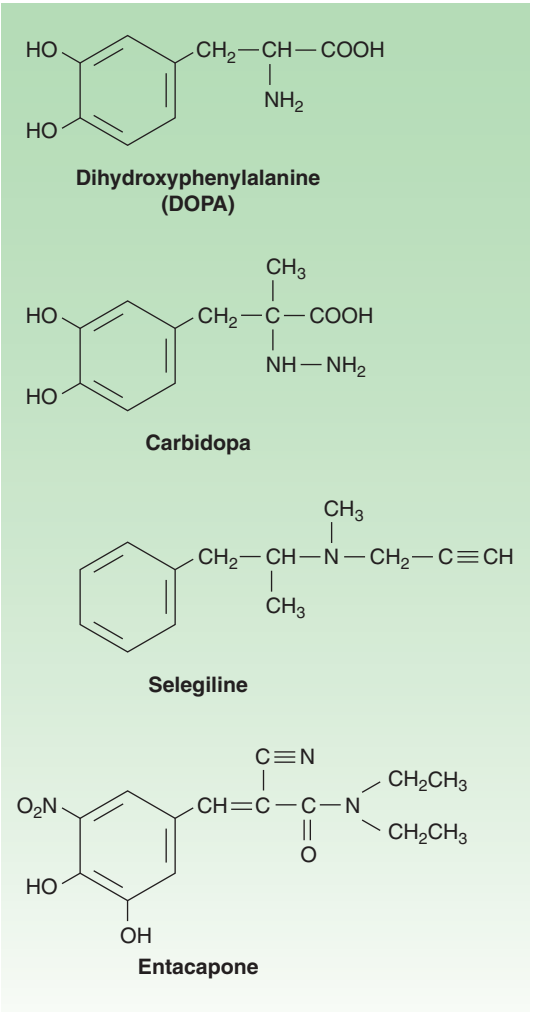



**FIGURE 28–3** Some drugs used in the treatment of parkinsonism.

(via an L-amino acid transporter, LAT), where it is decarboxylated to dopamine (see Figure 6–5). Several noncatecholamine dopamine receptor agonists have also been developed and may lead to clinical benefit, as discussed in the text that follows.

Dopamine receptors are discussed in detail in Chapters 21 and 29. Dopamine receptors of the $D_1$ type are located in the pars compacta of the substantia nigra and presynaptically on striatal axons coming from cortical neurons and from dopaminergic cells in the substantia nigra. The $D_2$ 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 $D_2$ receptors. However, $D_1$- receptor stimulation may also be required for maximal benefit and one of the newer drugs is $D_3$ selective. Dopamine agonist or partial agonist ergot derivatives such as lergotrile and bromocriptine that are powerful stimulators of the $D_2$ receptors have antiparkinsonism properties, whereas certain dopamine blockers that are selective $D_2$ antagonists can induce parkinsonism.

## Chemistry

Dopa is the amino acid precursor of dopamine and norepinephrine (discussed in Chapter 6). Its structure is shown in Figure 28–3. Levodopa is the levorotatory stereoisomer of dopa.

## 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. Ingestion of food delays 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 among 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-hydroxyphenyl acetic acid (homovanillic acid, HVA) and dihydroxyphenylacetic acid (DOPAC). Unfortunately, only about 1–3% of administered levodopa actually enters the brain unaltered; the remainder is metabolized extracerebrally, predominantly by decarboxylation to dopamine, which does not penetrate the blood-brain barrier. Accordingly, levodopa must be given in large amounts when used alone. However, when 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 28–4). Indeed, concomitant administration of a peripheral dopa decarboxylase inhibitor such as carbidopa may reduce the daily requirements of levodopa by approximately 75%.

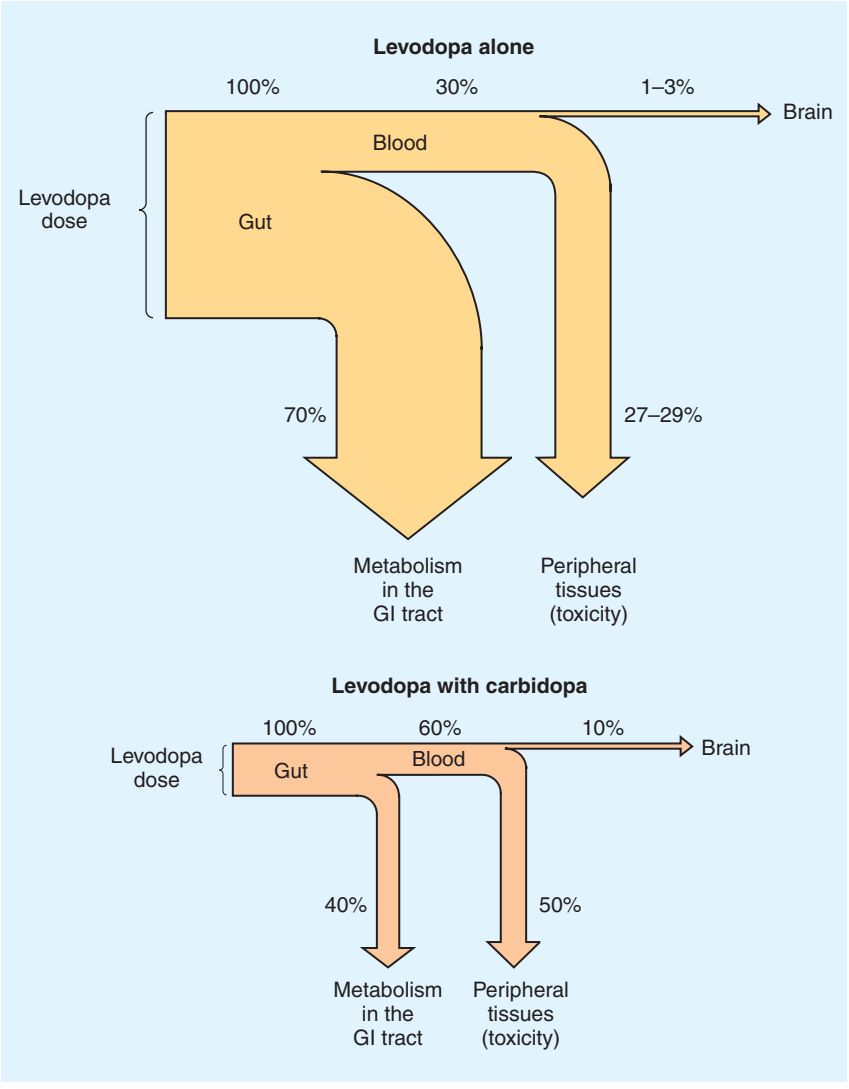



**FIGURE 28–4** Fate of orally administered levodopa and the effect of carbidopa, estimated from animal data. The width of each pathway indicates the absolute amount of the drug at each site, whereas the percentages shown denote the relative proportion of the administered dose. The benefits of coadministration of carbidopa include reduction of the amount of levodopa required for benefit and of the absolute amount 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 over time to avoid adverse effects at doses that were well tolerated initially. Some patients become less responsive to levodopa, perhaps because of loss of dopaminergic nigrostriatal nerve terminals or some pathologic process directly involving striatal dopamine receptors. For such reasons, the benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy, regardless 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 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 28–3), a peripheral dopa decarboxylase inhibitor, which reduces peripheral conversion to dopamine. Combination treatment is started with a small dose, eg, carbidopa 25 mg, levodopa 100 mg three times daily, and gradually increased. It should be taken 30–60 minutes before meals. Most patients ultimately require 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, carbidopa-levodopa 25/100 three times daily) when possible, and to use a dopamine agonist instead, to reduce the risk of development of response

fluctuations. A controlled-release formulation of carbidopa-levodopa is available and may be helpful in patients with established response fluctuations or as a means of reducing dosing frequency. A formulation of carbidopa-levodopa (10/100, 25/100, 25/250) that disintegrates in the mouth and is swallowed with the saliva (**Parcopa**) is now available commercially and is best taken about 1 hour before meals. The combination (**Stalevo**) of levodopa, carbidopa, and a catechol-*O*-methyltransferase (COMT) inhibitor (entacapone) is discussed in a later section. Finally, therapy by *intraduodenal infusion* of levodopa-carbidopa appears to be safe and is superior to a number of oral combination therapies in patients with response fluctuations. This approach has been used to a greater extent in Europe than the USA, but interest is growing.

Levodopa can ameliorate all 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, especially if they do not have classic Parkinson's disease.

## Adverse Effects

### A. 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 the chemoreceptor trigger zone located in the brainstem but outside the blood-brain barrier. Fortunately, tolerance to this emetic effect develops in many patients. 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, adverse gastrointestinal effects are much less frequent and troublesome, occurring in less than 20% of cases, so that patients can tolerate proportionately higher doses.

### B. 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.

Postural hypotension is common, but 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.

### C. 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 that have low affinity for dopamine $D_2$ receptors (clozapine, olanzapine, quetiapine, and risperidone; see Chapter 29) are now available and may be particularly helpful in counteracting such behavioral complications.

### D. Dyskinesias and Response Fluctuations

Dyskinesias occur in up to 80% of patients receiving levodopa therapy for more than 10 years. The character of dopa dyskinesias varies between patients but tends to remain constant in individual patients. 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.

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 (**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. For patients with severe off-periods who are unresponsive to other measures, subcutaneously injected apomorphine may provide temporary benefit. The phenomenon is most likely to occur in patients who responded well to treatment initially. The exact mechanism is unknown. The dyskinesias may relate to an unequal distribution of striatal dopamine. Dopaminergic denervation plus chronic pulsatile stimulation of dopamine receptors with levodopa has been associated with development of dyskinesias. A lower incidence of dyskinesias occurs when levodopa is administered continuously (eg, intraduodenally or intrajejunally), and with drug delivery systems that enable a more continuous delivery of dopaminergic medication.

### E. 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 (discontinuance of the drug for 3–21 days) may temporarily improve responsiveness to levodopa and alleviate some of its adverse effects but is usually of little help in the management of the on-off phenomenon. 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 not recommended.

## Drug Interactions

Pharmacologic doses of pyridoxine (vitamin $B_6$) 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 because 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; 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, it should be used with particular care in patients with a history of melanoma or with suspicious undiagnosed skin lesions; such patients should be monitored by a dermatologist regularly.

# DOPAMINE RECEPTOR AGONISTS

Drugs acting directly on dopamine receptors may have a beneficial effect in addition to that of levodopa (Figure 28–5). 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. A number of dopamine agonists have antiparkinsonism activity. The older dopamine agonists (bromocriptine and pergolide) are ergot (ergoline) derivatives (see Chapter 16), and are rarely—if ever—used to treat parkinsonism. Their side effects are of more concern than those of the newer agents (pramipexole and ropinirole).

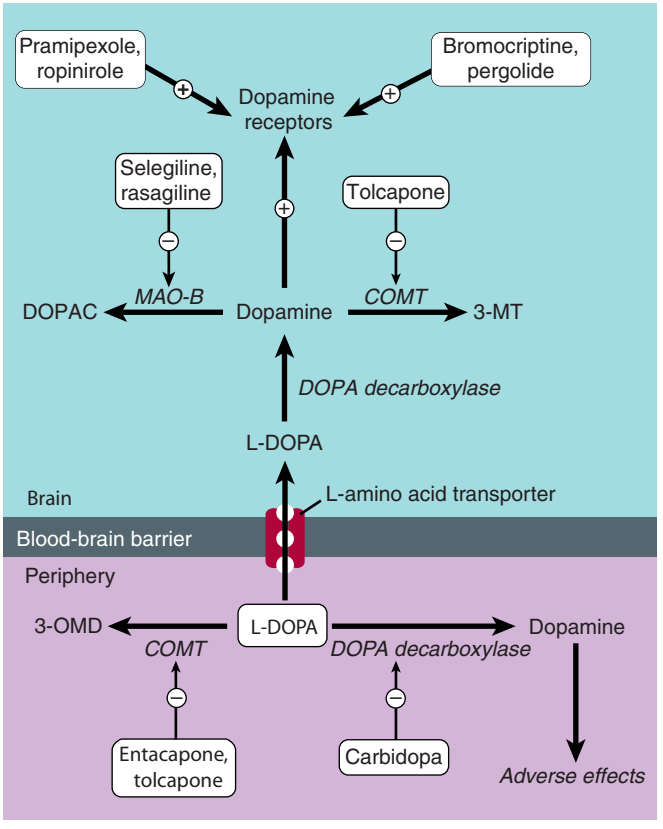



**FIGURE 28–5** Pharmacologic strategies for dopaminergic therapy of Parkinson's disease. Drugs and their effects are indicated (see text). MAO, monoamine oxidase; COMT, catechol-*O*-methyltransferase; DOPAC, dihydroxyphenylacetic acid; L-DOPA, levodopa; 3-OMD, 3-*O*-methyldopa; 3-MT, 3-methoxytyramine.

There is no evidence that one agonist is superior to another; individual patients, however, may respond to one but not another of these agents. Apomorphine is a potent dopamine agonist but is discussed separately in a later section in this chapter because it is used primarily as a rescue drug for patients with disabling response fluctuations to levodopa.

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 that occur 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 patients with parkinsonism who are taking levodopa and who have end-of-dose akinesia or on-off phenomenon or 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

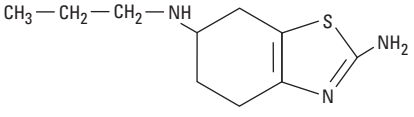
Bromocriptine is a $D_2$ agonist; its structure is shown in Table 16–6. This drug has been widely used to treat Parkinson's disease in the past but is now rarely used for this purpose, having been superseded by the newer dopamine agonists. The usual daily dose of bromocriptine for parkinsonism varies between 7.5 and 30 mg. To minimize adverse effects, the dose is built up slowly over 2 or 3 months depending on response or the development of adverse reactions.

## Pergolide

Pergolide, another ergot derivative, directly stimulates both $D_1$ and $D_2$ receptors. It too has been widely used for parkinsonism but is no longer available in the United States because its use has been associated with the development of valvular heart disease.

## Pramipexole

Pramipexole is not an ergot derivative, but it has preferential affinity for the $D_3$ family of receptors. It is effective as monotherapy for mild parkinsonism and is also helpful in patients with advanced disease, permitting the dose of levodopa to be reduced and smoothing out response fluctuations. Pramipexole 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.

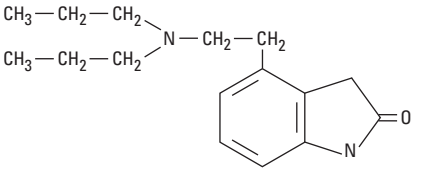



**Pramipexole**

Pramipexole is rapidly absorbed after oral administration, reaching peak plasma concentrations in approximately 2 hours, and is excreted largely unchanged in the urine. It is started at a dosage of 0.125 mg three times daily, 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. An extended-release preparation is now available and is taken once daily at a dose equivalent to the total daily dose of standard pramipexole. The extended-release preparation is generally more convenient for patients and avoids swings in blood levels of the drug over the day.

## Ropinirole

Another nonergoline derivative, ropinirole (now available in a generic preparation) is a relatively pure $D_2$ 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 at 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 dosage between 2 and 8 mg three times daily is necessary. Ropinirole is metabolized by CYP1A2; other drugs metabolized by this isoform may significantly reduce its clearance. A prolonged-release preparation taken once daily is now available.




**Ropinirole**

## Rotigotine

The dopamine agonist rotigotine, delivered daily through a skin patch, was approved in 2007 by the Food and Drug Administration (FDA) for treatment of early Parkinson's disease. It supposedly provides more continuous dopaminergic stimulation than oral medication in early disease; its efficacy in more advanced disease is less clear. Benefits and side effects are similar to those of other dopamine agonists but reactions may also occur at the application site and are sometimes serious. The product was recalled in the United States in 2008 because of crystal formation on the patches, affecting the availability and efficacy of the agonist. It is still available in Europe.

## Adverse Effects of Dopamine Agonists

### A. 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.

### B. 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. Cardiac valvulopathy may occur with pergolide.

### C. Dyskinesias

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

### D. Mental Disturbances

Confusion, hallucinations, delusions, and other psychiatric reactions are potential complications of dopaminergic treatment and are more common and severe with dopamine receptor agonists

than with levodopa. Disorders of impulse control may lead to compulsive gambling, shopping, betting, sexual activity, and other behaviors (see Chapter 32). They clear on withdrawal of the offending medication.

### E. Miscellaneous

Headache, nasal congestion, increased arousal, pulmonary infiltrates, pleural and retroperitoneal fibrosis, and erythromelalgia are other reported adverse effects of the ergot-derived dopamine agonists. Cardiac valvulopathies have occurred with pergolide. 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; this requires discontinuation of the 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 in the nervous system. Monoamine oxidase A metabolizes norepinephrine, serotonin, and dopamine; monoamine oxidase B metabolizes dopamine selectively. **Selegiline** (deprenyl) (Figure 28–3), a selective irreversible inhibitor of monoamine oxidase B at normal doses (at higher doses it inhibits monoamine oxidase A as well), retards the breakdown of dopamine (Figure 28–5); 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 of selegiline is 5 mg with breakfast and 5 mg with lunch. Selegiline may cause insomnia when taken later during the day.

Selegiline has only a minor therapeutic effect on parkinsonism when given alone. Studies in animals suggest that it may reduce disease progression, but trials to test the effect of selegiline on the progression of parkinsonism in humans have yielded ambiguous results. The findings in a large multicenter study were 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 being used for early symptomatic treatment. The standard dosage is 1 mg/d. Rasagiline is also used as adjunctive therapy at a dosage of 0.5 or 1 mg/d to prolong the effects of levodopa-carbidopa in patients with advanced disease. A large double-blind, placebo-controlled, delayed-start study (the ADAGIO trial) to evaluate whether it had neuroprotective benefit (ie, slowed the disease course) yielded unclear results: a daily dose of 1 mg met all the end points of the study and did seem to slow disease progression, but a 2-mg dose failed to do so. These findings are difficult to explain and the decision to use rasagiline for neuroprotective purposes therefore remains an individual one.

Neither selegiline nor rasagiline should be taken by patients receiving meperidine, tramadol, methadone, propoxyphene, cyclobenzaprine, or St. John's wort. The antitussive dextromethorphan should also be avoided by patients taking one of the monoamine oxidase B inhibitors; indeed, it is wise to advise patients to avoid all over-the-counter cold preparations. Rasagiline or selegiline should be used with care in patients receiving tricyclic antidepressants or serotonin reuptake inhibitors because of the theoretical risk of acute toxic interactions of the serotonin syndrome type (see Chapter 16), but this is rarely encountered in practice. The adverse effects of levodopa may be increased by these drugs.

The combined administration of levodopa and an inhibitor of both forms of monoamine oxidase (ie, a nonselective inhibitor) must be avoided, because 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 (3-OMD). Elevated levels of 3-OMD have been associated with a poor therapeutic response to levodopa, perhaps in part because 3-OMD 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 (Figure 28–5). 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 before 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 dosage 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 adverse 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 associated rarely 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.

A commercial preparation named Stalevo consists of a combination of levodopa with both carbidopa and entacapone. It is available in three strengths: Stalevo 50 (50 mg levodopa plus 12.5 mg carbidopa and 200 mg entacapone), Stalevo 100 (100 mg, 25 mg, and 200 mg, respectively), and Stalevo 150 (150 mg, 37.5 mg, and 200 mg). Use of this preparation simplifies the drug regimen and requires the consumption of a lesser number of tablets than otherwise. Stalevo is priced at or below the price of its individual components. The combination agent may provide greater symptomatic benefit than levodopa-carbidopa alone. However, despite the convenience of a single combination preparation, use of Stalevo rather than levodopa-carbidopa has been associated with earlier occurrence and increased frequency of dyskinesia. An investigation as to whether the use of Stalevo is associated with an increased risk for cardiovascular events (myocardial infarction, stroke, cardiovascular death) is ongoing.

## APOMORPHINE

Subcutaneous injection of apomorphine hydrochloride (**Apokyn**), a potent dopamine agonist, is effective for the temporary relief ("rescue") of off-periods of akinesia in patients on optimized dopaminergic therapy. It is rapidly taken up in the blood and then the brain, leading to clinical benefit that begins within about 10 minutes of injection and persists for up to 2 hours. The optimal dose is identified by administering increasing test doses until adequate benefit is achieved or a maximum of 10 mg is reached. Most patients require a dose of 3–6 mg, and this should be given no more than about three times daily.

Nausea is often troublesome, especially at the initiation of apomorphine treatment; accordingly, pretreatment with the antiemetic trimethobenzamide (300 mg three times daily) for 3 days is recommended before apomorphine is introduced and is then continued for at least 1 month, if not indefinitely. Other adverse effects include dyskinesias, drowsiness, chest pain, sweating, hypotension, and bruising at the injection site. Apomorphine should be prescribed only by physicians familiar with its potential complications and interactions.

## 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. It has been reported to antagonize the effects of adenosine at adenosine $A_{2A}$ receptors, which are receptors that may inhibit $D_2$ receptor function. Release of catecholamines from peripheral stores has also 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 efficacious 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 dosage is 100 mg orally two or three times daily. Amantadine may also help in reducing iatrogenic dyskinesias in patients with advanced disease.

### 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 1 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 to amantadine include headache, heart failure, postural hypotension, urinary retention, and gastrointestinal disturbances (eg, anorexia, nausea, constipation, and dry mouth).

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. Some of these drugs were discussed in Chapter 8. These agents may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia. Some of the more commonly used drugs are listed in Table 28–1.

**TABLE 28–1 Some drugs with antimuscarinic properties used in parkinsonism.**

| Drug | Usual Daily Dose (mg) |
|---|---|
| Benztropine mesylate | 1–6 |
| Biperiden | 2–12 |
| Orphenadrine | 150–400 |
| Procyclidine | 7.5–30 |
| Trihexyphenidyl | 6–20 |

### Clinical Use

Treatment is started with a low dose of one of the drugs in this category, the dosage gradually being increased until benefit occurs or until adverse effects limit further increments. If patients do not respond to one drug, a trial with another member of the drug class is warranted and may be successful.

### Adverse Effects

Antimuscarinic drugs have a number of undesirable central nervous system and peripheral effects (see Chapter 8) and are poorly tolerated by the elderly. 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 to prevent acute exacerbation of parkinsonism. For contraindications to the use of antimuscarinic drugs, see Chapter 8.

## SURGICAL PROCEDURES

In patients with advanced disease that is poorly responsive to pharmacotherapy, worthwhile benefit may follow thalamotomy (for conspicuous tremor) or posteroventral pallidotomy. Ablative surgical procedures, however, have generally been replaced by functional, reversible lesions induced by high-frequency deep brain stimulation, which has a lower morbidity.

Stimulation of the subthalamic nucleus or globus pallidus by an implanted electrode and stimulator has yielded good results for the management of the clinical fluctuations occurring in advanced parkinsonism. The anatomic substrate for such therapy is indicated in Figure 28–1. Such procedures are contraindicated in patients with secondary or atypical parkinsonism, dementia, or failure to respond to dopaminergic medication.

In a controlled trial of the transplantation of dopaminergic tissue (fetal substantia nigra tissue), symptomatic benefit occurred in younger (less than 60 years old) but not older parkinsonian patients. In another trial, benefits were inconsequential. Furthermore, uncontrollable dyskinesias occurred in some patients in both studies, perhaps from a relative excess of dopamine from continued fiber outgrowth from the transplant. Additional basic studies are required before further trials of cellular therapies—in particular, stem cell therapies—are undertaken, and such approaches therefore remain investigational.

## NEUROPROTECTIVE THERAPY

Among the compounds under investigation as potential neuroprotective agents that may slow disease progression are antioxidants, antiapoptotic agents, glutamate antagonists, intraparenchymally administered glial-derived neurotrophic factor, coenzyme Q10, creatine, 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. The possibility that rasagiline has a protective effect was discussed earlier.

## GENE THERAPY

Three phase 1 (safety) trials of gene therapy for Parkinson's disease have now been completed in the USA. All trials involved infusion into the striatum of adeno-associated virus type 2 as the vector for the gene. The genes were for glutamic acid decarboxylase (GAD, to facilitate synthesis of GABA, an inhibitory neurotransmitter), infused into the subthalamic nucleus to cause inhibition; for aromatic acid decarboxylase (AADC), infused into the putamen to increase metabolism of levodopa to dopamine; and for neurturin (a growth factor that may enhance the survival of dopaminergic neurons), infused into the putamen. All agents were deemed safe and the data suggested efficacy. A phase 2 study of the GAD gene has been completed and the results are encouraging. A similar study of AADC is planned but has not yet started. A phase 2 study of neurturin failed to show significant benefit, but a new phase 2 study has been initiated in which neurturin is infused into the substantia nigra as well as the putamen.

## THERAPY FOR NONMOTOR MANIFESTATIONS

Persons with cognitive decline may respond to rivastigmine (1.5–6 mg twice daily), memantine (5–10 mg daily), or donepezil (5–10 mg daily) (see Chapter 60); affective disorders to antidepressants or anxiolytic agents (see Chapter 30); excessive daytime sleepiness to modafinil (100–400 mg in the morning) (see Chapter 9); and bladder and bowel disorders to appropriate symptomatic therapy (see Chapter 8).

## GENERAL COMMENTS ON DRUG MANAGEMENT OF PATIENTS WITH PARKINSONISM

Parkinson's disease generally follows a progressive course. Moreover, the benefits of levodopa therapy often diminish with time, and serious adverse effects may complicate long-term levodopa treatment. Nevertheless, 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. Therefore, several strategies have evolved for optimizing dopaminergic therapy, as summarized in Figure 28–5. 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 symptomatic treatment becomes necessary, a trial of rasagiline, amantadine, or an antimuscarinic drug (in young patients) 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 carbidopa-levodopa therapy. Alternatively, especially in older patients, a dopamine agonist can be omitted and the patient started immediately on carbidopa-levodopa. Physical therapy is helpful in improving mobility. In patients with severe parkinsonism and long-term complications of levodopa therapy such as the on-off phenomenon, a trial of treatment with a COMT inhibitor or rasagiline may be helpful. Regulation of dietary protein intake may also improve response fluctuations. Deep brain stimulation is often helpful in patients who fail to respond adequately to these measures. Treating patients who are young or have mild parkinsonism with rasagiline may delay disease progression and merits consideration.

## DRUG-INDUCED PARKINSONISM

Reserpine and the related drug tetrabenazine deplete biogenic monoamines from their storage sites, whereas haloperidol, metoclopramide, and the phenothiazines block dopamine receptors. These drugs may therefore produce a parkinsonian syndrome, usually within 3 months after introduction. The disorder tends to be symmetric, with inconspicuous tremor, but this is not always the case. The syndrome is related to high dosage and clears over several 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 Box: MPTP & Parkinsonism.

## 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; this suggests that such tremor is mediated mainly by the $\beta_2$ receptors.

Essential tremor is a postural tremor, sometimes familial with autosomal dominant inheritance, which is clinically similar to physiologic tremor. At least three gene loci (*ETM1* on 3q13, *ETM2* on 2p24.1, and a locus on 6p23) have been described. 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

### 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 or rasagiline may retard the progression of Parkinson's disease in humans.

peripheral action is unclear. The pharmacokinetics, pharmacologic effects, and adverse reactions of propranolol are discussed in Chapter 10. Daily doses of propranolol on the order of 120 mg (range, 60–240 mg) are usually required, prescribed as 40–120 mg orally twice daily, 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), 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. **Alprazolam** (in doses up to 3 mg daily) or **gabapentin** (100–2400 mg/d) is helpful in some patients. Others are helped by intramuscular injections of botulinum toxin. Thalamic stimulation by an implanted electrode and stimulator is often worthwhile in advanced cases refractory to pharmacotherapy. Diazepam, chlordiazepoxide, mephenesin, and antiparkinsonism agents have been advocated in the past but are generally worthless. Anecdotal reports of benefit from mirtazapine were not confirmed in a double-blind study, which found no effect on the tremor in most patients. Small quantities of alcohol may suppress essential tremor for a short time but should not be recommended as a treatment strategy because of possible behavioral and other complications of alcohol.

**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

Huntington's disease is an autosomal dominant inherited disorder caused by an abnormality (expansion of a CAG trinucleotide repeat that codes for a polyglutamine tract) of the *huntingtin* gene on chromosome 4. An autosomal recessive form may also occur. Huntington disease–like (HDL) disorders are not associated with an abnormal CAG trinucleotide repeat number of the *huntingtin* gene. Autosomal dominant (*HDL1*, 20pter-p12; *HDL2*, 16q24.3) and recessive forms (*HDL3*, 4p15.3) occur.

Huntington's disease 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 28–6). 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

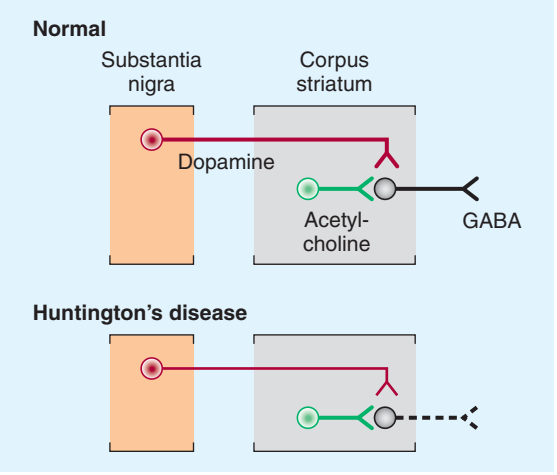



**FIGURE 28–6** Schematic representation of the sequence of neurons involved in Huntington's chorea. **Top:** Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect. **Bottom:** In Huntington's chorea, some cholinergic neurons may be lost, but even more GABAergic neurons (black) degenerate.

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, but with disappointing results. 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 the latter drugs, however, reduction of abnormal movements may be associated with iatrogenic parkinsonism.

**Reserpine** depletes cerebral dopamine by preventing intraneuronal storage (see Chapter 6); 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** (12.5–50 mg orally three times daily) resembles reserpine in depleting cerebral dopamine and has less troublesome adverse effects. 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 useful; 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. Selective serotonin reuptake inhibitors may reduce depression, aggression, and agitation.

## Other Forms of Chorea

Benign hereditary chorea is inherited (usually autosomal dominant; possibly also autosomal recessive) or arises spontaneously. Chorea develops in early childhood and does not progress during adult life; dementia does not occur. In patients with *TITF-1* gene mutations, thyroid and pulmonary abnormalities may also be present (brain-thyroid-lung syndrome). Familial chorea may also occur as part of the chorea-acanthocytosis syndrome, together with orolingual tics, vocalizations, cognitive changes, seizures, peripheral neuropathy, and muscle atrophy; serum β-lipoproteins are normal. Mutations of the gene encoding chorein at 9q21 may be causal. Treatment of these hereditary disorders is symptomatic.

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. A subset of patients respond well to levodopa medication (dopa-responsive dystonia), which is therefore worthy of trial. Occasional patients with dystonia may respond to diazepam, amantadine, antimuscarinic drugs (in high dosage), carbamazepine, baclofen, haloperidol, or phenothiazines. A trial of these pharmacologic approaches is worthwhile, though often not successful. Patients with focal dystonias such as blepharospasm or torticollis often benefit from injection of botulinum toxin into the overactive muscles. Deep brain stimulation may be helpful in medically intractable cases.

## Tics

The pathophysiologic basis of tics is unknown. Chronic multiple tics (**Gilles de la Tourette's syndrome**) may require symptomatic treatment if the disorder is severe or is having a significant impact on the patient's life. Education of patients, family, and teachers is important.

A common pharmacologic approach is with **haloperidol**. 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 gradually (eg, by 0.25 mg every 4 or 5 days) over the following weeks depending on response and tolerance. Most patients ultimately require a total daily dose of 3–8 mg. Adverse effects include extrapyramidal movement disorders, sedation, dryness of the mouth, blurred vision, and gastrointestinal disturbances. **Pimozide**, another dopamine receptor antagonist, may be helpful in patients as a first-line treatment or in those who are either unresponsive to or intolerant of haloperidol. Treatment is started at 1 mg/d, and the dosage is increased by 1 mg every 5 days; most patients require 7–16 mg/d. It has similar side effects to haloperidol but may cause irregularities of cardiac rhythm.

Although not approved by the FDA for the treatment of tics or Tourette's syndrome, certain α-adrenergic agonists may be preferred as an initial treatment because they are less likely to cause extrapyramidal side effects than neuroleptics agents. **Clonidine** reduces motor or vocal tics in about 50% of children so treated. It may act by reducing activity in noradrenergic neurons in the locus caeruleus. It is introduced at a dose of 2–3 mcg/kg/d, increasing after 2 weeks to 4 mcg/kg/d and then, if required, to 5 mcg/kg/d. It may cause an initial transient fall in blood pressure. The most common adverse effect is sedation; other adverse effects include reduced or excessive salivation and diarrhea. **Guanfacine,** another α-adrenergic agonist, has also been used.

Phenothiazines such as fluphenazine sometimes help the tics, as do dopamine agonists. Atypical antipsychotics, such as risperidone and aripiprazole, have a more favorable side-effect profile and may be especially worthwhile in patients with significant behavioral problems. Clonazepam and carbamazepine have also been used. The pharmacologic properties of these drugs are discussed elsewhere in this book.

Injection of botulinum toxin A at the site of problematic tics is sometimes helpful. Treatment of any associated attention deficit disorder (eg, with clonidine patch, guanfacine, pemoline, methylphenidate, or dextroamphetamine) or obsessive-compulsive disorder (selective serotonin reuptake inhibitors or clomipramine) may be required. Deep brain stimulation is sometimes worthwhile in otherwise intractable cases but is best regarded as an investigational approach at this time.

## Drug-Induced Dyskinesias

Levodopa or dopamine agonists produce diverse dyskinesias as a dose-related phenomenon in patients with Parkinson's disease; dose reduction reverses them. Chorea may also develop in patients receiving phenytoin, carbamazepine, amphetamines, lithium, and oral contraceptives, and it resolves with discontinuance of the offending medication. Dystonia has resulted from administration

of dopaminergic agents, lithium, serotonin reuptake inhibitors, carbamazepine, and metoclopramide; and postural tremor from theophylline, caffeine, lithium, valproic acid, thyroid hormone, tricyclic antidepressants, and isoproterenol.

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, whereas 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 or metoclopramide drug treatment (see Chapter 29). Its precise pharmacologic basis is unclear. A reduction in dose of the offending medication, a dopamine receptor blocker, commonly worsens the dyskinesia, whereas 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.

**Tardive dystonia** is usually segmental or focal; generalized dystonia is less common and occurs in younger patients. Treatment is the same as for tardive dyskinesia, but anticholinergic drugs may also be helpful; focal dystonias may also respond to local injection of botulinum A toxin. **Tardive akathisia** is treated similarly to drug-induced parkinsonism. **Rabbit syndrome,** another neuroleptic-induced disorder, is manifested by rhythmic vertical movements about the mouth; it may respond to anticholinergic drugs.

Because the tardive syndromes that develop in adults are often irreversible and have no satisfactory treatment, care must be taken to reduce the likelihood of their 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 agent 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, because the combination may increase the likelihood of dyskinesia.

**Neuroleptic malignant syndrome,** a rare complication of treatment with neuroleptics, is characterized by rigidity, fever, changes in mental status, and autonomic dysfunction (see Table 16–4). Symptoms typically develop over 1–3 days (rather than minutes to hours as in malignant hyperthermia) and may occur at any time during treatment. Treatment includes withdrawal of antipsychotic drugs, lithium, and anticholinergics; reduction of body temperature; and rehydration. Dantrolene, dopamine agonists, levodopa, or amantadine may be helpful, but there is a high mortality rate (up to 20%) with neuroleptic malignant syndrome.

## Restless Legs Syndrome

Restless legs syndrome is characterized by an unpleasant creeping discomfort that seems to arise deep within the legs and occasionally the arms. Symptoms occur particularly when patients are relaxed, especially when they are lying down or sitting, and they lead to an urge to move about. Such symptoms may delay the onset of sleep. A sleep disorder associated with periodic movements during sleep may also occur. The cause is unknown, but the disorder is especially common among pregnant women and also among uremic or diabetic patients with neuropathy. In most patients, no obvious predisposing cause is found, but several genetic loci have been associated with it (12q12-q21, 14q13-q31, 9p24-p22, 2q33, and 20p13).

Symptoms may resolve with correction of coexisting iron-deficiency anemia and often respond to dopamine agonists, levodopa, diazepam, clonazepam, gabapentin, or opiates. Dopaminergic therapy is the preferred treatment for restless legs syndrome and should be initiated with long-acting dopamine agonists (eg, **pramipexole** 0.125–0.75 mg or **ropinirole** 0.25–4.0 mg once daily) to avoid the augmentation that may be associated with levodopa-carbidopa (100/25 or 200/50 taken about 1 hour before bedtime). Augmentation refers to the earlier onset or enhancement of symptoms; earlier onset of symptoms at rest; and a briefer response to medication. When augmentation occurs with levodopa, the daily dose should be reduced or a dopamine agonist substituted. If it occurs in patients receiving an agonist, the daily dose should be lowered or divided, or opioids substituted. When opiates are required, those with long half-lives or low addictive potential should be used. Oxycodone is often effective; the dose is individualized. Gabapentin is an alternative to opioids and is taken once or twice daily (in the evening and before sleep); the starting dose is 300 mg daily, building up depending on response and tolerance (to approximately 1800 mg daily). A recent study suggests that pregabalin, a related drug, is also effective at a daily total dosage of 150–300 mg, taken in divided doses.

## Wilson's Disease

A recessively inherited (13q14.3–q21.1) disorder of copper metabolism, Wilson's disease 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. Neurologic signs include tremor, choreiform movements, rigidity, hypokinesia, and dysarthria and dysphagia. Siblings of affected patients should be screened for asymptomatic Wilson's disease.

Treatment involves the removal of excess copper, followed by maintenance of copper balance. Dietary copper should also be kept below 2 mg daily. **Penicillamine** (dimethylcysteine) has been used for many years as the primary agent to remove copper. It is 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. In about 10% of instances, neurologic worsening occurs with penicillamine. Treatment should be monitored by frequent urinalysis and complete blood counts.

**Trientine hydrochloride**, another chelating agent, is preferred by many over penicillamine because of the lesser likelihood of drug reactions or neurologic worsening. It 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. **Tetrathiomolybdate** may be better than trientine for preserving neurologic function in patients with neurologic involvement and is taken both with and between meals. It is not yet commercially available.

Zinc acetate administered orally increases the fecal excretion of copper and can be used in combination with these other agents. 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 that of other anticopper agents, although it may cause gastric irritation when introduced.

Liver transplantation is sometimes necessary. The role of hepatocyte transplantation and gene therapy is currently under investigation.

## SUMMARY Drugs Used for Movement Disorders

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities, Interactions |
|---|---|---|---|---|
| **LEVODOPA AND COMBINATIONS** | | | | |
| • Levodopa | Transported into the central nervous system (CNS) and converted to dopamine (which does not enter the CNS); also converted to dopamine in the periphery | Ameliorates all symptoms of Parkinson's disease and causes significant peripheral dopaminergic effects (see text) | Parkinson's disease: Most efficacious therapy but not always used as the first drug due to development of disabling response fluctuations over time | Oral • ~ 6–8 h effect • *Toxicity:* Gastrointestinal upset, arrhythmias, dyskinesias, on-off and wearing-off phenomena, behavioral disturbances • *Interactions:* Use with carbidopa greatly diminishes required dosage • use with COMT or MAO-B inhibitors prolongs duration of effect |
| • *Levodopa + carbidopa (Sinemet, others): Carbidopa inhibits peripheral metabolism of levodopa to dopamine and reduces required dosage and toxicity; carbidopa does not enter CNS* | | | | |
| • *Levodopa + carbidopa + entacapone (Stalevo): Entacapone is a catechol-O-methyltransferase (COMT) inhibitor (see below)* | | | | |
| **DOPAMINE AGONISTS** | | | | |
| • Pramipexole | Direct agonist at $D_3$ receptors, nonergot | Reduces symptoms of parkinsonism • smooths out fluctuations in levodopa response | Parkinson's disease: Can be used as initial therapy • also effective in on-off phenomenon | Oral • ~ 8 h effect • *Toxicity:* Nausea and vomiting, postural hypotension, dyskinesias, confusion, impulse control disorders, sleepiness |
| • *Ropinirole: Similar to pramipexole; nonergot; relatively pure $D_2$ agonist* | | | | |
| • *Bromocriptine: Ergot derivative; potent agonist at $D_2$ receptors; more toxic than pramipexole or ropinirole; now rarely used for antiparkinsonian effect* | | | | |
| • *Apomorphine: Nonergot; subcutaneous route useful for rescue treatment in levodopa-induced dyskinesia; high incidence of nausea and vomiting* | | | | |
| **MONOAMINE OXIDASE (MAO) INHIBITORS** | | | | |
| • Rasagiline | Inhibits MAO-B selectively; higher doses also inhibit MAO-A | Increases dopamine stores in neurons; may have neuroprotective effects | Parkinson's disease: Adjunctive to levodopa • smooths levodopa response | Oral • *Toxicity & interactions:* May cause serotonin syndrome with meperidine, and theoretically also with selective serotonin reuptake inhibitors, tricyclic antidepressants |
| • *Selegiline: Like rasagiline, adjunctive use with levodopa; may be less potent than rasagiline* | | | | |
| **COMT INHIBITORS** | | | | |
| • Entacapone | Inhibits COMT in periphery • does not enter CNS | Reduces metabolism of levodopa and prolongs its action | Parkinson's disease | Oral • *Toxicity:* Increased levodopa toxicity • nausea, dyskinesias, confusion |
| • *Tolcapone: Like entacapone but enters CNS; some evidence of hepatotoxicity, elevation of liver enzymes* | | | | |

(*continued*)

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities, Interactions |
|---|---|---|---|---|
| **ANTIMUSCARINIC AGENTS** | | | | |
| • Benztropine | Antagonist at M receptors in basal ganglia | Reduces tremor and rigidity • little effect on bradykinesia | Parkinson's disease | Oral • *Toxicity:* Typical antimuscarinic effects— sedation, mydriasis, urinary retention, constipation, confusion, dry mouth |
| • *Biperiden, orphenadrine, procyclidine, trihexyphenidyl: Similar antimuscarinic agents with CNS effects* | | | | |
| **DRUGS USED IN HUNTINGTON'S DISEASE** | | | | |
| • Tetrabenazine, reserpine | Deplete amine transmitters, especially dopamine, from nerve endings | Reduce chorea severity | Huntington's disease • other applications, see Chapter 11 | Oral • *Toxicity:* Hypotension, sedation, depression, diarrhea • tetrabenazine somewhat less toxic |
| • *Haloperidol, other neuroleptics: Sometimes helpful* | | | | |
| **DRUGS USED IN TOURETTE'S SYNDROME** | | | | |
| • Haloperidol, pimozide | Block central $D_2$ receptors | Reduce vocal and motor tic frequency, severity | Tourette's syndrome • other applications, see Chapter 29 | Oral • *Toxicity:* Parkinsonism, other dyskinesias • sedation • blurred vision • dry mouth • gastrointestinal disturbances • pimozide may cause cardiac rhythm disturbances |
| • *Clonidine: Effective in ~ 50% of patients; see Chapter 11 for basic pharmacology* | | | | |
| • *Phenothiazines, benzodiazepines, carbamazepine: Sometimes of value* | | | | |

## PREPARATIONS AVAILABLE

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

**Apomorphine (Apokyn)**
Subcutaneous injection titration kit: 10 mg/mL

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

**Carbidopa/levodopa/entacapone (Stalevo)**
Oral: 12.5 mg carbidopa, 50 mg levodopa, 200 mg entacapone; 18.75 mg carbidopa, 75 mg levodopa, 200 mg entacapone; 25 mg carbidopa, 100 mg levodopa, 200 mg entacapone; 31.25 mg carbidopa, 125 mg levodopa, 200 mg entacapone; 37.5 mg carbidopa, 150 mg levodopa, 200 mg entacapone; 50 mg carbidopa, 200 mg levodopa, 200 mg entacapone

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

**Levodopa (Dopar, others)**
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, other)**[1]
Oral: 0.05, 0.25, 1 mg tablets

**Pramipexole (Mirapex)**
Oral: 0.125, 0.25, 0.75, 1, 1.5 mg tablets; 0.375, 0.75, 1.5, 3.0, 4.5 mg extended-release tablets

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

**Rasagiline (Azilect)**
Oral: 0.5, 1 mg tablets

**Ropinirole (Requip, Requip XL)**
Oral: 0.25, 0.5, 1, 2, 3, 4, 5 mg tablets; 2, 4, 6, 8, 12 mg extended-release tablets

**Selegiline (deprenyl) (generic, Eldepryl)**
Oral: 5 mg tablets, capsules; 6, 9, 12 mg transdermal patch

**Tetrabenazine (Xenazine)**
Oral: 12.5, 25 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

[1] Not available in the USA.

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## CASE STUDY ANSWER

The relation of the tremor to activity (rest tremor) in this case is characteristic of parkinsonism. Examination reveals the classic findings of Parkinson's disease—rest tremor, rigidity, bradykinesia, and a gait disturbance; an asymmetry of the abnormalities is common in Parkinson's disease. The prognosis is that symptoms will become more generalized with time. Pharmacologic treatment would involve a dopamine agonist (pramipexole or ropinirole) but may not need to be started now unless the patient is disturbed by his symptoms. Although the evidence is incomplete, rasagiline may slow disease progression and could also be introduced.

CHAPTER 29

# Antipsychotic Agents & Lithium

Herbert Meltzer, MD, PhD*

## CASE STUDY

A 17-year-old male high school student is referred to the psychiatry clinic for evaluation of suspected schizophrenia. After a diagnosis is made, haloperidol is prescribed at a gradually increasing dose on an outpatient basis. The drug improves the patient's positive symptoms but ultimately causes intolerable side effects. Although more costly, risperidone is then prescribed, which, over the course of several weeks of treatment, improves his symptoms and is tolerated by the patient. What signs and symptoms would support an initial diagnosis of schizophrenia? In the treatment of schizophrenia, what benefits do the atypical antipsychotic drugs offer over the traditional agents such as haloperidol? In addition to the management of schizophrenia, what other clinical indications warrant consideration of the use of drugs nominally classified as antipsychotics?

## ANTIPSYCHOTIC AGENTS

Antipsychotic drugs are able to reduce psychotic symptoms in a wide variety of conditions, including schizophrenia, bipolar disorder, psychotic depression, senile psychoses, various organic psychoses, and drug-induced psychoses. They are also able to improve mood and reduce anxiety and sleep disturbances, but they are not the treatment of choice when these symptoms are the primary disturbance in nonpsychotic patients. A **neuroleptic** is a subtype of antipsychotic drug that produces a high incidence of extrapyramidal side effects (EPS) at clinically effective doses, or catalepsy in laboratory animals. The **"atypical" antipsychotic drugs,** are now the most widely used type of antipsychotic drug.

### History

Reserpine and chlorpromazine were the first drugs found to be useful to reduce psychotic symptoms in schizophrenia. Reserpine was used only briefly for this purpose and is no longer of interest as an antipsychotic agent. Chlorpromazine is a neuroleptic agent; that is, it produces catalepsy in rodents and EPS in humans. The discovery that its antipsychotic action was related to dopamine (D or DA)-receptor blockade led to the identification of other compounds as antipsychotics between the 1950s and 1970s. The discovery of clozapine in 1959 led to the realization that antipsychotic drugs need not cause EPS in humans at clinically effective doses. Clozapine was called an atypical antipsychotic drug because of this dissociation; it produces fewer EPS at equivalent antipsychotic doses in man and laboratory animals. As a result, there has been a major shift in clinical practice away from typical antipsychotic drugs towards the use of an ever increasing number of atypical drugs, which have other advantages as well. The introduction of antipsychotic drugs led to massive changes in disease management, including brief instead of life-long hospitalizations. These drugs have also proved to be of great value in studying the pathophysiology of schizophrenia and other psychoses. It should be noted that schizophrenia and bipolar disorder are no longer believed by many to be separate disorders but rather to be part of a continuum of brain disorders with psychotic features.

*The author acknowledges the contributions of the previous author of this chapter, William Z. Potter, MD, PhD.

## Nature of Psychosis & Schizophrenia

The term "psychosis" denotes a variety of mental disorders: the presence of delusions (false beliefs), various types of hallucinations, usually auditory or visual, but sometimes tactile or olfactory, and grossly disorganized thinking in a clear sensorium. Schizophrenia is a particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance. Psychosis is not unique to schizophrenia and is not present in all patients with schizophrenia at all times.

Schizophrenia is considered to be a neurodevelopmental disorder. This implies that structural and functional changes in the brain are present even in utero in some patients, or that they develop during childhood and adolescence, or both. Twin, adoption, and family studies have established that schizophrenia is a genetic disorder with high heritability. No single gene is involved. Current theories involve multiple genes with common and rare mutations, including large deletions and insertions (copy number variations), combining to produce a very variegated clinical presentation and course.

## THE SEROTONIN HYPOTHESIS OF SCHIZOPHRENIA

The discovery that indole hallucinogens such as LSD (lysergic acid diethylamide) and mescaline are serotonin (5-HT) agonists led to the search for endogenous hallucinogens in the urine, blood, and brains of patients with schizophrenia. This proved fruitless, but the identification of many 5-HT-receptor subtypes led to the pivotal discovery that 5-$HT_{2A}$-receptor and possibly 5-$HT_{2C}$ stimulation was the basis for the hallucinatory effects of these agents.

It has been found that 5-$HT_{2A}$-receptor blockade is a key factor in the mechanism of action of the main class of atypical antipsychotic drugs, of which clozapine is the prototype, and includes, in order of their introduction around the world, melperone, risperidone, zotepine, blonanseine olanzapine, quetiapine, ziprasidone, aripiprazole, sertindole, paliperidone, iloperidone, asenapine, and lurasidone. These drugs are *inverse agonists* of the 5-$HT_{2A}$ receptor; that is, they block the constitutive activity of these receptors. These receptors modulate the release of dopamine, norepinephrine, glutamate, GABA and acetylcholine, among other neurotransmiters in the cortex, limbic region, and striatum. Stimulation of 5-$HT_{2A}$ receptors leads to depolarization of glutamate neurons, but also stabilization of *N*-methyl-D-aspartate (NMDA) receptors on postsynaptic neurons. Recently, it has been found that hallucinogens can modulate the stability of a complex consisting of 5-$HT_{2A}$ and NMDA receptors.

5-$HT_{2C}$-receptor stimulation provides a further means of modulating cortical and limbic dopaminergic activity. Stimulation of 5-$HT_{2C}$ receptors leads to inhibition of cortical and limbic dopamine release. Many atypical antipsychotic drugs, eg, clozapine, asenapine, olanzapine are 5-$HT_{2C}$ inverse agonists. 5-$HT_{2C}$ agonists are currently being studied as antipsychotic agents.

## THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

The dopamine hypothesis for schizophrenia was the second neurotransmitter-based concept to be developed but is no longer considered adequate to explain all aspects of schizophrenia, especially the cognitive impairment. Nevertheless, it is still highly relevant to understanding the major dimensions of schizophrenia, such as positive and negative symptoms (emotional blunting, social withdrawal, lack of motivation), cognitive impairment, and possibly depression. It is also essential to understanding the mechanisms of action of most and probably all antipsychotic drugs.

Several lines of evidence suggest that excessive limbic dopaminergic activity plays a role in psychosis. (1) Many antipsychotic drugs strongly block postsynaptic $D_2$ receptors in the central nervous system, especially in the mesolimbic and striatal-frontal system; this includes partial dopamine agonists, such as aripiprazole and bifeprunox. (2) Drugs that increase dopaminergic activity, such as levodopa, amphetamines, and bromocriptine and apomorphine, either aggravate schizophrenia psychosis 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) Some but not all postmortem studies of schizophrenic subjects have reported increased dopamine levels and $D_2$-receptor density in the nucleus accumbens, caudate, and putamen. (5) Imaging studies have shown increased amphetamine-induced striatal dopamine release, increased baseline occupancy of striatal $D_2$ receptors by extracellular dopamine, and other measures consistent with increased striatal dopamine synthesis and release.

However, the dopamine hypothesis is far from a complete explanation of all aspects of schizophrenia. *Diminished* cortical or hippocampal dopaminergic activity has been suggested to underlie the cognitive impairment and negative symptoms of schizophrenia. Postmortem and in vivo imaging studies of cortical, limbic, nigral, and striatal dopaminergic neurotransmission in schizophrenic subjects have reported findings consistent with diminished dopaminergic activity in these regions. Decreased dopaminergic innervation in medial temporal cortex, dorsolateral prefrontal cortex, and hippocampus, and decreased levels of DOPAC, a metabolite of dopamine, in the anterior cingulate have been reported in postmortem studies. Imaging studies have found increased prefrontal $D_1$-receptor levels that correlated with working memory impairments.

The fact that several of the atypical antipsychotic drugs have much less effect on $D_2$ receptors and yet are effective in schizophrenia has redirected attention to the role of other dopamine receptors and to nondopamine receptors. Serotonin receptors—particularly the 5-$HT_{2A}$-receptor subtype—may mediate synergistic effects or protect against the extrapyramidal consequences of $D_2$ 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, eg, serotonin and

glutamate. The atypical antipsychotic drugs share the property of weak $D_2$-receptor antagonism and more potent 5-$HT_{2A}$-receptor blockade.

## THE GLUTAMATE HYPOTHESIS OF SCHIZOPHRENIA

Glutamate is the major excitatory neurotransmitter in the brain (see Chapter 21). Phencyclidine and ketamine are noncompetitive inhibitors of the NMDA receptor that exacerbate both cognitive impairment and psychosis in patients with schizophrenia. PCP and a related drug, MK-801, increase locomotor activity and, acutely or chronically, a variety of cognitive impairments in rodents and primates. These effects are widely employed as a means to develop novel antipsychotic and cognitive-enhancing drugs. Selective 5-$HT_{2A}$ antagonists, as well as atypical antipsychotic drugs, are much more potent than $D_2$ antagonists in blocking these effects of PCP and MK-801. This was the starting point for the hypothesis that hypofunction of NMDA receptors, located on GABAergic interneurons, leading to diminished inhibitory influences on neuronal function, contributed to schizophrenia. The diminished GABAergic activity can induce disinhibition of downstream glutamatergic activity, which can lead to hyperstimulation of cortical neurons through non-NMDA receptors. Preliminary evidence suggests that LY2140023, a drug that acts as an agonist of the metabotropic 2/3 glutamate receptor (mGLuR2/3), may be effective in schizophrenia.

The NMDA receptor, an ion channel, requires glycine for full activation. It has been suggested that in patients with schizophrenia, the glycine site of the NMDA receptor is not fully saturated. There have been several trials of high doses of glycine to promote glutamatergic activity, but the results are far from convincing. Currently, glycine transport inhibitors are in development as possible antipsychotic agents.

Ampakines are drugs that potentiate currents mediated by AMPA-type glutamate receptors. In behavioral tests, ampakines are effective in correcting behaviors in various animal models of schizophrenia and depression. They protect neurons against neurotoxic insults, in part by mobilizing growth factors such as brain-derived neurotrophic factor (BDNF, see also Chapter 30).

## 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.

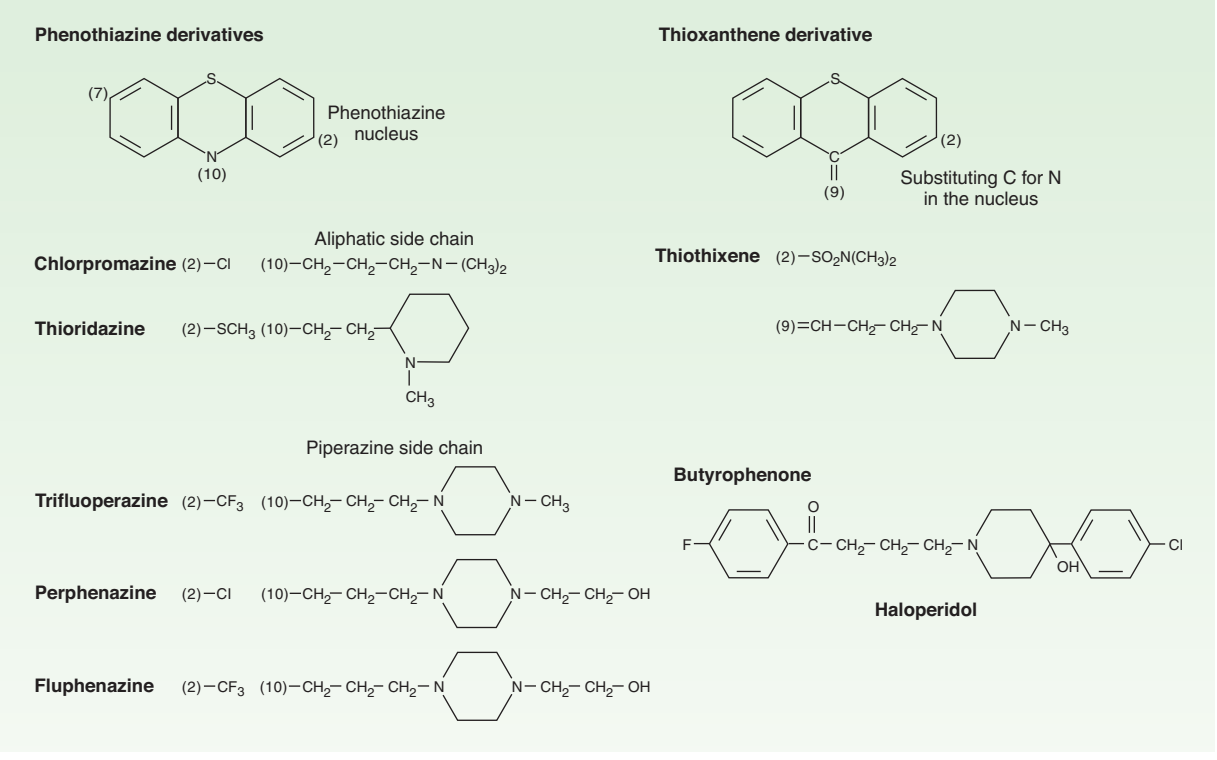


**FIGURE 29–1** Structural formulas of some older antipsychotic drugs: phenothiazines, thioxanthenes, and butyrophenones. Only representative members of each type are shown.

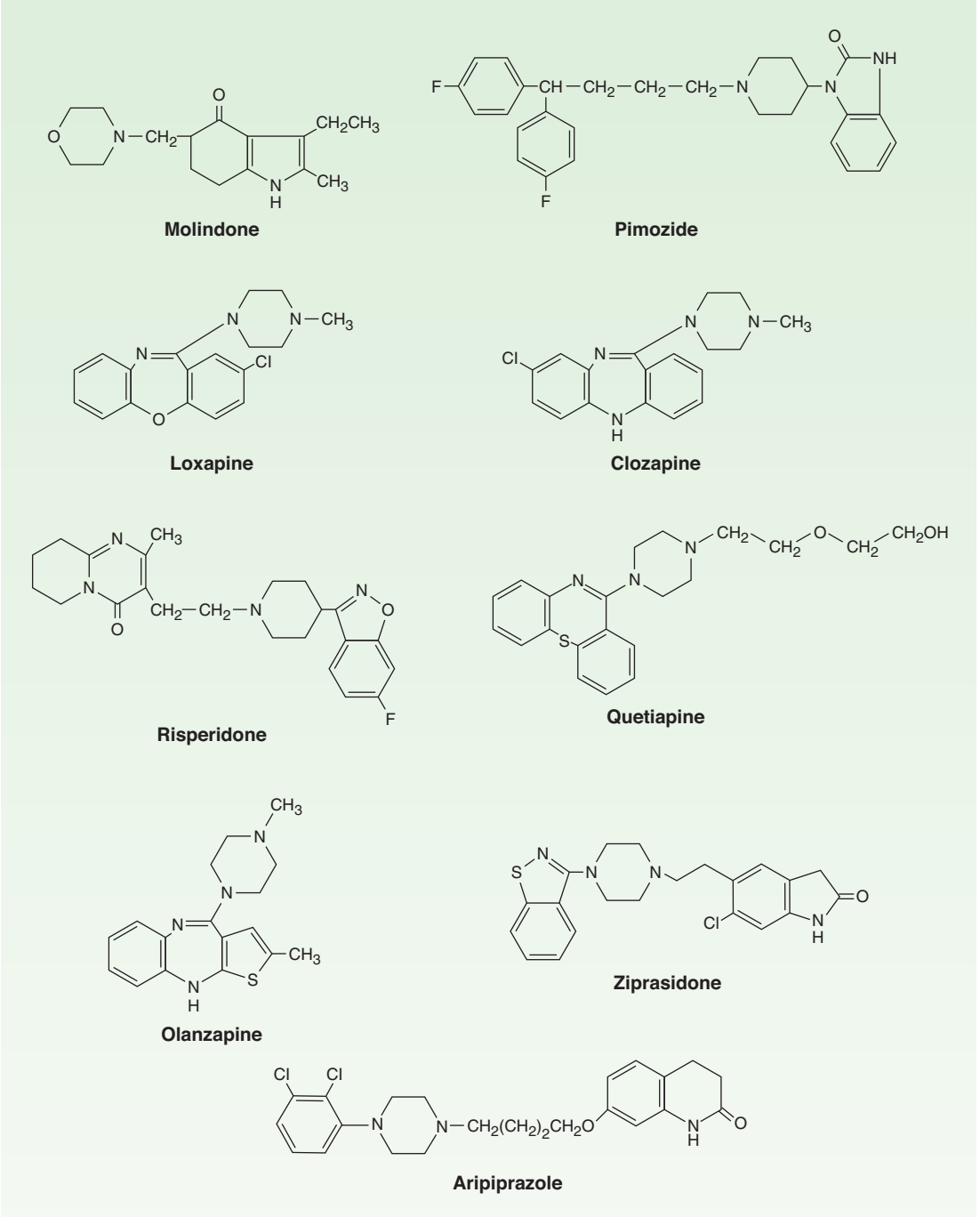


**FIGURE 29–2** Structural formulas of some newer antipsychotic drugs.

### A. Phenothiazine Derivatives

Three subfamilies of phenothiazines, based primarily on the side chain of the molecule, were once the most widely used of the antipsychotic agents. Aliphatic derivatives (eg, **chlorpromazine**) and piperidine derivatives (eg, **thioridazine**) are the least potent. These drugs produce more sedation and weight gain. Piperazine derivatives are more potent (effective in lower doses) but not necessarily more efficacious. Perphenazine, a piperazine derivative, was the typical antipsychotic drug used in the CATIE study described in the following text. The piperazine derivatives are also more selective in their pharmacologic effects (Table 29–1).

Recently, a large study in the USA (CATIE) reported that perphenazine was as effective as atypical antipsychotic drugs, with the modest exception of olanzapine, and concluded that typical antipsychotic drugs are the treatment of choice for schizophrenia based on their lower cost. However, there were numerous flaws in the design, execution and analysis of this study, leading to it having only modest impact on clinical practice. In particular, it failed to consider issues such as dosage of olanzapine, inclusion of treatment

**TABLE 29–1 Antipsychotic drugs: Relation of chemical structure to potency and toxicities.**

| Chemical Class | Drug | $D_2$/5-$HT_{2A}$ Ratio[1] | Clinical Potency | Extrapyramidal Toxicity | Sedative Action | Hypotensive Actions |
|---|---|---|---|---|---|---|
| Phenothiazines | | | | | | |
| Aliphatic | Chlorpromazine | High | Low | Medium | High | High |
| Piperazine | Fluphenazine | High | High | High | Low | Very low |
| Thioxanthene | Thiothixene | Very high | High | Medium | Medium | Medium |
| Butyrophenone | Haloperidol | Medium | High | Very high | Low | Very low |
| Dibenzodiazepine | Clozapine | Very low | Medium | Very low | Low | Medium |
| Benzisoxazole | Risperidone | Very low | High | Low[2] | Low | Low |
| Thienobenzodiazepine | Olanzapine | Low | High | Very low | Medium | Low |
| Dibenzothiazepine | Quetiapine | Low | Low | Very low | Medium | Low to medium |
| Dihydroindolone | Ziprasidone | Low | Medium | Very low | Low | Very low |
| Dihydrocarbostyril | Aripiprazole | Medium | High | Very low | Very low | Low |

[1]Ratio of affinity for $D_2$ receptors to affinity for 5-$HT_{2A}$ receptors.

[2]At dosages below 8 mg/d.

resistant patients, encouragement of patients to switch medications inherent in the design, risk for tardive dyskinesia following long term use of even low dose typical antipsychotics, and the necessity of large sample sizes in equivalency studies.

### B. Thioxanthene Derivatives

This group of drugs is exemplified primarily by thiothixene.

### C. Butyrophenone Derivatives

This group, of which **haloperidol** is the most widely used, has a very different structure from those of the two preceding groups. Haloperidol, a butyrophenone, is the most widely used typical antipsychotic drug, despite its high level of EPS relative to typical antipsychotic drugs. Diphenylbutylpiperidines are closely related compounds. The butyrophenones and congeners tend to be more potent and to have fewer autonomic effects but greater extrapyramidal effects than phenothiazines (Table 29–1).

### D. Miscellaneous Structures

Pimozide and molindone are typical antipsychotic drugs. There is no significant difference in efficacy between these newer typical and the older typical antipsychotic drugs.

### E. Atypical Antipsychotic Drugs

**Clozapine, asenapine, olanzapine, quetiapine, paliperidone, risperidone, sertindole, ziprasidone, zotepine,** and **aripiprazole** are atypical antipsychotic drugs (Figure 29–2). Clozapine is the prototype. Paliperidone is 9-hydroxyrisperidone, the active metabolite of risperidone. Risperidone is rapidly converted to 9-hydroxyrisperidone in vivo in most patients, except for about 10% of patients who are poor metabolizers. Sertindole is approved in some European countries but not in the USA.

These drugs have complex pharmacology but they share a greater ability to alter 5-$HT_{2A}$-receptor activity than to interfere with $D_2$-receptor action. In most cases, they act as partial agonists at the 5-$HT_{1A}$ receptor, which produces synegistic effects with 5-$HT_{2A}$ receptor antagonism. Most are either 5-$HT_6$ or 5-$HT_7$ receptor antagonists.

Sulpride and sulpiride constitute another class of atypical agents. They have equivalent potency for $D_2$ and $D_3$ receptors, but they are also 5-$HT_7$ antagonists. They dissociate EPS and antipsychotic efficacy. However, they also produce marked increases in serum prolactin levels and are not as free of the risk of tardive dyskinesia as are drugs such as clozapine and quetiapine.

## Pharmacokinetics

### A. Absorption and Distribution

Most antipsychotic drugs are readily but incompletely absorbed. Furthermore, many undergo significant first-pass metabolism. Thus, oral doses of chlorpromazine and thioridazine have systemic availability of 25–35%, whereas haloperidol, which has less first-pass metabolism, has an average systemic availability of about 65%.

Most antipsychotic drugs are highly lipid soluble and protein bound (92–99%). They tend to have large volumes of distribution (usually more than 7 L/kg). They generally have a much longer clinical duration of action than would be estimated from their plasma half-lives. This is paralleled by prolonged occupancy of $D_2$ dopamine receptors in the brain by the typical antipsychotic drugs.

Metabolites of chlorpromazine may be excreted in the urine weeks after the last dose of chronically administered drug. Long-acting injectable formulations may cause some blockade of $D_2$ receptors 3–6 months after the last injection. Time to recurrence of psychotic symptoms is highly variable after discontinuation of antipsychotic drugs. The average time for relapse in stable patients with schizophrenia who discontinue their medication is 6 months. Clozapine is an exception in that relapse after discontinuation is usually rapid and severe. Thus, clozapine should never be discontinued abruptly unless clinically needed because of adverse effects

such as myocarditis or agranulocytosis, which are true medical emergencies.

### B. Metabolism

Most antipsychotic drugs are almost completely metabolized by oxidation or demethylation, catalyzed by liver microsomal cytochrome P450 enzymes. CYP2D6, CYP1A2, and CYP3A4 are the major isoforms involved (see Chapter 4). Drug-drug interactions should be considered when combining antipsychotic drugs with various other psychotropic drugs or drugs—such as ketoconazole—that inhibit various cytochrome P450 enzymes. At the typical clinical doses, antipsychotic drugs do not usually interfere with the metabolism of other drugs.

## Pharmacodynamics

The first phenothiazine antipsychotic drugs, with chlorpromazine as the prototype, proved to have a wide variety of central nervous system, autonomic, and endocrine effects. Although efficacy of these drugs is primarily driven by $D_2$-receptor blockade, their adverse actions were traced to blocking effects at a wide range of receptors including α adrenoceptors and muscarinic, $H_1$ histaminic, and 5-$HT_2$ receptors.

### A. Dopaminergic Systems

Five dopaminergic systems or pathways are important for understanding schizophrenia and the mechanism of action of antipsychotic drugs. The first pathway—the one most closely related to behavior and psychosis—is the **mesolimbic-mesocortical** pathway, which projects from cell bodies in the ventral tegmentum in separate bundles of axons to the limbic system and neocortex. The second system—the **nigrostriatal** pathway—consists of neurons that project from the substantia nigra to the dorsal striatum, which includes the caudate and putamen; it is involved in the coordination of voluntary movement. Blockade of the $D_2$ receptors in the nigrostriatal pathway is responsible for EPS. The third pathway—the **tuberoinfundibular** system—arises in the arcuate nuclei and periventricular neurons and releases dopamine into the pituitary portal circulation. Dopamine released by these neurons physiologically inhibits prolactin secretion from the anterior pituitary. The fourth dopaminergic system—the **medullary-periventricular** pathway—consists of neurons in the motor nucleus of the vagus whose projections are not well defined. This system may be involved in eating behavior. The fifth pathway—the **incertohypothalamic** pathway—forms connections from the medial zona incerta to the hypothalamus and the amygdala. It appears to regulate the anticipatory motivational phase of copulatory behavior in rats.

After dopamine was identified as a neurotransmitter in 1959, it was shown that its effects on electrical activity in central synapses and on production of the second messenger cAMP synthesized by adenylyl cyclase could be blocked by antipsychotic drugs such as chlorpromazine, haloperidol, and thiothixene. This evidence led to the conclusion in the early 1960s that these drugs should be considered **dopamine-receptor antagonists** and was a key factor in the development of dopamine hypothesis of schizophrenia described earlier in this chapter. The antipsychotic action is now thought to be produced (at least in part) by their ability to block the effect of dopamine to inhibit the activity of adenylyl cyclase in the mesolimbic system.

### B. Dopamine Receptors and Their Effects

At present, five dopamine receptors have been described, consisting of two separate families, the $D_1$-like and $D_2$-like receptor groups. The $D_1$ receptor is coded by a gene on chromosome 5, increases cAMP by $G_s$-coupled activation of adenylyl cyclase, and is located mainly in the putamen, nucleus accumbens, and olfactory tubercle and cortex. The other member of this family, $D_5$, is coded by a gene on chromosome 4, also increases cAMP, and is found in the hippocampus and hypothalamus. The therapeutic potency of antipsychotic drugs does not correlate with their affinity for binding to the $D_1$ receptor (Figure 29–3, top)

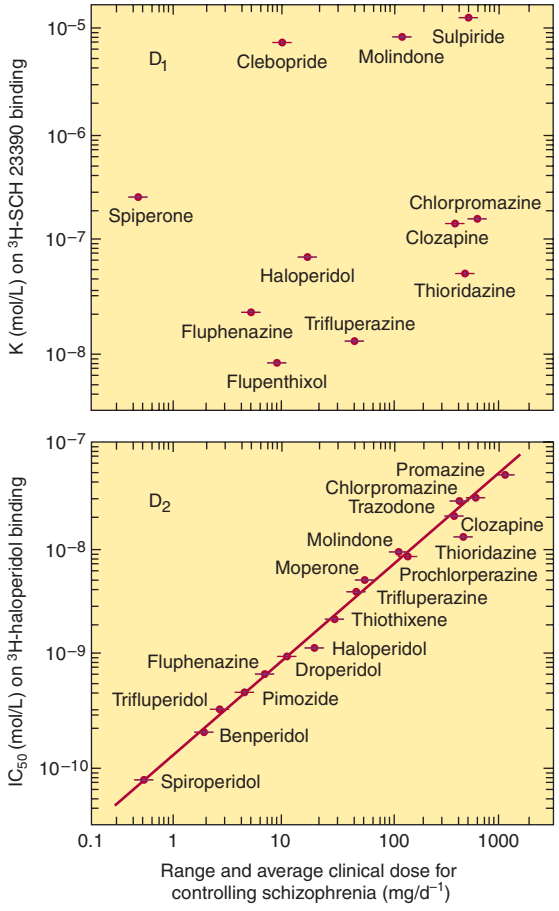


**FIGURE 29–3** Correlations between the therapeutic potency of antipsychotic drugs and their affinity for binding to dopamine $D_1$ (*top*) or $D_2$ receptors (*bottom*). Potency is indicated on the horizontal axes; it decreases to the right. Binding affinity for $D_1$ receptors was measured by displacing the selective $D_1$ ligand SCH 23390; affinity for $D_2$ receptors was similarly measured by displacing the selective $D_2$ ligand haloperidol. Binding affinity decreases upward. (Modified and reproduced, with permission, from Seeman P: Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987;1:133.)

nor did a selective $D_1$ antagonist prove to be an effective antipsychotic in patients with schizophrenia. The $D_2$ receptor is coded on chromosome 11, decreases cAMP (by $G_i$-coupled inhibition of adenylyl cyclase), and inhibits calcium channels but opens potassium channels. It is found both pre- and postsynaptically on neurons in the caudate-putamen, nucleus accumbens, and olfactory tubercle. A second member of this family, the $D_3$ receptor, also coded by a gene on chromosome 11, is thought to also decrease cAMP and is located in the frontal cortex, medulla, and midbrain. $D_4$ receptors also decrease cAMP and are concentrated in the cortex.

The typical antipsychotic agents block $D_2$ receptors stereoselectively for the most part, and their binding affinity is very strongly correlated with clinical antipsychotic and extrapyramidal potency (Figure 29–3, bottom). In vivo imaging studies of $D_2$-receptor occupancy indicate that for antipsychotic efficacy, the typical antipsychotic drugs must be given in sufficient doses to achieve at least 60% occupancy of striatal $D_2$ receptors. This is not required for the atypical antipsychotic drugs such as clozapine and olanzapine, which are effective at lower occupancy levels of 30–50%, most likely because of their concurrent high occupancy of 5-$HT_{2A}$ receptors. The typical antipsychotic drugs produce EPS when the occupancy of striatal $D_2$ receptors reaches 80% or higher.

Positron emission tomography (PET) studies with aripiprazole show very high occupancy of $D_2$ receptors, but this drug does not cause EPS because it is a partial $D_2$-receptor agonist. Aripiprazole also gains therapeutic efficacy through its 5-$HT_{2A}$ antagonism and possibly 5-$HT_{1A}$ partial agonism.

These findings have been incorporated into the dopamine hypothesis of schizophrenia. However, additional factors complicate interpretation of dopamine receptor data. For example, dopamine receptors exist in both high- and low-affinity forms, and it is not known whether schizophrenia or the antipsychotic drugs alter the proportions of receptors in these two forms.

Ît has not been convincingly demonstrated that antagonism of any dopamine receptor other than the $D_2$ receptor plays a role in the action of antipsychotic drugs. Selective and relatively specific $D_1$, $D_3$-, and $D_4$-receptor antagonists have been tested repeatedly with no evidence of antipsychotic action. Most of the newer atypical antipsychotic agents and some of the traditional ones have a higher affinity for the 5-$HT_{2A}$ receptor than for the $D_2$ receptor (Table 29–1), suggesting an important role for the serotonin 5-HT system in the etiology of schizophrenia and the action of these drugs.

## C. Differences among Antipsychotic Drugs

Although all effective antipsychotic drugs block $D_2$ receptors, the degree of this blockade in relation to other actions on receptors varies considerably among drugs. Vast numbers of ligand-receptor binding experiments have been performed in an effort to discover a single receptor action that would best predict antipsychotic efficacy. A summary of the relative receptor-binding affinities of several key agents in such comparisons illustrates the difficulty in drawing simple conclusions from such experiments:

Chlorpromazine: $\alpha_1 = 5\text{-}HT_{2A} > D_2 > D_1$
Haloperidol: $D_2 > \alpha_1 > D_4 > 5\text{-}HT_{2A} > D_1 > H_1$
Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_{2A} > D_2 = D_1$
Olanzapine: $5\text{-}HT_{2A} > H_1 > D_4 > D_2 > \alpha_1 > D_1$
Aripiprazole: $D_2 = 5\text{-}HT_{2A} > D_4 > \alpha_1 = H_1 >> D_1$
Quetiapine: $H_1 > \alpha_1 > M_{1,3} > D_2 > 5\text{-}HT_{2A}$

Thus, most of the atypical and some typical antipsychotic agents are at least as potent in inhibiting 5-$HT_2$ receptors as they are in inhibiting $D_2$ receptors. The newest, aripiprazole, appears to be a partial agonist of $D_2$ receptors. Varying degrees of antagonism of $\alpha_2$ adrenoceptors are also seen with risperidone, clozapine, olanzapine, quetiapine, and aripiprazole.

Current research is directed toward discovering atypical antipsychotic compounds that are either more selective for the mesolimbic system (to reduce their effects on the extrapyramidal system) or have effects on central neurotransmitter receptors—such as those for acetylcholine and excitatory amino acids—that have been proposed as new targets for antipsychotic action.

In contrast to the difficult search for receptors responsible for antipsychotic *efficacy*, the differences in receptor effects of various antipsychotics do explain many of their *toxicities* (Tables 29–1 and 29–2). In particular, extrapyramidal toxicity appears to be consistently associated with high $D_2$ potency.

## D. Psychological Effects

Most antipsychotic drugs cause unpleasant subjective effects in nonpsychotic individuals. The mild to severe EPS, including akathisia, sleepiness, restlessness, and autonomic effects are unlike any associated with more familiar sedatives or hypnotics.

**TABLE 29–2 Adverse pharmacologic effects of antipsychotic drugs.**

| Type | Manifestations | Mechanism |
|---|---|---|
| Autonomic nervous system | Loss of accommodation, dry mouth, difficulty urinating, constipation | Muscarinic cholinoceptor blockade |
| | Orthostatic hypotension, impotence, failure to ejaculate | α-Adrenoceptor blockade |
| Central nervous system | Parkinson's syndrome, akathisia, dystonias | Dopamine-receptor blockade |
| | Tardive dyskinesia | Supersensitivity of dopamine receptors |
| | Toxic-confusional state | Muscarinic blockade |
| Endocrine system | Amenorrhea-galactorrhea, infertility, impotence | Dopamine-receptor blockade resulting in hyperprolactinemia |
| Other | Weight gain | Possibly combined $H_1$ and 5-$HT_2$ blockade |

Nevertheless, low doses of some of these drugs, particularly quetiapine, are used to promote sleep onset and maintenance, although there is no approved indication for such usage.

People without psychiatric illness given antipsychotic drugs, even at low doses, experience impaired performance as judged by a number of psychomotor and psychometric tests. Psychotic individuals, however, may actually show improvement in their performance as the psychosis is alleviated. The ability of the atypical antipsychotic drugs to improve some domains of cognition in patients with schizophrenia and bipolar disorder is controversial. Some individuals experience marked improvement, and for that reason, cognition should be assessed in all patients with schizophrenia and a trial of an atypical agent considered, even if positive symptoms are well controlled by typical agents.

### E. Electroencephalographic Effects

Antipsychotic drugs produce shifts in the pattern of electroencephalographic (EEG) frequencies, usually slowing them and increasing their synchronization. The slowing (hypersynchrony) is sometimes focal or unilateral, which may lead to erroneous diagnostic interpretations. Both the frequency and the amplitude changes induced by psychotropic drugs are readily apparent and can be quantitated by sophisticated electrophysiologic techniques. Some of the neuroleptic agents lower the seizure threshold and induce EEG patterns typical of seizure disorders; however, with careful dosage titration, most can be used safely in epileptic patients.

### F. Endocrine Effects

Older typical antipsychotic drugs, as well as risperidone and paliperidone, produce elevations of prolactin, see Adverse Effects, below. Newer antipsychotics such as olanzapine, quetiapine, and aripiprazole cause no or minimal increases of prolactin and reduced risks of extrapyramidal system dysfunction and tardive dyskinesia, reflecting their *diminished* $D_2$ antagonism.

### G. Cardiovascular Effects

The low-potency phenothiazines frequently cause orthostatic hypotension and tachycardia. Mean arterial pressure, peripheral resistance, and stroke volume are decreased. These effects are predictable from the autonomic actions of these agents (Table 29–2). Abnormal electrocardiograms have been recorded, especially with thioridazine. Changes include prolongation of QT interval and abnormal configurations of the ST segment and T waves. These changes are readily reversed by withdrawing the drug. Thioridazine, however, is *not* associated with increased risk of torsades more than other typical antipsychotics, whereas haloperidol, which does not increase $QT_c$, is.

Among the newest atypical antipsychotics, prolongation of the QT or $QT_c$ interval has received much attention. Because this was believed to indicate an increased risk of dangerous arrhythmias, approval of sertindole has been delayed and ziprasidone and quetiapine are accompanied by warnings. There is, however, no evidence that this has actually translated into increased incidence of arrhythmias.

### H. Animal Screening Tests

Inhibition of conditioned (but not unconditioned) avoidance behavior is one of the most predictive tests of antipsychotic action. Another is the inhibition of amphetamine- or apomorphine-induced stereotyped behavior. Other tests that may predict antipsychotic action are reduction of exploratory behavior without undue sedation, induction of a cataleptic state, inhibition of intracranial self-stimulation of reward areas, and prevention of apomorphine-induced vomiting. Most of these tests are difficult to relate to any model of clinical psychosis.

The psychosis produced by phencyclidine (PCP) has been used as a model for schizophrenia. Because this drug is an antagonist of the NMDA glutamate receptor, attempts have been made to develop antipsychotic drugs that work as NMDA agonists. Sigma receptor and cholecystokinin type b ($CCK_b$) antagonism have also been suggested as potential targets. Thus far, NMDA receptor-based models have pointed to agents that modulate glutamate release as potential antipsychotics. 5-$HT_{2A}$ inverse agonists such as pimavanserin, ritanserin, and M100907 are potent inhibitors of PCP-induced locomotor activity, whereas $D_2$ antagonists are relatively weak in comparison. Thus, atypical antipsychotic drugs that act as 5-$HT_{2A}$ antagonists appear much more potent than typical antipsychotic drugs in PCP models.

# CLINICAL PHARMACOLOGY OF ANTIPSYCHOTIC AGENTS

## Indications

### A. Psychiatric Indications

**Schizophrenia** is the primary indication for antipsychotic agents. Antipsychotic drugs are also used very extensively in patients with psychotic bipolar disorder (BP1), psychotic depression, and treatment-resistant depression.

**Catatonic** forms of schizophrenia are best managed by intravenous benzodiazepines. Antipsychotic drugs may be needed to treat psychotic components of that form of the illness after catatonia has ended, and they remain the mainstay of treatment for this condition. Unfortunately, many patients show little response, and virtually none show a complete response.

Antipsychotic drugs are also indicated for **schizoaffective disorders,** which share characteristics of both schizophrenia and affective disorders. No fundamental difference between these two diagnoses has been reliably demonstrated. It is most likely that they are part of a continuum with bipolar psychotic disorder. The psychotic aspects of the illness require treatment with antipsychotic drugs, which may be used with other drugs such as antidepressants, lithium, or valproic acid. The manic phase in **bipolar affective disorder** often requires treatment with antipsychotic agents, although lithium or valproic acid supplemented with high-potency benzodiazepines (eg, lorazepam or clonazepam) may suffice in milder cases. Recent controlled trials support the efficacy of monotherapy with atypical antipsychotics in the acute phase (up to 4 weeks) of mania. Aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone have been approved for

treatment of various phases of bipolar disorder. They are most effective for the manic phase and for maintenance treatment.

As mania subsides, the antipsychotic drug may be withdrawn, although maintenance treatment with atypical antipsychotic agents has become more common. Nonmanic excited states may also be managed by antipsychotics, often in combination with benzodiazepines.

Other indications for the use of antipsychotics include **Tourette's syndrome,** disturbed behavior in patients with **Alzheimer's disease,** and, with antidepressants, **psychotic depression.** Antipsychotics are not indicated for the treatment of various withdrawal syndromes, eg, opioid withdrawal. In small doses, antipsychotic drugs have been promoted (wrongly) for the relief of anxiety associated with minor emotional disorders. The antianxiety sedatives (see Chapter 22) are preferred in terms of both safety and acceptability to patients.

### B. Nonpsychiatric Indications

Most older typical antipsychotic drugs, with the exception of thioridazine, have a strong **antiemetic** effect. This action is due to dopamine-receptor blockade, both centrally (in the chemoreceptor trigger zone of the medulla) and peripherally (on receptors in the stomach). Some drugs, such as prochlorperazine and benzquinamide, are promoted solely as antiemetics.

Phenothiazines with shorter side chains have considerable **$H_1$-receptor-blocking** action and have been used for relief of pruritus or, in the case of promethazine, as preoperative sedatives. The butyrophenone droperidol is used in combination with an opioid, fentanyl, in **neuroleptanesthesia.** The use of these drugs in anesthesia practice is described in Chapter 25.

## Drug Choice

Choice among antipsychotic drugs is based mainly on differences in adverse effects and possible differences in efficacy. Since use of the older drugs is still widespread, especially for patients treated in the public sector, knowledge of such agents as chlorpromazine and haloperidol remains relevant. Thus, one should be familiar with one member of each of the three subfamilies of phenothiazines, a member of the thioxanthene and butyrophenone group, and all of the newer compounds—clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Each may have special benefits for selected patients. A representative group of antipsychotic drugs is presented in Table 29–3.

**TABLE 29–3 Some representative antipsychotic drugs.**

| Drug Class | Drug | Advantages | Disadvantages |
|---|---|---|---|
| Phenothiazines | | | |
| Aliphatic | Chlorpromazine[1] | Generic, inexpensive | Many adverse effects, especially autonomic |
| Piperidine | Thioridazine[2] | Slight extrapyramidal syndrome; generic | 800 mg/d limit; no parenteral form; cardiotoxicity |
| Piperazine | Fluphenazine[3] | Depot form also available (enanthate, decanoate) | (?) Increased tardive dyskinesia |
| Thioxanthene | Thiothixene | Parenteral form also available; (?) decreased tardive dyskinesia | Uncertain |
| Butyrophenone | Haloperidol | Parenteral form also available; generic | Severe extrapyramidal syndrome |
| Dibenzoxazepine | Loxapine | (?) No weight gain | Uncertain |
| Dibenzodiazepine | Clozapine | May benefit treatment-resistant patients; little extrapyramidal toxicity | May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold |
| Benzisoxazole | Risperidone | Broad efficacy; little or no extrapyramidal system dysfunction at low doses | Extrapyramidal system dysfunction and hypotension with higher doses |
| Thienobenzodiazepine | Olanzapine | Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction | Weight gain; dose-related lowering of seizure threshold |
| Dibenzothiazepine | Quetiapine | Similar to olanzapine; perhaps less weight gain | May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing |
| Dihydroindolone | Ziprasidone | Perhaps less weight gain than clozapine, parenteral form available | $QT_c$ prolongation |
| Dihydrocarbostyril | Aripiprazole | Lower weight gain liability, long half-life, novel mechanism potential | Uncertain, novel toxicities possible |

[1]Other aliphatic phenothiazines: promazine, trifluprom azine.

[2]Other piperidine phenothiazines: piperacetazine, mesoridazine.

[3]Other piperazine phenothiazines: acetophenazine, perphenazine, carphenazine, prochlorperazine, trifluoperazine.

For approximately 70% of patients with schizophrenia, and probably for a similar proportion of patients with bipolar disorder with psychotic features, typical and atypical antipsychotic drugs are of equal efficacy for treating positive symptoms. However, the evidence favors atypical drugs for benefit for negative symptoms and cognition, for diminished risk of tardive dyskinesia and other forms of EPS, and for lesser increases in prolactin levels.

Some of the atypical antipsychotic drugs produce more weight gain and increases in lipids than some typical antipsychotic drugs. A small percentage of patients develop diabetes mellitus, most often seen with clozapine and olanzapine. Ziprasidone is the atypical drug causing the least weight gain. Risperidone, paliperidone, and aripiprazole usually produce small increases in weight and lipids. Asenapine and quetiapine have an intermediate effect. Clozapine and olanzapine frequently result in large increases in weight and lipids. Thus, these drugs should be considered as second-line drugs unless there is a specific indication. That is the case with clozapine, which at high doses (300–900 mg/d) is effective in the majority of patients with schizophrenia refractory to other drugs, provided that treatment is continued for up to 6 months. Case reports and several clinical trials suggest that high-dose olanzapine, ie, doses of 30–45 mg/d, may also be efficacious in refractory schizophrenia when given over a 6-month period. Clozapine is the only atypical antipsychotic drug indicated to reduce the risk of suicide. All patients with schizophrenia who have made life-threatening suicide attempts should be seriously evaluated for switching to clozapine.

New antipsychotic drugs have been shown in some trials to be more effective than older ones for treating negative symptoms. The floridly psychotic form of the illness accompanied by uncontrollable behavior probably responds equally well to all potent antipsychotics but is still frequently treated with older drugs that offer intramuscular formulations for acute and chronic treatment. Moreover, the low cost of the older drugs contributes to their widespread use despite their risk of adverse EPS effects. Several of the newer antipsychotics, including clozapine, risperidone, and olanzapine, show superiority over haloperidol in terms of overall response in some controlled trials. More comparative studies with aripiprazole are needed to evaluate its relative efficacy. Moreover, the superior adverse-effect profile of the newer agents and low to absent risk of tardive dyskinesia suggest that these should provide the first line of treatment.

The best guide for selecting a drug for an individual patient is the patient's past responses to drugs. At present, clozapine is limited to those patients who have failed to respond to substantial doses of conventional antipsychotic drugs. The agranulocytosis and seizures associated with this drug prevent more widespread use. Risperidone's superior side-effect profile (compared with that of haloperidol) at dosages of 6 mg/d or less and the lower risk of tardive dyskinesia have contributed to its widespread use. Olanzapine and quetiapine may have even lower risk and have also achieved widespread use.

## Dosage

The range of effective dosages among various antipsychotic agents is broad. Therapeutic margins are substantial. At appropriate dosages, antipsychotics—with the exception of clozapine and perhaps olanzapine—are of equal efficacy in broadly selected groups of patients. However, some patients who fail to respond to one drug may respond to another; for this reason, several drugs may have to be tried to find the one most effective for an individual patient. Patients who have become refractory to two or three antipsychotic agents given in substantial doses become candidates for treatment with clozapine or high-dose olanzapine. Thirty to fifty percent of patients previously refractory to standard doses of other antipsychotic drugs respond to these drugs. In such cases, the increased risk of clozapine can well be justified.

Some dosage relationships between various antipsychotic drugs, as well as possible therapeutic ranges, are shown in Table 29–4.

**TABLE 29–4 Dose relationships of antipsychotics.**

| | Minimum Effective Therapeutic Dose (mg) | Usual Range of Daily Doses (mg) |
|---|---|---|
| Chlorpromazine | 100 | 100–1000 |
| Thioridazine | 100 | 100–800 |
| Trifluoperazine | 5 | 5–60 |
| Perphenazine | 10 | 8–64 |
| Fluphenazine | 2 | 2–60 |
| Thiothixene | 2 | 2–120 |
| Haloperidol | 2 | 2–60 |
| Loxapine | 10 | 20–160 |
| Molindone | 10 | 20–200 |
| Clozapine | 50 | 300–600 |
| Olanzapine | 5 | 10–30 |
| Quetiapine | 150 | 150–800 |
| Risperidone | 4 | 4–16 |
| Ziprasidone | 40 | 80–160 |
| Aripiprazole | 10 | 10–30 |

## Parenteral Preparations

Well-tolerated parenteral forms of the high-potency older drugs haloperidol and fluphenazine are available for rapid initiation of treatment as well as for maintenance treatment in noncompliant patients. Since the parenterally administered drugs may have much greater bioavailability than the oral forms, doses should be only a fraction of what might be given orally, and the manufacturer's literature should be consulted. Fluphenazine decanoate and haloperidol decanoate are suitable for long-term parenteral maintenance therapy in patients who cannot or will not take oral medication.

## Dosage Schedules

Antipsychotic drugs are often given in divided daily doses, titrating to an effective dosage. The low end of the dosage range in Table 29–4 should be tried for at least several weeks. After an

effective daily dosage has been defined for an individual patient, doses can be given less frequently. Once-daily doses, usually given at night, are feasible for many patients during chronic maintenance treatment. Simplification of dosage schedules leads to better compliance.

## Maintenance Treatment

A very small minority of schizophrenic patients may recover from an acute episode and require no further drug therapy for prolonged periods. In most cases, the choice is between "as needed" increased doses or the addition of other drugs for exacerbations versus continual maintenance treatment with full therapeutic dosage. The choice depends on social factors such as the availability of family or friends familiar with the symptoms of early relapse and ready access to care.

## Drug Combinations

Combining antipsychotic drugs confounds evaluation of the efficacy of the drugs being used. Use of combinations, however, is widespread, with more emerging experimental data supporting such practices. Tricyclic antidepressants or, more often, selective serotonin reuptake inhibitors (SSRIs) are often used with antipsychotic agents for symptoms of depression complicating schizophrenia. The evidence for the usefulness of this polypharmacy is minimal. Electroconvulsive therapy (ECT) is a useful adjunct for antipsychotic drugs, not only for treating mood symptoms, but for positive symptom control as well. Electroconvulsive therapy can augment clozapine when maximum doses of clozapine are ineffective. In contrast, adding risperidone to clozapine is not beneficial. Lithium or valproic acid is sometimes added to antipsychotic agents with benefit to patients who do not respond to the latter drugs alone. There is some evidence that lamotrigine is more effective than any of the other mood stabilizers for this indication (see below). It is uncertain whether instances of successful combination therapy represent misdiagnosed cases of mania or schizoaffective disorder. Benzodiazepines may be useful for patients with anxiety symptoms or insomnia not controlled by antipsychotics.

## Adverse Reactions

Most of the unwanted effects of antipsychotic drugs are extensions of their known pharmacologic actions (Tables 29–1 and 29–2), but a few effects are allergic in nature and some are idiosyncratic.

### A. Behavioral Effects

The older typical antipsychotic drugs are unpleasant to take. Many patients stop taking these drugs because of the adverse effects, which may be mitigated by giving small doses during the day and the major portion at bedtime. A "pseudodepression" that may be due to drug-induced akinesia usually responds to treatment with antiparkinsonism drugs. Other pseudodepressions may be due to higher doses than needed in a partially remitted patient, in which case decreasing the dose may relieve the symptoms. Toxic-confusional states may occur with very high doses of drugs that have prominent antimuscarinic actions.

### B. Neurologic Effects

Extrapyramidal reactions occurring early during treatment with older agents include typical **Parkinson's syndrome, akathisia** (uncontrollable restlessness), and **acute dystonic reactions** (spastic retrocollis or torticollis). Parkinsonism can be treated, when necessary, with conventional antiparkinsonism drugs of the antimuscarinic type or, in rare cases, with amantadine. (Levodopa should never be used in these patients.) Parkinsonism may be self-limiting, so that an attempt to withdraw antiparkinsonism drugs should be made every 3–4 months. Akathisia and dystonic reactions also respond to such treatment, but many clinicians prefer to use a sedative antihistamine with anticholinergic properties, eg, diphenhydramine, which can be given either parenterally or orally.

**Tardive dyskinesia,** as the name implies, is a late-occurring syndrome of abnormal choreoathetoid movements. It is the most important unwanted effect of antipsychotic drugs. It has been proposed that it is caused by a relative cholinergic deficiency secondary to supersensitivity of dopamine receptors in the caudate-putamen. The prevalence varies enormously, but tardive dyskinesia is estimated to have occurred in 20–40% of chronically treated patients before the introduction of the newer atypical antipsychotics. Early recognition is important, since advanced cases may be difficult to reverse. Any patient with tardive dyskinesia treated with a typical antipsychotic drug or possibly risperidone or paliperidone should be switched to quetiapine or clozapine, the atypical agents with the least likelihood of causing tardive dyskinesia. Many treatments have been proposed, but their evaluation is confounded by the fact that the course of the disorder is variable and sometimes self-limited. Reduction in dosage may also be considered. Most authorities agree that the first step should be to discontinue or reduce the dose of the current antipsychotic agent or switch to one of the newer atypical agents. A logical second step would be to eliminate all drugs with central anticholinergic action, particularly antiparkinsonism drugs and tricyclic antidepressants. These two steps are often enough to bring about improvement. If they fail, the addition of diazepam in doses as high as 30–40 mg/d may add to the improvement by enhancing GABAergic activity.

**Seizures,** though recognized as a complication of chlorpromazine treatment, were so rare with the high-potency older drugs as to merit little consideration. However, de novo seizures may occur in 2–5% of patients treated with clozapine. Use of an anticonvulsant is able to control seizures in most cases.

### C. Autonomic Nervous System Effects

Most patients are able to tolerate the antimuscarinic adverse effects of antipsychotic drugs. Those who are made too uncomfortable or who develop urinary retention or other severe symptoms can be switched to an agent without significant antimuscarinic action. Orthostatic hypotension or impaired

ejaculation—common complications of therapy with chlorpromazine or mesoridazine—should be managed by switching to drugs with less marked adrenoceptor-blocking actions.

### D. Metabolic and Endocrine Effects

Weight gain is very common, especially with clozapine and olanzapine, and requires monitoring of food intake, especially carbohydrates. Hyperglycemia may develop, but whether secondary to weight gain-associated insulin resistance or to other potential mechanisms remains to be clarified. Hyperlipidemia may occur. The management of weight gain, insulin resistance, and increased lipids should include monitoring of weight at each visit and measurement of fasting blood sugar and lipids at 3–6 month intervals. Measurement of hemoglobin $A_{1C}$ may be useful when it is impossible to be sure of obtaining a fasting blood sugar. Diabetic ketoacidosis has been reported in a few cases. The triglyceride:HDL ratio should be less than 3.5 in fasting samples. Levels higher than that indicate increased risk of atherosclerotic cardiovascular disease.

Hyperprolactinemia in women results in the amenorrhea-galactorrhea syndrome and infertility; in men, loss of libido, impotence, and infertility may result. Hyperprolactinemia may cause osteoporosis, particularly in women. If dose reduction is not indicated, or ineffective in controlling this pattern, switching to one of the atypical agents that do not raise prolactin levels, eg, aripiprazole, may be indicated.

### E. Toxic or Allergic Reactions

Agranulocytosis, cholestatic jaundice, and skin eruptions occur rarely with the high-potency antipsychotic drugs currently used.

In contrast to other antipsychotic agents, clozapine causes agranulocytosis in a small but significant number of patients—approximately 1–2% of those treated. This serious, potentially fatal effect can develop rapidly, usually between the 6th and 18th weeks of therapy. It is not known whether it represents an immune reaction, but it appears to be reversible upon discontinuance of the drug. *Because of the risk of agranulocytosis, patients receiving clozapine must have weekly blood counts for the first 6 months of treatment and every 3 weeks thereafter.*

### F. Ocular Complications

Deposits in the anterior portions of the eye (cornea and lens) are a common complication of chlorpromazine therapy. They may accentuate the normal processes of aging of the lens. Thioridazine is the only antipsychotic drug that causes retinal deposits, which in advanced cases may resemble retinitis pigmentosa. The deposits are usually associated with "browning" of vision. The maximum daily dose of thioridazine has been limited to 800 mg/d to reduce the possibility of this complication.

### G. Cardiac Toxicity

Thioridazine in doses exceeding 300 mg daily is almost always associated with minor abnormalities of T waves that are easily reversible. Overdoses of thioridazine are associated with major ventricular arrhythmias, eg, torsades de pointes, cardiac conduction block, and sudden death; it is not certain whether thioridazine can cause these same disorders when used in therapeutic doses. In view of possible additive antimuscarinic and quinidine-like actions with various tricyclic antidepressants, thioridazine should be combined with the latter drugs only with great care. Among the atypical agents, ziprasidone carries the greatest risk of QT prolongation and therefore should not be combined with other drugs that prolong the QT interval, including thioridazine, pimozide, and group 1A or 3 antiarrhythmic drugs. Clozapine is sometimes associated with myocarditis and must be discontinued if myocarditis manifests. Sudden death due to arrhythmias is common in schizophrenia. It is not always drug-related, and there are no studies that definitively show increased risk with particular drugs. Monitoring of $QT_c$ prolongation has proved to be of little use unless the values increase to more than 500 ms and this is manifested in multiple rhythm strips or a Holter monitor study. A 20,000 patient study of ziprasidone versus olanzapine showed minimal or no increased risk of torsades de pointes or sudden death in patients who were randomized to ziprasidone.

### H. Use in Pregnancy; Dysmorphogenesis

Although antipsychotic drugs appear to be relatively safe in pregnancy, a small increase in teratogenic risk could be missed. Questions about whether to use these drugs during pregnancy and whether to abort a pregnancy in which the fetus has already been exposed must be decided individually. If a pregnant woman could manage to be free of antipsychotic drugs during pregnancy, this would be desirable because of their effects on the neurotransmitters involved in neurodevelopment.

### I. Neuroleptic Malignant Syndrome

This life-threatening disorder occurs in patients who are extremely sensitive to the extrapyramidal effects of antipsychotic agents (see also Chapter 16). The initial symptom is marked muscle rigidity. If sweating is impaired, as it often is during treatment with anticholinergic drugs, fever may ensue, often reaching dangerous levels. The stress leukocytosis and high fever associated with this syndrome may erroneously suggest an infectious process. Autonomic instability, with altered blood pressure and pulse rate, is often present.

Muscle-type creatine kinase levels are usually elevated, reflecting muscle damage. This syndrome is believed to result from an excessively rapid blockade of postsynaptic dopamine receptors. A severe form of extrapyramidal syndrome follows. Early in the course, vigorous treatment of the extrapyramidal syndrome with antiparkinsonism drugs is worthwhile. Muscle relaxants, particularly diazepam, are often useful. Other muscle relaxants, such as dantrolene, or dopamine agonists, such as bromocriptine, have been reported to be helpful. If fever is present, cooling by physical measures should be tried. Various minor forms of this syndrome are now recognized. Switching to an atypical drug after recovery is indicated.

## Drug Interactions

Antipsychotics produce more important pharmacodynamic than pharmacokinetic interactions because of their multiple effects.

Additive effects may occur when these drugs are combined with others that have sedative effects, α-adrenoceptor–blocking action, anticholinergic effects, and—for thioridazine and ziprasidone—quinidine-like action.

A variety of pharmacokinetic interactions have been reported, but none are of major clinical significance.

### Overdoses

Poisonings with antipsychotic agents (unlike tricyclic antidepressants) are rarely fatal, with the exception of those due to mesoridazine and thioridazine. In general, drowsiness proceeds to coma, with an intervening period of agitation. Neuromuscular excitability may be increased and proceed to convulsions. Pupils are miotic, and deep tendon reflexes are decreased. Hypotension and hypothermia are the rule, although fever may be present later in the course. The lethal effects of mesoridazine and thioridazine are related to induction of ventricular tachyarrhythmias. Patients should be given the usual "ABCD" treatment for poisonings (see Chapter 58) and treated supportively. Management of overdoses of thioridazine and mesoridazine, which are complicated by cardiac arrhythmias, is similar to that for tricyclic antidepressants (see Chapter 30).

### Psychosocial Treatment & Cognitive Remediation

Patients with schizophrenia need psychosocial support based around activities of daily living, including housing, social activities, returning to school, obtaining the optimal level of work they may be capable of, and restoring social interactions. Unfortunately, funding for this crucial component of treatment has been minimized in recent years. Case management and therapy services are a vital part of the treatment program that should be provided to patients with schizophrenia. First-episode patients are particularly needful of this support because they often deny their illness and are noncompliant with medication.

### Benefits & Limitations of Drug Treatment

As noted at the beginning of this chapter, antipsychotic drugs have had a major impact on psychiatric treatment. First, they have shifted the vast majority of patients from long-term hospitalization to the community. For many patients, this shift has provided a better life under more humane circumstances and in many cases has made possible life without frequent use of physical restraints. For others, the tragedy of an aimless existence is now being played out in the streets of our communities rather than in mental institutions.

Second, these antipsychotic drugs have markedly shifted psychiatric thinking to a more biologic orientation. Partly because of research stimulated by the effects of these drugs on schizophrenia, we now know much more about central nervous system physiology and pharmacology than was known before the introduction of these agents. However, despite much research, schizophrenia remains a scientific mystery and a personal disaster for the patient. Although most schizophrenic patients obtain some degree of benefit from these drugs—in some cases substantial benefit—none are made well by them.

## LITHIUM, MOOD-STABILIZING DRUGS, & OTHER TREATMENT FOR BIPOLAR DISORDER

Bipolar disorder, once known as manic-depressive illness, was conceived of as a psychotic disorder distinct from schizophrenia at the end of the 19th century. Before that both of these disorders were considered part of a continuum. It is ironic that the weight of the evidence today is that there is profound overlap in these disorders. This is not to say that there are no pathophysiologically important differences or that some drug treatments are differentially effective in these disorders. According to *DSM-IV*, they are separate disease entities while research continues to define the dimensions of these illnesses and their genetic and other biologic markers.

Lithium was the first agent shown to be useful in the treatment of the manic phase of bipolar disorder that was not also an antipsychotic drug. Lithium has no known use in schizophrenia. Lithium continues to be used for acute-phase illness as well as for prevention of recurrent manic and depressive episodes.

A group of mood-stabilizing drugs that are also anticonvulsant agents has become more widely used than lithium. It includes **carbamazepine** and **valproic acid** for the treatment of acute mania and for prevention of its recurrence. **Lamotrigine** is approved for prevention of recurrence. **Gabapentin, oxcarbazepine,** and **topiramate** are sometimes used to treat bipolar disorder but are not approved by the Food and Drug Administration for this indication. **Aripiprazole, chlorpromazine, olanzapine, quetiapine, risperidone,** and **ziprasidone** are approved by the FDA for treatment of the manic phase of bipolar disorder. Olanzapine plus fluoxetine in combination and quetiapine are approved for treatment of bipolar depression.

### Nature of Bipolar Affective Disorder

Bipolar affective (manic-depressive) disorder occurs in 1–3% of the adult population. It may begin in childhood, but most cases are first diagnosed in the third and fourth decades of life. The key symptoms of bipolar disorder in the manic phase are excitement, hyperactivity, impulsivity, disinhibition, aggression, diminished need for sleep, psychotic symptoms in some (but not all) patients, and cognitive impairment. Depression in bipolar patients is phenomenologically similar to that of major depression, with the key features being depressed mood, diurnal variation, sleep disturbance, anxiety, and sometimes, psychotic symptoms. Mixed manic and depressive symptoms are also seen. Patients with bipolar disorder are at high risk for suicide.

The sequence, number, and intensity of manic and depressive episodes are highly variable. The cause of the mood swings

characteristic of bipolar affective disorder is unknown, although a preponderance of catecholamine-related activity may 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, and there is abundant evidence that bipolar disorder is genetically determined.

Many of the genes that increase vulnerability to bipolar disorder are common to schizophrenia but some genes appear to be unique to each disorder. Genome-wide association studies of psychotic bipolar disorder have shown replicated linkage to chromosomes 8p and 13q. Several candidate genes have shown association with bipolar disorder with psychotic features and with schizophrenia. These include genes for dysbindin, *DAOA/G30*, disrupted-inschizophrenia-1 (*DISC-1*), and neuregulin 1.

# BASIC PHARMACOLOGY OF LITHIUM

Lithium was first used therapeutically in the mid-19th century in patients with gout. It was briefly used as a substitute for sodium chloride in hypertensive patients in the 1940s but was banned after it proved too toxic for use without monitoring. In 1949, Cade discovered that lithium was an effective treatment for bipolar disorder, engendering a series of controlled trials that confirmed its efficacy as monotherapy for the manic phase of bipolar disorder.

## Pharmacokinetics

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

## Pharmacodynamics

Despite considerable investigation, the biochemical basis for mood stabilizer therapies including lithium and anticonvulsant mood stabilizers is not clearly understood. Lithium directly inhibits two signal transduction pathways. It both suppresses inositol signaling through depletion of intracellular inositol and inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase. GSK-3 is a component of diverse intracellular signaling pathways. These include signaling via insulin/insulin-like growth factor, brain-derived neurotrophic factor (BDNF), and the Wnt pathway. All of these lead to inhibition of GSK-3. GSK-3 phosphorylates β-catenin, resulting in interaction with transcription factors. The pathways that are facilitated in this manner modulate energy metabolism, provide neuroprotection, and increase neuroplasticity.

Studies on the enzyme prolyl oligopeptidase and the sodium myoinositol transporter support an inositol depletion mechanism for mood-stabilizer action. Valproic acid may indirectly reduce GSK-3 activity and can up-regulate gene expression through inhibition of histone deacetylase. Valproic acid also inhibits inositol signaling through an inositol depletion mechanism. There is no evidence of GSK-3 inhibition by carbamazepine, a second antiepileptic mood stabilizer. In contrast, this drug alters neuronal morphology through an inositol depletion mechanism, as seen with lithium and valproic acid. The mood stabilizers may also have indirect effects on neurotransmitters and their release.

### A. 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; that is, $Li^+$-$Na^+$ exchange is gradually slowed after lithium is introduced into the body. At therapeutic concentrations (around 1 mmol/L), it does not significantly affect the $Na^+$-$Ca^{2+}$ exchanger or the $Na^+/K^+$-ATPase pump.

### B. Effects on Second Messengers

Some of the enzymes affected by lithium are listed in Table 29–6. One of the best-defined effects of lithium is its action on inositol

**TABLE 29–5 Pharmacokinetics of lithium.**

| | |
|---|---|
| Absorption | Virtually complete within 6–8 hours; peak plasma levels in 30 minutes to 2 hours |
| Distribution | In total body water; slow entry into intracellular compartment. Initial volume of distribution is 0.5 L/kg, rising to 0.7–0.9 L/kg; some sequestration in bone. No protein binding. |
| Metabolism | None |
| Excretion | Virtually entirely in urine. Lithium clearance about 20% of creatinine. Plasma half-life about 20 hours. |
| Target plasma concentration | 0.6–1.4 mEq/L |
| Dosage | 0.5 mEq/kg/d in divided doses |

**TABLE 29–6 Enzymes affected by lithium at therapeutic concentrations.**

| Enzyme | Enzyme Function; Action of Lithium |
|---|---|
| Inositol monophosphatase | The rate-limiting enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for $IP_3$ production (Figure 29–4) |
| Inositol polyphosphate 1-phosphatase | Another enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for $IP_3$ production (Figure 29–4) |
| Bisphosphate nucleotidase | Involved in AMP production; inhibited by lithium; may be target that results in lithium-induced nephrogenic diabetes insipidus |
| Fructose 1,6-biphosphatase | Involved in gluconeogenesis; inhibition by lithium of unknown relevance |
| Phosphoglucomutase | Involved in glycogenolysis; inhibition by lithium of unknown relevance |
| Glycogen synthase kinase-3 | Constitutively active enzyme that appears to limit neurotrophic and neuroprotective processes; lithium inhibits |

AMP, adenosine monophosphate; $IP_3$, inositol 1,4,5-trisphosphate.

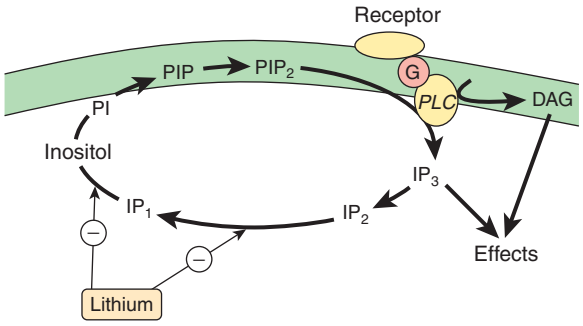


**FIGURE 29–4** Effect of lithium on the $IP_3$ (inositol trisphosphate) and DAG (diacylglycerol) second-messenger system. The schematic diagram shows the synaptic membrane of a neuron. ($PIP_2$, phosphatidylinositol-4,5-bisphosphate; PLC, phospholipase C; G, coupling protein; Effects, activation of protein kinase C, mobilization of intracellular $Ca^{2+}$, etc.) Lithium, by inhibiting the recycling of inositol substrates, may cause depletion of the second-messenger source $PIP_2$ and therefore reduce the release of $IP_3$ and DAG. Lithium may also act by other mechanisms.

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 ($IP_3$) and diacylglycerol (DAG) were discovered. As described in Chapter 2, inositol trisphosphate and diacylglycerol are important second messengers for both α-adrenergic and muscarinic transmission. Lithium inhibits inositol monophosphatase (IMPase) and other important enzymes in the normal recycling of membrane phosphoinositides, including conversion of $IP_2$ (inositol diphosphate) to $IP_1$ (inositol monophosphate) and the conversion of $IP_1$ to inositol (Figure 29–4). This block leads to a depletion of free inositol and ultimately of phosphatidylinositol-4,5-bisphosphate ($PIP_2$), the membrane precursor of $IP_3$ and DAG. Over time, the effects of transmitters on the cell diminish in proportion to the amount of activity in the $PIP_2$-dependent pathways. The activity of these pathways is postulated to be markedly increased during a manic episode. Treatment with lithium would be expected to diminish the activity in these circuits.

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 $IP_3$ mechanisms is currently unknown.

Because 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 thyroid-stimulating hormone (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, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone for this indication, a smaller percentage 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 can be as high as 80% but lower among patients who require hospitalization. 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 and benzodiazepines and lithium continued as maintenance therapy.

The depressive phase of manic-depressive disorder often requires concurrent use of an antidepressant drug (see Chapter 30). 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 promise but—like tricyclic antidepressants—may induce mania 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 monoamine oxidase inhibitors may be the antidepressant of choice. Quetiapine and the combination of olanzapine and fluoxetine has been approved for use in bipolar depression.

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, although it can produce nausea and tremor. Most important is that the prophylactic use of lithium can prevent both mania and depression. Many experts believe that the aggressive marketing of newer drugs has inappropriately produced a shift to drugs that are less effective than lithium for substantial numbers of patients.

## Other Applications

**Recurrent endogenous depression** with a cyclic pattern is controlled by either lithium or imipramine, both of which are superior to placebo.

**Schizoaffective disorder,** another condition with an affective component characterized by a mixture of schizophrenic symptoms and depression or excitement, is treated with antipsychotic drugs alone or combined with lithium. Various antidepressants are added if depression is present.

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

An interesting application of lithium that is relatively well supported by controlled studies is as an adjunct to tricyclic antidepressants and SSRIs 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 rely on measurements of serum lithium concentrations for assessing both the dosage required for treatment of acute mania and for prophylactic maintenance. 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. 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 after 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 episode has subsided. Patients who have one or more episodes of illness per year are candidates for maintenance treatment. Although some patients can be maintained with serum levels as low as 0.6 mEq/L, the best results 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 atypical 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.

### A. Neurologic and Psychiatric Adverse Effects

**Tremor** is one of the most common adverse effects of lithium treatment, and it occurs with therapeutic doses. 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. Appearance of any new neurologic or psychiatric symptoms or signs is a clear indication for temporarily stopping treatment with lithium and for close monitoring of serum levels.

### B. Decreased 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.

### C. Nephrogenic Diabetes Insipidus and Other Renal Adverse Effects

Polydipsia and polyuria are common but reversible concomitants of lithium treatment, occurring at therapeutic serum concentrations. The principal physiologic lesion involved is loss of responsiveness to antidiuretic hormone (nephrogenic diabetes insipidus). Lithium-induced diabetes insipidus is resistant to vasopressin but responds to amiloride.

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.

### D. Edema

Edema is a common 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.

### E. 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 electrocardiogram but is of questionable significance.

### F. 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 after 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 lithium-induced dysmorphogenesis is not settled. An earlier report suggested an increase in cardiac anomalies—especially Ebstein's anomaly—in lithium babies, and it is listed as such in Table 59–1 in this book. However, more recent data suggest that lithium carries a relatively low risk of teratogenic effects. Further research is needed in this important area.

### G. 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 of lithium 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. Because lithium is a small ion, it is dialyzed readily. Both peritoneal dialysis and hemodialysis are effective, although the latter is preferred.

# VALPROIC ACID

Valproic acid (valproate), discussed in detail in Chapter 24 as an antiepileptic, has been demonstrated to have antimanic effects and is now being widely used for this indication in the USA. (Gabapentin is not effective, leaving the mechanism of action of valproate unclear.) Overall, valproic acid shows efficacy equivalent to that of lithium during the early weeks of treatment. It is significant that 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 dosage 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 dosage is 750 mg/d, increasing rapidly to the 1500–2000 mg range with a recommended maximum dosage 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 an appropriate first-line treatment for mania, although it is not clear that it will be as effective as lithium as a maintenance treatment in all subsets of patients. Many clinicians advocate 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. The mode of action of carbamazepine is unclear, and oxcarbazepine is not effective. Carbamazepine may be used to treat acute mania and also for prophylactic therapy. Adverse effects (discussed in Chapter 24) are generally no greater and sometimes less than those associated with lithium. Carbamazepine may be used alone or, in refractory patients, in combination with lithium or, rarely, valproate.

The use of carbamazepine as a mood stabilizer is similar to its use as an anticonvulsant (see Chapter 24). 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, although no therapeutic range has been established. Blood dyscrasias have figured prominently in the adverse effects of carbamazepine when it is used as an anticonvulsant, but they have not been a major problem with its use as a mood stabilizer. Overdoses of carbamazepine are a major emergency and should generally be managed like overdoses of tricyclic antidepressants (see Chapter 58).

# OTHER DRUGS

Lamotrigine has been reported to be useful in preventing the depression that often follows the manic phase of bipolar disorder. A number of novel agents are under investigation for bipolar depression, including riluzole, a neuroprotective agent that is approved for use in amyotrophic lateral sclerosis; ketamine, a noncompetitive NMDA antagonist previously discussed as a drug believed to model schizophrenia but thought to act by producing relative enhancement of AMPA receptor activity; and AMPA receptor potentiators.

## SUMMARY Antipsychotic Drugs & Lithium

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities, Interactions |
|---|---|---|---|---|
| **PHENOTHIAZINES**<br>• Chlorpromazine<br>• Fluphenazine<br>• Thioridazine<br>**THIOXANTHENE**<br>• Thiothixene | Blockade of $D_2$ receptors >> 5-$HT_{2A}$ receptors | α-Receptor blockade (fluphenazine least) • muscarinic (M)-receptor blockade (especially chlorpromazine and thioridazine) • $H_1$-receptor blockade (chlorpromazine, thiothixene) • central nervous system (CNS) depression (sedation) • decreased seizure threshold • QT prolongation (thioridazine) | Psychiatric: schizophrenia (alleviate positive symptoms), bipolar disorder (manic phase) • nonpsychiatric: antiemesis, preoperative sedation (promethazine) • pruritus | Oral and parenteral forms, long half-lives with metabolism-dependent elimination • *Toxicity*: Extensions of effects on α- and M-receptors • blockade of dopamine receptors may result in akathisia, dystonia, parkinsonian symptoms, tardive dyskinesia, and hyperprolactinemia |
| **BUTYROPHENONE**<br>• Haloperidol | Blockade of $D_2$ receptors >> 5-$HT_{2A}$ receptors | Some α blockade, but minimal M-receptor blockade and much less sedation than the phenothiazines | Schizophrenia (alleviates positive symptoms), bipolar disorder (manic phase), Huntington's chorea, Tourette's syndrome | Oral and parenteral forms with metabolism-dependent elimination • *Toxicity*: Extrapyramidal dysfunction is major adverse effect |
| **ATYPICAL ANTIPSYCHOTICS**<br>• Aripiprazole<br>• Clozapine<br>• Olanzapine<br>• Quetiapine<br>• Risperidone<br>• Ziprasidone | Blockade of 5-$HT_{2A}$ receptors > blockade of $D_2$ receptors | Some α blockade (clozapine, risperidone, ziprasidone) and M-receptor blockade (clozapine, olanzapine) • variable $H_1$-receptor blockade (all) | Schizophrenia—improve both positive and negative symptoms • bipolar disorder (olanzapine or risperidone adjunctive with lithium) • agitation in Alzheimer's and Parkinson's patients (low doses) • major depression (aripiprazole) | *Toxicity*: Agranulocytosis (clozapine), diabetes (clozapine, olanzapine), hypercholesterolemia (clozapine, olanzapine), hyperprolactinemia (risperidone), QT prolongation (ziprasidone), weight gain (clozapine, olanzapine) |
| **LITHIUM** | Mechanism of action uncertain • suppresses inositol signaling and inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase | No significant antagonistic actions on autonomic nervous system receptors or specific CNS receptors • no sedative effects | Bipolar affective disorder—prophylactic use can prevent mood swings between mania and depression | Oral absorption, renal elimination • half-life 20 h • narrow therapeutic window (monitor blood levels) • *Toxicity:* Tremor, edema, hypothyroidism, renal dysfunction, dysrhythmias • pregnancy category D • *Interactions:* Clearance decreased by thiazides and some NSAIDs |
| **NEWER AGENTS FOR BIPOLAR DISORDER**<br>• Carbamazepine<br>• Lamotrigine<br>• Valproic acid | Mechanism of action in bipolar disorder unclear (see Chapter 24 for putative actions in seizure disorders) | Carbamazepine causes dose-related diplopia and ataxia • lamotrigine causes nausea, dizziness, and headache • valproic acid causes gastrointestinal distress, possible weight gain, alopecia | Valproic acid is increasingly used as first choice in acute mania • carbamazepine and lamotrigine are also used both in acute mania and for prophylaxis in depressive phase | Oral absorption • once-daily dosing • carbamazepine forms active metabolite • lamotrigine and valproic acid form conjugates • *Toxicity:* Hematotoxicity and induction of P450 drug metabolism (carbamazepine), rash (lamotrigine), tremor, liver dysfunction, weight gain, inhibition of drug metabolism (valproic acid) |

# PREPARATIONS AVAILABLE

## ANTIPSYCHOTIC AGENTS

**Aripiprazole (Abilify)**
Oral: 2, 5, 10, 15, 20, 30 mg tablets; 1 mg/mL solution
Parenteral: 7.5 mg/mL for IM injection

**Asenapine (Saphris)**
Oral: 5, 10 mg sublingual tablets

**Chlorpromazine (generic, Thorazine)**
Oral: 10, 25, 50, 100, 200 mg tablets; 100 mg/mL concentrate
Rectal: 100 mg suppositories
Parenteral: 25 mg/mL for IM injection

**Clozapine (generic, Clozaril)**
Oral: 12.5, 25, 50, 100, 200 mg tablets; 25, 100 mg orally disintegrating tablets

**Fluphenazine (generic, Prolixin)**
Oral: 1, 2.5, 5, 10 mg tablets; 2.5 mg/5 mL elixir
Parenteral: (fluphenazine HCl): 2.5 mg/mL for IM injection

**Fluphenazine decanoate (generic, Prolixin)**
Parenteral: 25 mg/mL for IM or SC injection

**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 (generic, Loxitane)**
Oral: 5, 10, 25, 50 mg capsules

**Molindone (Moban)**
Oral: 5, 10, 25, 50 mg tablets

**Olanzapine (Zyprexa)**
Oral: 2.5, 5, 7.5, 10, 15, 20 mg tablets; 5, 10, 15, 20 mg orally disintegrating tablets
Parenteral: 10 mg powder for injection

**Paliperidone (Invega)**
Oral: 3, 6, 9 mg extended-release tablets

**Perphenazine (generic)**
Oral: 2, 4, 8, 16 mg tablets; 16 mg/5 mL concentrate

**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

**Quetiapine (Seroquel)**
Oral: 25, 50, 100, 200, 300, 400 mg tablets; 200, 300, 400 mg extended-release tablets

**Risperidone (Risperdal)**
Oral: 0.25, 0.5, 1, 2, 3, 4 mg tablets; 0.5, 1, 2, 3, 4 mg orally disintegrating tablets; 1 mg/mL oral solution
Parenteral: 12.5, 25, 37.5, 50 mg powder for injection; long-acting injectable 25, 37.5, 50 mg

**Thioridazine (generic, Mellaril)**
Oral: 10, 15, 25, 50, 100, 150, 200 mg tablets; 30 mg/mL concentrate

**Thiothixene (generic, Navane)**
Oral: 1, 2, 5, 10, 20 mg capsules

**Trifluoperazine (generic)**
Oral: 1, 2, 5, 10 mg tablets

**Ziprasidone (Geodon)**
Oral: 20, 40, 60, 80 mg capsules
Parenteral: 20 mg powder for IM injection

## MOOD STABILIZERS

**Carbamazepine (generic, Tegretol)**
Oral: 200 mg tablets, 100 mg chewable tablets; 100 mg/5 mL oral suspension
Oral extended-release: 100, 200, 400 mg tablets; 100, 200, 300 mg capsules

**Divalproex (Depakote)**
Oral: 125, 250, 500 mg delayed-release tablets

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

**Topiramate (Topamax)**
Oral: 25, 50, 100, 200 mg tablets

**Valproic acid (generic, Depakene)**
Oral: 250 mg capsules; 250 mg/5 mL syrup

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## CASE STUDY ANSWER*

Schizophrenia is characterized by a disintegration of thought processes and emotional responsiveness. Symptoms commonly include auditory hallucinations, paranoid or bizarre delusions, disorganized thinking and speech, and social and occupational dysfunction. For many patients, typical (eg, haloperidol) and atypical agents (eg, risperidone) are of equal efficacy for treating positive symptoms. Atypical agents are often more effective for treating negative symptoms and cognitive dysfunction and have lower risk of tardive dyskinesia and hyperprolactinemia. Other indications for the use of selected antipsychotics include bipolar disorder, psychotic depression, Tourette's syndrome, disturbed behavior in patients with Alzheimer's disease and in the case of older drugs (eg, chlorpromazine), treatment of emesis and pruritus.

*Case Study Answer contributed by A.J. Trevor

CHAPTER 30

# Antidepressant Agents

Charles DeBattista, MD

## CASE STUDY

A 47-year-old woman presents to her primary care physician with a chief complaint of fatigue. She indicates that she was promoted to senior manager in her company approximately 11 months earlier. Although her promotion was welcome and came with a sizable raise in pay, it resulted in her having to move away from an office and group of colleagues she very much enjoyed. In addition, her level of responsibility increased dramatically. The patient reports that for the last 7 weeks, she has been waking up at 3 AM every night and been unable to go back to sleep. She dreads the day and the stresses of the workplace. As a consequence, she is not eating as well as she might and has dropped 7% of her body weight in the last 3 months. She also reports being so stressed that she breaks down crying in the office occasionally and has been calling in sick frequently. When she comes home, she finds she is less motivated to attend to chores around the house and has no motivation, interest, or energy to pursue recreational activities that she once enjoyed such as hiking. She describes herself as "chronically miserable and worried all the time." Her medical history is notable for chronic neck pain from a motor vehicle accident for which she is being treated with tramadol and meperidine. In addition, she is on hydrochlorothiazide and propranolol for hypertension. The patient has a history of one depressive episode after a divorce that was treated successfully with fluoxetine. Medical workup including complete blood cell count, thyroid function tests, and a chemistry panel reveals no abnormalities. She is started on fluoxetine for a presumed major depressive episode and referred for cognitive behavioral psychotherapy. What CYP450 and pharmacodynamic interactions might be associated with fluoxetine use in this patient? Which class of antidepressants would be contraindicated in this patient?

The diagnosis of depression still rests primarily on the clinical interview. Major depressive disorder (MDD) is characterized by depressed mood most of the time for at least 2 weeks and/or loss of interest or pleasure in most activities. In addition, depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy. Thoughts of guilt, worthlessness, and suicide are common. Coronary artery disease, diabetes, and stroke appear to be more common in depressed patients, and depression may considerably worsen the prognosis for patients with a variety of comorbid medical conditions.

According to a 2007 report by the Centers for Disease Control and Prevention, antidepressant drugs were the most commonly prescribed medications in the USA at the time of the survey. The wisdom of such widespread use of antidepressants is debated. However, it is clear that American physicians have been increasingly inclined to use antidepressants to treat a host of conditions and that patients have been increasingly receptive to their use.

The primary indication for antidepressant agents is the treatment of MDD. Major depression, with a lifetime prevalence of around 17% in the USA and a point prevalence of 5%, is associated with substantial morbidity and mortality. MDD represents one of the most common causes of disability in the developed world. In addition, major depression is commonly associated with a variety of medical conditions—from chronic pain to coronary artery disease. When depression coexists with other medical conditions, the patient's disease burden increases, and the quality of life—and often the prognosis for effective treatment—decreases significantly.

Some of the growth in antidepressant use may be related to the broad application of these agents for conditions other than major depression. For example, antidepressants have received Food and Drug Administration (FDA) approvals for the treatment

of panic disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). In addition, antidepressants are commonly used to treat pain disorders such as neuropathic pain and the pain associated with fibromyalgia. Some antidepressants are used for treating premenstrual dysphoric disorder (PMDD), mitigating the vasomotor symptoms of menopause, and treating stress urinary incontinence. Thus, antidepressants have a broad spectrum of use in medical practice. However, their primary use remains the treatment for MDD.

## Pathophysiology of Major Depression

There has been a marked shift in the last decade in our understanding of the pathophysiology of major depression. In addition to the older idea that a deficit in function or amount of monoamines (the **monoamine hypothesis**) is central to the biology of depression, there is evidence that neurotrophic and endocrine factors play a major role (the **neurotrophic hypothesis**). Histologic studies, structural and functional brain imaging research, genetic findings, and steroid research all suggest a complex pathophysiology for MDD with important implications for drug treatment.

## Neurotrophic Hypothesis

There is substantial evidence that nerve growth factors such as **brain-derived neurotrophic factor (BDNF)** are critical in the regulation of neural plasticity, resilience, and neurogenesis. The evidence suggests that depression is associated with the loss of neurotrophic support and that effective antidepressant therapies increase neurogenesis and synaptic connectivity in cortical areas such as the hippocampus. BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia (Figure 30–1).

Several lines of evidence support the neurotrophic hypothesis. Animal and human studies indicate that stress and pain are associated with a drop in BDNF levels and that this loss of neurotrophic support contributes to atrophic structural changes in the hippocampus and perhaps other areas such as the medial frontal cortex and anterior cingulate. The hippocampus is known to be

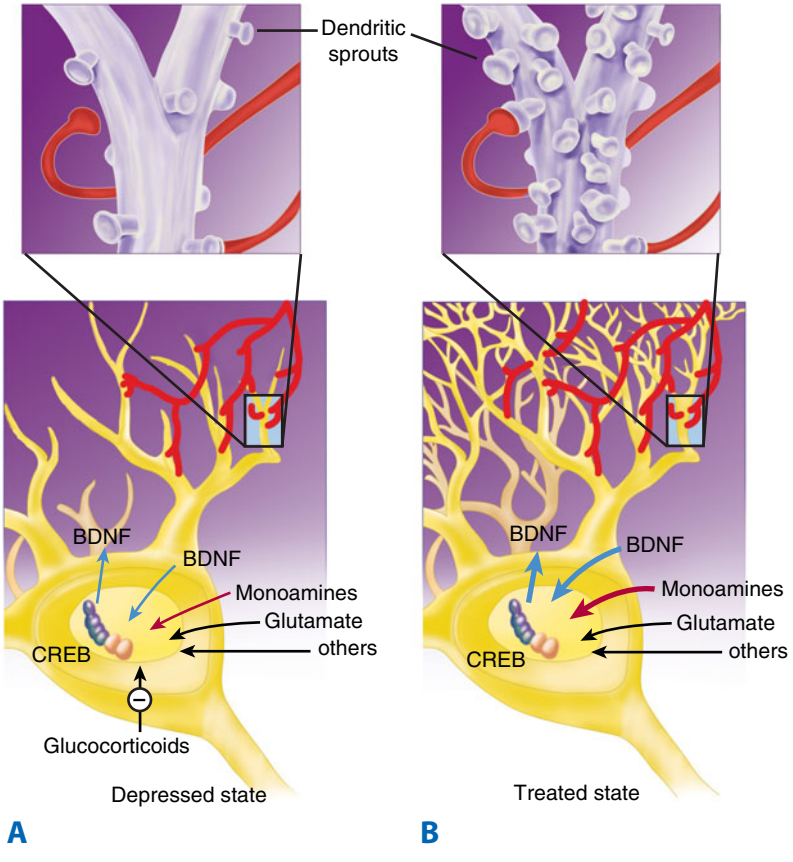



**FIGURE 30–1** The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor, BDNF) and hormones appear to play a major role in the development of major depression (**A**). Successful treatment results in changes in these factors (**B**). CREB, cAMP response element-binding (protein). BDNF, brain-derived neurotrophic factor. (Redrawn, with permission, from Nestler EJ: Neurobiology of depression. Neuron 2002;34[1]:13–25.)

important both in contextual memory and regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Likewise, the anterior cingulate plays a role in the integration of emotional stimuli and attention functions, whereas the medial orbital frontal cortex is also thought to play a role in memory, learning, and emotion.

Over 30 structural imaging studies suggest that major depression is associated with a 5–10% loss of volume in the hippocampus, although some studies have not replicated this finding. Depression and chronic stress states have also been associated with a substantial loss of volume in the anterior cingulate and medial orbital frontal cortex. Loss of volume in structures such as the hippocampus also appears to increase as a function of the duration of illness and the amount of time that the depression remains untreated.

Another source of evidence supporting the neurotrophic hypothesis of depression comes from studies of the direct effects of BDNF on emotional regulation. Direct infusion of BDNF into the midbrain, hippocampus, and lateral ventricles of rodents has an antidepressant-like effect in animal models. Moreover, all known classes of antidepressants are associated with an increase in BDNF levels in animal models with chronic (but not acute) administration. This increase in BDNF levels is consistently associated with increased neurogenesis in the hippocampus in these animal models. Other interventions thought to be effective in the treatment of major depression, including electroconvulsive therapy, also appear to robustly stimulate BDNF levels and hippocampus neurogenesis in animal models.

Human studies seem to support the animal data on the role of neurotrophic factors in stress states. Depression appears to be associated with a drop in BDNF levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity. Conversely, administration of antidepressants increases BDNF levels in clinical trials and may be associated with an increase in hippocampus volume in some patients.

Much evidence supports the neurotrophic hypothesis of depression, but not all evidence is consistent with this concept. Animal studies in BDNF knockout mice have not always suggested an increase in depressive or anxious behaviors that would be expected with a deficiency of BDNF. In addition, some animal studies have found an increase in BDNF levels after some types of social stress and an increase rather than a decrease in depressive behaviors with lateral ventricle injections of BDNF.

A proposed explanation for the discrepant findings on the role of neurotrophic factors in depression is that there are polymorphisms for BDNF that may yield very different effects. Mutations in the *BDNF* gene have been found to be associated with altered anxiety and depressive behavior in both animal and human studies.

Thus, the neurotrophic hypothesis continues to be intensely investigated and has yielded new insights and potential targets in the treatment of MDD.

## Monoamines and Other Neurotransmitters

The monoamine hypothesis of depression (Figure 30–2) suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT), norepinephrine (NE), and dopamine (DA).

Evidence to support the monoamine hypothesis comes from several sources. It has been known for many years that reserpine treatment, which is known to deplete monoamines, is associated with depression in a subset of patients. Similarly, depressed patients who respond to serotonergic antidepressants such as fluoxetine often rapidly suffer relapse when given diets free of tryptophan, a precursor of serotonin synthesis. Patients who respond to noradrenergic antidepressants such as desipramine are less likely to relapse on a tryptophan-free diet. Moreover, depleting catecholamines in depressed patients who have previously responded to noradrenergic agents likewise tends to be associated with relapse. Administration of an inhibitor of norepinephrine synthesis is also associated with a rapid return of depressive symptoms in patients who respond to noradrenergic but not necessarily in patients who had responded to serotonergic antidepressants.

Another line of evidence supporting the monoamine hypothesis comes from genetic studies. A functional polymorphism exists for the promoter region of the serotonin transporter gene, which regulates how much of the transporter protein is available. Subjects who are homozygous for the s (short) allele may be more vulnerable to developing major depression and suicidal behavior in response to stress. In addition, homozygotes for the s allele may also be less likely to respond to and tolerate serotonergic antidepressants. Conversely, subjects with the l (long) allele tend to be more resistant to stress and may be more likely to respond to serotonergic antidepressants.

Studies of depressed patients have sometimes shown an alteration in monoamine function. For example, some studies have found evidence of alteration in serotonin receptor numbers ($5\text{-HT}_{1A}$ and $5\text{-HT}_{2C}$) or norepinephrine ($\alpha_2$) receptors in depressed and suicidal patients, but these findings have not been consistent. A reduction in the primary serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid is associated with violent and impulsive behavior, including violent suicide attempts. However, this finding is not specific to major depression and is associated more generally with violent and impulsive behavior.

Finally, perhaps the most convincing line of evidence supporting the monoamine hypothesis is the fact that (at the time of this writing) all available antidepressants appear to have significant effects on the monoamine system. All classes of antidepressants appear to enhance the synaptic availability of 5-HT, norepinephrine, or dopamine. Attempts to develop antidepressants that work on other neurotransmitter systems have not been effective to date.

The monoamine hypothesis, like the neurotrophic hypothesis, is at best incomplete. Many studies have not found an alteration in function or levels of monoamines in depressed patients. In addition, some candidate antidepressant agents under study do not act directly on the monoamine system. These include glutamate antagonists, melatonin agonists, and glucocorticoid-specific agents. Thus, monoamine function appears to be an important but not exclusive factor in the pathophysiology of depression.

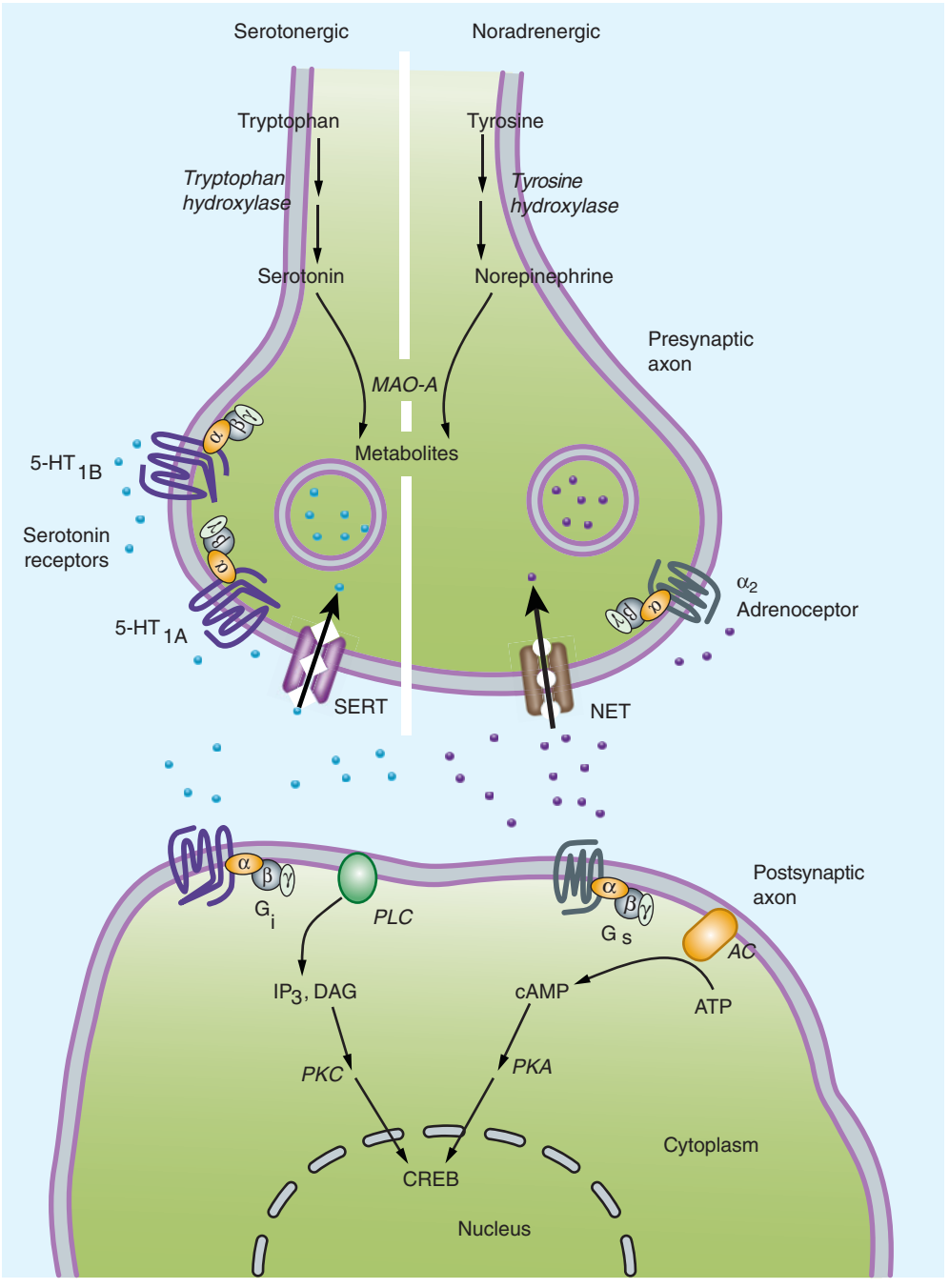



**FIGURE 30–2** The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; $IP_3$, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter. (Redrawn, with permission, from Belmaker R, Agam G: Major depressive disorder. N Engl J Med 2008;358:59.)

## Neuroendocrine Factors in the Pathophysiology of Depression

Depression is known to be associated with a number of hormonal abnormalities. Among the most replicated of these findings are abnormalities in the HPA axis in patients with MDD. Moreover, MDD is associated with elevated cortisol levels (Figure 30–1), nonsuppression of adrenocorticotropic hormone (ACTH) release in the dexamethasone suppression test, and chronically elevated levels of corticotropin-releasing hormone. The significance of these HPA abnormalities is unclear, but they are thought to indicate a dysregulation of the stress hormone axis. More severe types of depression, such as psychotic depression, tend to be associated with HPA abnormalities more commonly than milder forms of major depression. It

is well known that both exogenous glucocorticoids and endogenous elevation of cortisol are associated with mood symptoms and cognitive deficits similar to those seen in MDD.

Thyroid dysregulation has also been reported in depressed patients. Up to 25% of depressed patients are reported to have abnormal thyroid function. These include a blunting of response of thyrotropin to thyrotropin-releasing hormone, and elevations in circulating thyroxine during depressed states. Clinical hypothyroidism often presents with depressive symptoms, which resolve with thyroid hormone supplementation. Thyroid hormones are also commonly used in conjunction with standard antidepressants to augment therapeutic effects of the latter.

Finally, sex steroids are also implicated in the pathophysiology of depression. Estrogen deficiency states, which occur in the postpartum and postmenopausal periods, are thought to play a role in the etiology of depression in some women. Likewise, severe testosterone deficiency in men is sometimes associated with depressive symptoms. Hormone replacement therapy in hypogonadal men and women may be associated with an improvement in mood and depressive symptoms.

## Integration of Hypotheses Regarding the Pathophysiology of Depression

The several pathophysiologic hypotheses just described are not mutually exclusive. It is evident that the monoamine, neuroendocrine, and neurotrophic systems are interrelated in important ways. For example, HPA and steroid abnormalities may contribute to suppression of transcription of the *BDNF* gene. Glucocorticoid receptors are found in high density in the hippocampus. Binding of these hippocampal glucocorticoid receptors by cortisol during chronic stress states such as major depression may decrease BDNF synthesis and may result in volume loss in stress-sensitive regions such as the hippocampus. The chronic activation of monoamine receptors by antidepressants appears to have the opposite effect of stress and results in an increase in BDNF transcription. In addition, activation of monoamine receptors appears to down-regulate the HPA axis and may normalize HPA function.

One of the weaknesses of the monoamine hypothesis is the fact that amine levels increase immediately with antidepressant use, but maximum beneficial effects of antidepressants are not seen for many weeks. The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects. Appreciable protein synthesis of products such as BDNF typically takes 2 weeks or longer and coincides with the clinical course of antidepressant treatment.

# ■ BASIC PHARMACOLOGY OF ANTIDEPRESSANTS

## Chemistry & Subgroups

The currently available antidepressants make up a remarkable variety of chemical types. These differences and the differences in their molecular targets provide the basis for distinguishing several subgroups.

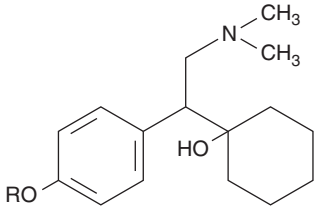
### A. Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) represent a chemically diverse class of agents that have as their primary action the inhibition of the serotonin transporter (SERT) (Figure 30–3). Fluoxetine was introduced in the United States in 1988 and quickly became one of the most commonly prescribed medications in medical practice. The development of fluoxetine emerged out of the search for chemicals that had high affinity for monoamine receptors but lacked the affinity for histamine, acetylcholine, and α adrenoceptors that is seen with the tricyclic antidepressants (TCAs). There are currently six available SSRIs, and they are the most common antidepressants in clinical use. In addition to their use in major depression, SSRIs have indications in GAD, PTSD, OCD, panic disorder, PMDD, and bulimia. **Fluoxetine, sertraline,** and **citalopram** exist as isomers and are formulated in the racemic forms, whereas **paroxetine** and **fluvoxamine** are not optically active. **Escitalopram** is the *S* enantiomer of citalopram. As with all antidepressants, SSRIs are highly lipophilic. The popularity of SSRIs stems largely from their ease of use, safety in overdose, relative tolerability, cost (all except escitalopram are generically available), and broad spectrum of uses.

### B. Serotonin-Norepinephrine Reuptake Inhibitors

Two classes of antidepressants act as combined serotonin and norepinephrine reuptake inhibitors: selective **serotonin-norepinephrine reuptake inhibitors (SNRIs)** and **TCAs.**

***1. Selective serotonin-norepinephrine reuptake inhibitors***—The SNRIs include **venlafaxine,** its metabolite **desvenlafaxine,** and **duloxetine.** Another SNRI, **milnacipran,** has been approved for the treatment of fibromyalgia in the USA but has been studied extensively as an antidepressant. It has been available in Europe for several years. In addition to their use in major depression, other applications of the SNRIs include the treatment of pain disorders including neuropathies and fibromyalgia. SNRIs are also used in the treatment of generalized anxiety, stress urinary incontinence, and vasomotor symptoms of menopause.




R = $CH_3$ : **Venlafaxine**
R = H : **Desvenlafaxine**

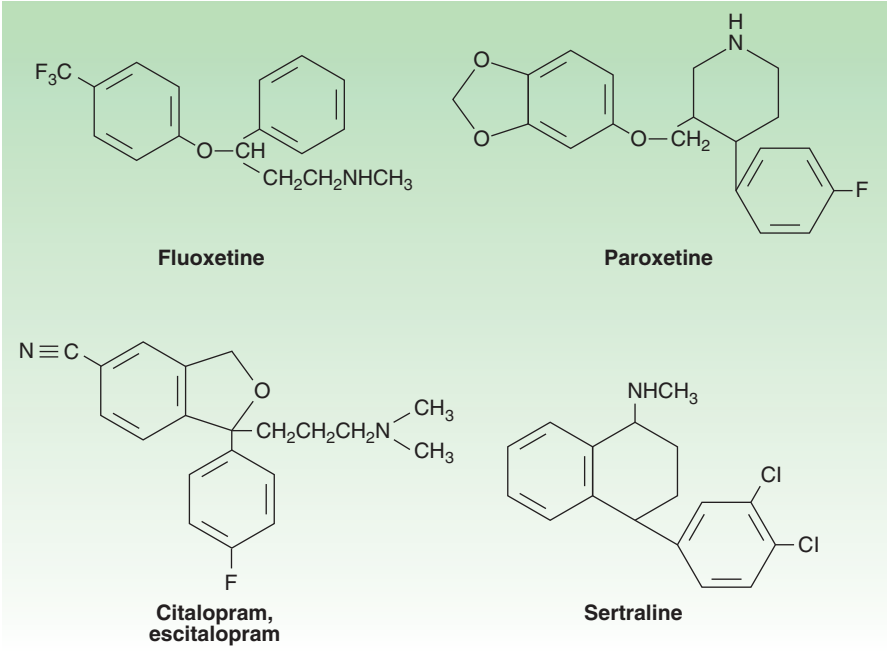
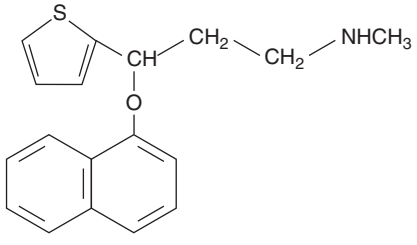



**FIGURE 30–3** Structures of several selective serotonin reuptake inhibitors.

SNRIs are chemically unrelated to each other. Venlafaxine was discovered in the process of evaluating chemicals that inhibit binding of imipramine. Venlafaxine's in vivo effects are similar to those of imipramine but with a more favorable adverse-effect profile. All SNRIs bind the serotonin (SERT) and norepinephrine (NET) transporters, as do the TCAs. However, unlike the TCAs, the SNRIs do not have much affinity for other receptors. Venlafaxine and desvenlafaxine are bicyclic compounds, whereas duloxetine is a three-ring structure unrelated to the TCAs. Milnacipran contains a cyclopropane ring and is provided as a racemic mixture.



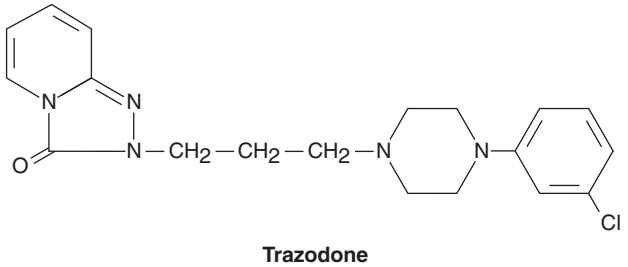

**Duloxetine**

***2. Tricyclic antidepressants—***The TCAs were the dominant class of antidepressants until the introduction of SSRIs in the 1980s and 1990s. Nine TCAs are available in the USA, and they all have an iminodibenzyl (tricyclic) core (Figure 30–4). The chemical differences between the TCAs are relatively subtle. For example, the prototype TCA **imipramine** and its metabolite, **desipramine,** differ by only a methyl group in the propylamine side chain. However, this minor difference results in a substantial change in their pharmacologic profiles. Imipramine is highly anticholinergic and is a relatively strong serotonin as well as norepinephrine reuptake inhibitor. In contrast, desipramine is much less anticholinergic and is a more potent and somewhat more selective norepinephrine reuptake inhibitor than is imipramine.

At the present time, the TCAs are used primarily in depression that is unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs. Their loss of popularity stems in large part from relatively poorer tolerability compared with newer agents, to difficulty of use, and to lethality in overdose. Other uses for TCAs include the treatment of pain conditions, enuresis, and insomnia.

### C. 5-HT$_2$ Antagonists

Two antidepressants are thought to act primarily as antagonists at the 5-HT$_2$ receptor: **trazodone** and **nefazodone**. Trazodone's structure includes a triazolo moiety that is thought to impart antidepressant effects. Its primary metabolite, m-chlorphenylpiperazine (m-cpp), is a potent 5-HT$_2$ antagonist. Trazodone was among the most commonly prescribed antidepressants until it was supplanted by the SSRIs in the late 1980s. The most common use of trazodone in current practice is as an unlabeled hypnotic, since it is highly sedating and not associated with tolerance or dependence.




**Trazodone**

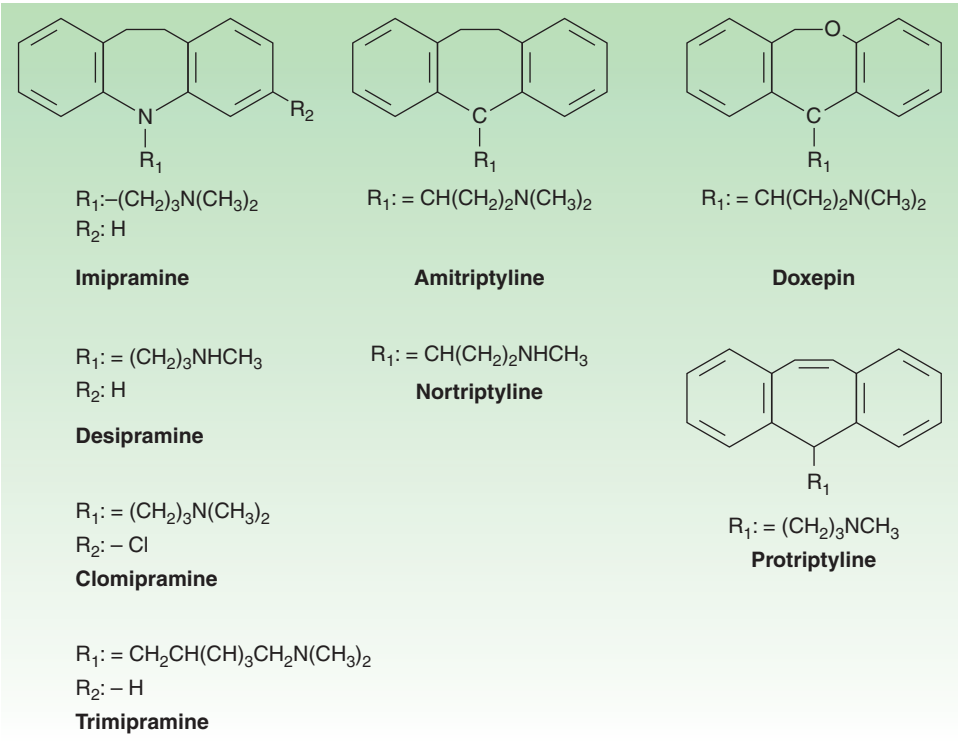
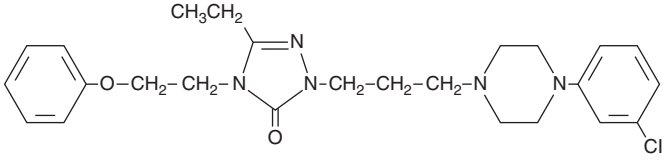



**FIGURE 30–4** Structures of the tricyclic antidepressants (TCAs).

Nefazodone is chemically related to trazodone. Its primary metabolites, hydroxynefazodone and m-cpp are both inhibitors of the 5-$HT_2$ receptor. Nefazodone received an FDA black box warning in 2001 implicating it in hepatotoxicity, including lethal cases of hepatic failure. Though still available generically, nefazodone is no longer commonly prescribed. The primary indications for both nefazodone and trazodone are major depression, although both have also been used in the treatment of anxiety disorders.




**Nefazodone**

## D. Tetracyclic and Unicyclic Antidepressants

A number of antidepressants do not fit neatly into the other classes. Among these are **bupropion, mirtazapine, amoxapine,** and **maprotiline** (Figure 30–5). Bupropion has a unicyclic aminoketone structure. Its unique structure results in a different side-effect profile than most antidepressants (described below). Bupropion somewhat resembles amphetamine in chemical structure and, like the stimulant, has central nervous system (CNS) activating properties.

Mirtazapine was introduced in 1994 and, like bupropion, is one of the few antidepressants not commonly associated with sexual side effects. It has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds.

Mirtazapine, amoxapine, and maprotiline have tetracyclic structures. Amoxapine is the *N*-methylated metabolite of loxapine, an older antipsychotic drug. Amoxapine and maprotiline share structural similarities and side effects comparable to the TCAs. As a result, these tetracyclics are not commonly prescribed in current practice. Their primary use is in MDD that is unresponsive to other agents.

## E. Monoamine Oxidase Inhibitors

Arguably the first modern class of antidepressants, monoamine oxidase inhibitors (MAOIs) were introduced in the 1950s but are now rarely used in clinical practice because of toxicity and potentially lethal food and drug interactions. Their primary use now is in the treatment of depression unresponsive to other antidepressants. However, MAOIs have also been used historically to treat anxiety states, including social anxiety and panic disorder. In addition, selegiline is used for the treatment of Parkinson's disease (see Chapter 28).

Current MAOIs include the hydrazine derivatives **phenelzine** and **isocarboxazid** and the non-hydrazines **tranylcypromine, selegiline,** and **moclobemide** (the latter is not available in the USA). The hydrazines and tranylcypromine bind irreversibly and nonselectively with MAO-A and -B, whereas other MAOIs may have more selective or reversible properties. Some of the MAOIs

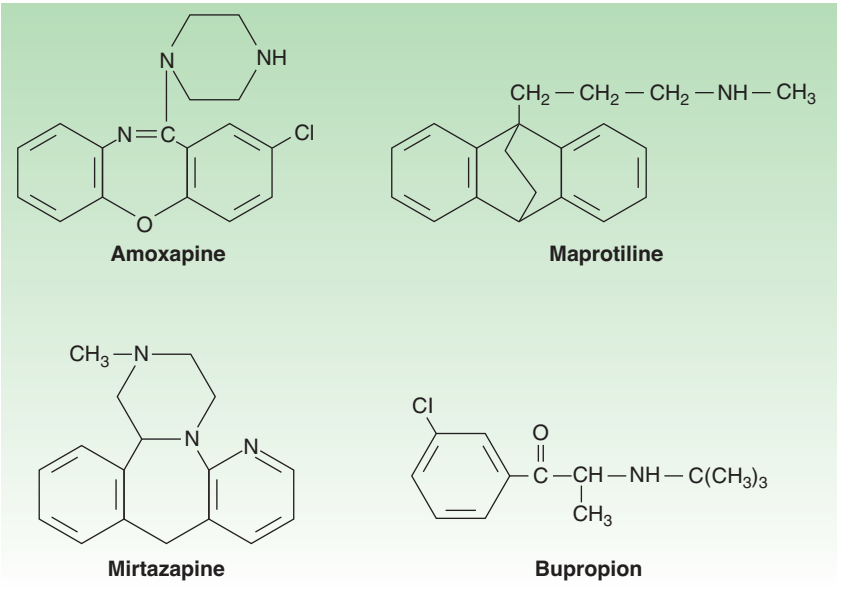
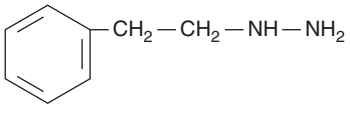
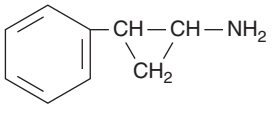



**FIGURE 30–5** Structures of the tetracyclics, amoxapine, maprotiline, and mirtazapine and the unicyclic, bupropion.

such as tranylcypromine resemble amphetamine in chemical structure, whereas other MAOIs such as selegiline have amphetamine-like metabolites. As a result, these MAOIs tend to have substantial CNS-stimulating effects.



Phenelzine



Tranylcypromine

## Pharmacokinetics

The antidepressants share several pharmacokinetic features (Table 30–1). Most have fairly rapid oral absorption, achieve peak plasma levels within 2–3 hours, are tightly bound to plasma proteins, undergo hepatic metabolism, and are renally cleared. However, even within classes, the pharmacokinetics of individual antidepressants varies considerably.

### A. Selective Serotonin Reuptake Inhibitors

The prototype SSRI, fluoxetine, differs from other SSRIs in some important respects (Table 30–1). Fluoxetine is metabolized to an active product, norfluoxetine, which may have plasma concentrations greater than those of fluoxetine. The elimination half-life of norfluoxetine is about three times longer than fluoxetine and contributes to the longest half-life of all the SSRIs. As a result, fluoxetine has to be discontinued 4 weeks or longer before an MAOI can be administered to mitigate the risk of serotonin syndrome.

Fluoxetine and paroxetine are potent inhibitors of the CYP2D6 isoenzyme, and this contributes to potential drug interactions (see Drug Interactions). In contrast, fluvoxamine is an inhibitor of CYP3A4, whereas citalopram, escitalopram, and sertraline have more modest CYP interactions.

### B. Serotonin-Norepinephrine Reuptake Inhibitors

***1. Selective serotonin-norepinephrine reuptake inhibitors—***Venlafaxine is extensively metabolized in the liver via the CYP2D6 isoenzyme to *O*-desmethylvenlafaxine (desvenlafaxine). Both have similar half-lives of about 11 hours. Despite the relatively short half-lives, both drugs are available in formulations that allow once-daily dosing. Venlafaxine and desvenlafaxine have the lowest protein binding of all antidepressants (27–30%). Unlike most antidepressants, desvenlafaxine is conjugated and does not undergo extensive oxidative metabolism. At least 45% of desvenlafaxine is excreted unchanged in the urine compared with 4–8% of venlafaxine.

Duloxetine is well absorbed and has a half-life of about 12 hours but is dosed once daily. It is tightly bound to protein (97%) and undergoes extensive oxidative metabolism via CYP2D6 and CYP1A2. Hepatic impairment significantly alters duloxetine levels unlike desvenlafaxine.

***2. Tricyclic antidepressants—***The TCAs tend to be well absorbed and have long half-lives (Table 30–1). As a result, most are dosed once daily at night because of their sedating effects. TCAs undergo extensive metabolism via demethylation, aromatic hydroxylation, and glucuronide conjugation. Only about 5% of TCAs are excreted unchanged in the urine. The TCAs are

**TABLE 30–1 Pharmacokinetic profiles of selected antidepressants.**

| Class, Drug | Bioavailability (%) | Plasma $t_{1/2}$ (hours) | Active Metabolite $t_{1/2}$ (hours) | Volume of Distribution (L/kg) | Protein Binding (%) |
|---|---|---|---|---|---|
| **SSRIs** | | | | | |
| Citalopram | 80 | 33–38 | ND | 15 | 80 |
| Escitalopram | 80 | 27–32 | ND | 12–15 | 80 |
| Fluoxetine | 70 | 48–72 | 180 | 12–97 | 95 |
| Fluvoxamine | 90 | 14–18 | 14–16 | 25 | 80 |
| Paroxetine | 50 | 20–23 | ND | 28–31 | 94 |
| Sertraline | 45 | 22–27 | 62–104 | 20 | 98 |
| **SNRIs** | | | | | |
| Duloxetine | 50 | 12–15 | ND | 10–14 | 90 |
| Milnacipran | 85–90 | 6–8 | ND | 5–6 | 13 |
| Venlafaxine[1] | 45 | 8–11 | 9–13 | 4–10 | 27 |
| **Tricyclics** | | | | | |
| Amitriptyline | 45 | 31–46 | 20–92 | 5–10 | 90 |
| Clomipramine | 50 | 19–37 | 54–77 | 7–20 | 97 |
| Imipramine | 40 | 9–24 | 14–62 | 15–30 | 84 |
| **5-$HT_2$ antagonists** | | | | | |
| Nefazodone | 20 | 2–4 | ND | 0.5–1 | 99 |
| Trazodone | 95 | 3–6 | ND | 1–3 | 96 |
| **Tetracyclics and unicyclic** | | | | | |
| Amoxapine | ND | 7–12 | 5–30 | 0.9–1.2 | 90 |
| Bupropion | 70 | 11–14 | 15–25 | 20–30 | 84 |
| Maprotiline | 70 | 43–45 | ND | 23–27 | 88 |
| Mirtazapine | 50 | 20–40 | 20–40 | 3–7 | 85 |
| **MAOIs** | | | | | |
| Phenelzine | ND | 11 | ND | ND | ND |
| Selegiline | 4 | 8–10 | 9–11 | 8–10 | 99 |

[1]Desvenlafaxine has similar properties but is less completely metabolized.

MAOIs, monoamine oxidase inhibitors; ND, no data found; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

substrates of the CYP2D6 system, and the serum levels of these agents tend to be substantially influenced by concurrent administration of drugs such as fluoxetine. In addition, genetic polymorphism for CYP2D6 may result in low or extensive metabolism of the TCAs.

The secondary amine TCAs, including desipramine and nortriptyline, lack active metabolites and have fairly linear kinetics. These TCAs have a wide therapeutic window, and serum levels are reliable in predicting response and toxicity.

### C. 5-$HT_2$ Antagonists

Trazodone and nefazodone are rapidly absorbed and undergo extensive hepatic metabolism. Both drugs are extensively bound to protein and have limited bioavailability because of extensive metabolism. Their short half-lives generally require split dosing when used as antidepressants. However, trazodone is often prescribed as a single dose at night as a hypnotic in lower doses than are used in the treatment of depression. Both trazodone and nefazodone have active metabolites that also exhibit 5-$HT_2$ antagonism. Nefazodone is a potent inhibitor of the CYP3A4 system and may interact with drugs metabolized by this enzyme (see Drug Interactions).

### D. Tetracyclic and Unicyclic Agents

Bupropion is rapidly absorbed and has a mean protein binding of 85%. It undergoes extensive hepatic metabolism and has a substantial first-pass effect. It has three active metabolites including hydroxybupropion; the latter is being developed as an antidepressant. Bupropion has a biphasic elimination with the first phase lasting about 1 hour and the second phase lasting 14 hours.

Amoxapine is also rapidly absorbed with protein binding of about 85%. The half-life is variable, and the drug is often given in

divided doses. Amoxapine undergoes extensive hepatic metabolism. One of the active metabolites, 7-hydroxyamoxapine, is a potent $D_2$ blocker and is associated with antipsychotic effects. Maprotiline is similarly well absorbed orally and 88% bound to protein. It undergoes extensive hepatic metabolism.

Mirtazapine is demethylated followed by hydroxylation and glucuronide conjugation. Several CYP isozymes are involved in the metabolism of mirtazapine, including 2D6, 3A4, and 1A2. The half-life of mirtazapine is 20–40 hours, and it is usually dosed once in the evening because of its sedating effects.

### E. Monoamine Oxidase Inhibitors

The different MAOIs are metabolized via different pathways but tend to have extensive first-pass effects that may substantially decrease bioavailability. Tranylcypromine is ring hydroxylated and *N*-acetylated, whereas acetylation appears to be a minor pathway for phenelzine. Selegiline is *N*-demethylated and then hydroxylated. The MAOIs are well absorbed from the gastrointestinal tract.

Because of the prominent first-pass effects and their tendency to inhibit MAO in the gut (resulting in tyramine pressor effects), alternative routes of administration are being developed. For example, selegiline is available in both transdermal and sublingual forms that bypass both gut and liver. These routes decrease the risk of food interactions and provide substantially increased bioavailability.

## Pharmacodynamics

As previously noted, all currently available antidepressants enhance monoamine neurotransmission by one of several mechanisms. The most common mechanism is inhibition of the activity of SERT, NET, or both monoamine transporters (Table 30–2). Antidepressants that inhibit SERT, NET, or both include the SSRIs and SNRIs (by definition), and the TCAs. Another mechanism for increasing the availability of monoamines is inhibition of their enzymatic degradation (the MAOIs). Additional strategies for enhancing monoamine tone include binding presynaptic autoreceptors (mirtazapine) or specific postsynaptic receptors (5-$HT_2$ antagonists and mirtazapine). Ultimately, the increased availability of monoamines for binding in the synaptic cleft results in a cascade of events that enhance the transcription of some proteins and the inhibition of others. It is the net production of these proteins, including BDNF, glucocorticoid receptors, β adrenoceptors, and other proteins, that appears to determine the benefits as well as the toxicity of a given agent.

**TABLE 30–2 Antidepressant effects on several receptors and transporters.**

| Antidepressant | ACh M | $\alpha_1$ | $H_1$ | 5-$HT_2$ | NET | SERT |
|---|---|---|---|---|---|---|
| Amitriptyline | +++ | +++ | ++ | 0/+ | + | ++ |
| Amoxapine | + | ++ | + | +++ | ++ | + |
| Bupropion | 0 | 0 | 0 | 0 | 0/+ | 0 |
| Citalopram, escitalopram | 0 | 0 | 0 | | 0 | +++ |
| Clomipramine | + | ++ | + | + | + | +++ |
| Desipramine | + | + | + | 0/+ | +++ | + |
| Doxepin | ++ | +++ | +++ | 0/+ | + | + |
| Fluoxetine | 0 | 0 | 0 | 0/+ | 0 | +++ |
| Fluvoxamine | 0 | 0 | 0 | 0 | 0 | +++ |
| Imipramine | ++ | + | + | 0/+ | + | ++ |
| Maprotiline | + | + | ++ | 0/+ | ++ | 0 |
| Mirtazapine | 0 | 0 | +++ | + | + | 0 |
| Nefazodone | 0 | + | 0 | ++ | 0/+ | + |
| Nortriptyline | + | + | + | + | ++ | + |
| Paroxetine | + | 0 | 0 | 0 | + | +++ |
| Protriptyline | +++ | + | + | + | +++ | + |
| Sertraline | 0 | 0 | 0 | 0 | 0 | +++ |
| Trazodone | 0 | ++ | 0/+ | ++ | 0 | + |
| Trimipramine | ++ | ++ | +++ | 0/+ | 0 | 0 |
| Venlafaxine | 0 | 0 | 0 | 0 | + | ++ |

ACh M, acetylcholine muscarinic receptor; $\alpha_1$, alpha$_1$-adrenoceptor; $H_1$, histamine$_1$ receptor; 5-$HT_2$, serotonin 5-$HT_2$ receptor; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

### A. Selective Serotonin Reuptake Inhibitors

The serotonin transporter (SERT) is a glycoprotein with 12 transmembrane regions embedded in the axon terminal and cell body membranes of serotonergic neurons. When extracellular serotonin binds to receptors on the transporter, conformational changes occur in the transporter and serotonin, $Na^+$, and $Cl^-$ are moved into the cell. Binding of intracellular $K^+$ then results in return of the transporter to its original conformation and the release of serotonin inside the cell. SSRIs allosterically inhibit the transporter by binding the receptor at a site other than active binding site for serotonin. At therapeutic doses, about 80% of the activity of the transporter is inhibited. Functional polymorphisms exist for SERT that determine the activity of the transporter.

SSRIs have modest effects on other neurotransmitters. Unlike TCAs and SNRIs, there is little evidence that SSRIs have prominent effects on β adrenoceptors or the norepinephrine transporter, NET. Binding to the serotonin transporter is associated with tonic inhibition of the dopamine system, although there is substantial interindividual variability in this effect. The SSRIs do not bind aggressively to histamine, muscarinic, or other receptors.

### B. Drugs That Block Both Serotonin and Norepinephrine Transporters

A large number of antidepressants have mixed inhibitory effects on both serotonin and norepinephrine transporters. The newer agents in this class (venlafaxine and duloxetine) are denoted by the acronym SNRIs, whereas the agents in the older group are termed TCAs.

***1. Serotonin-norepinephrine reuptake inhibitors—***SNRIs bind both the serotonin and the norepinephrine transporters. The NET is structurally very similar to the 5-HT transporter. Like the serotonin transporter, it is a 12-transmembrane domain complex that allosterically binds norepinephrine. The NET also has a moderate affinity for dopamine.

Venlafaxine is a weak inhibitor of NET, whereas desvenlafaxine, duloxetine, and milnacipran are more balanced inhibitors of both SERT and NET. Nonetheless, the affinity of most SNRIs tends to be much greater for SERT than for NET. The SNRIs differ from the TCAs in that they lack the potent antihistamine, α-adrenergic blocking, and anticholinergic effects of the TCAs. As a result, the SNRIs tend to be favored over the TCAs in the treatment of MDD and pain syndromes because of their better tolerability.

***2. Tricyclic antidepressants—***The TCAs resemble the SNRIs in function, and their antidepressant activity is thought to relate primarily to their inhibition of 5-HT and norepinephrine reuptake. Within the TCAs, there is considerable variability in affinity for SERT versus NET. For example, clomipramine has relatively very little affinity for NET but potently binds SERT. This selectivity for the serotonin transporter contributes to clomipramine's known benefits in the treatment of OCD. On the other hand, the secondary amine TCAs, desipramine and nortriptyline, are relatively more selective for NET. Although the tertiary amine TCA imipramine has more serotonin effects initially, its metabolite, desipramine, then balances this effect with more NET inhibition.

Common adverse effects of the TCAs, including dry mouth and constipation, are attributable to the potent antimuscarinic effects of many of these drugs. The TCAs also tend to be potent antagonists of the histamine $H_1$ receptor. TCAs such as doxepin are sometimes prescribed as hypnotics and used in treatments for pruritus because of their antihistamine properties. The blockade of α adrenoceptors can result in substantial orthostatic hypotension, particularly in older patients.

### C. 5-$HT_2$ Antagonists

The principle action of both nefazodone and trazodone appears to be blockade of the 5-$HT_{2A}$ receptor. Inhibition of this receptor in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects. Conversely, agonists of the 5-$HT_{2A}$ receptor, eg, lysergic acid (LSD) and mescaline, are often hallucinogenic and anxiogenic. The 5-$HT_{2A}$ receptor is a G protein-coupled receptor and is distributed throughout the neocortex.

Nefazodone is a weak inhibitor of both SERT and NET but is a potent antagonist of the postsynaptic 5-$HT_{2A}$ receptor, as are its metabolites. Trazodone is also a weak but selective inhibitor of SERT with little effect on NET. Its primary metabolite, m-cpp, is a potent 5-$HT_2$ antagonist, and much of trazodone's benefits as an antidepressant might be attributed to this effect. Trazodone also has weak-to-moderate presynaptic α-adrenergic–blocking properties and is a modest antagonist of the $H_1$ receptor.

### D. Tetracyclic and Unicyclic Antidepressants

The actions of bupropion remain poorly understood. Bupropion and its major metabolite hydroxybupropion are modest-to-moderate inhibitors of norepinephrine and dopamine reuptake in animal studies. However, these effects seem less than are typically associated with antidepressant benefit. A more significant effect of bupropion is presynaptic release of catecholamines. In animal studies, bupropion appears to substantially increase the presynaptic availability of norepinephrine, and dopamine to a lesser extent. Bupropion has virtually no direct effects on the serotonin system.

Mirtazapine has a complex pharmacology. It is an antagonist of the presynaptic $\alpha_2$ autoreceptor and enhances the release of both norepinephrine and 5-HT. In addition, mirtazapine is an antagonist of 5-$HT_2$ and 5-$HT_3$ receptors. Finally, mirtazapine is a potent $H_1$ antagonist, which is associated with the drug's sedative effects.

The actions of amoxapine and maprotiline resemble those of TCAs such as desipramine. Both are potent NET inhibitors and less potent SERT inhibitors. In addition, both possess anticholinergic properties. Unlike the TCAs or other antidepressants, amoxapine is a moderate inhibitor of the postsynaptic $D_2$ receptor. As such, amoxapine possesses some antipsychotic properties.

### E. Monoamine Oxidase Inhibitors

MAOIs act by mitigating the actions of monoamine oxidase in the neuron and increasing monoamine content. There are two forms of monoamine oxidase. MAO-A is present in both dopamine and norepinephrine neurons and is found primarily in the brain, gut, placenta, and liver; its primary substrates are norepinephrine,

epinephrine, and serotonin. MAO-B is found primarily in serotonergic and histaminergic neurons and is distributed in the brain, liver, and platelets. MAO-B acts primarily on tyramine, phenylethylamine, and benzylamine. Both MAO-A and -B metabolize tryptamine and dopamine.

MAOIs are classified by their specificity for MAO-A or -B and whether their effects are reversible or irreversible. Phenelzine and tranylcypromine are examples of irreversible, nonselective MAOIs. Moclobemide is a reversible and selective inhibitor of MAO-A but is not available in the USA. Moclobemide can be displaced from MAO-A by tyramine, and this mitigates the risk of food interactions. In contrast, selegiline is an irreversible MAO-B–specific agent at low doses. Selegiline is useful in the treatment of Parkinson's disease at these low doses, but at higher doses it becomes a nonselective MAOI similar to other agents.

# CLINICAL PHARMACOLOGY OF ANTIDEPRESSANTS

## Clinical Indications

### A. Depression

The FDA indication for the use of the antidepressants in the treatment of major depression is fairly broad. Most antidepressants are approved for both acute and long-term treatment of major depression. Acute episodes of MDD tend to last about 6–14 months untreated, but at least 20% of episodes last 2 years or longer.

The goal of acute treatment of MDD is remission of all symptoms. Since antidepressants may not achieve their maximum benefit for 1–2 months or longer, it is not unusual for a trial of therapy to last 8–12 weeks at therapeutic doses. The antidepressants are successful in achieving remission in about 30–40% of patients within a single trial of 8–12 weeks. If an inadequate response is obtained, therapy is often switched to another agent or augmented by addition of another drug. For example, bupropion, an atypical antipsychotic, or mirtazapine might be added to an SSRI or SNRI to augment antidepressant benefit if monotherapy is unsuccessful. Seventy to eighty percent of patients are able to achieve remission with sequenced augmentation or switching strategies. Once an adequate response is achieved, continuation therapy is recommended for a minimum of 6–12 months to reduce the substantial risk of relapse.

Approximately 85% of patients who have a single episode of MDD will have at least one recurrence in a lifetime. Many patients have multiple recurrences, and these recurrences may progress to more serious, chronic, and treatment-resistant episodes. Thus, it is not unusual for patients to require maintenance treatment to prevent recurrences. Although maintenance treatment studies of more than 5 years are uncommon, long-term studies with TCAs, SNRIs, and SSRIs suggest a significant protective benefit when given chronically. Thus, it is commonly recommended that patients be considered for long-term maintenance treatment if they have had two or more serious MDD episodes in the previous 5 years or three or more serious episodes in a lifetime.

It is not clear whether antidepressants are useful for all subtypes of depression. For example, patients with bipolar depression may not benefit much from antidepressants even when added to mood stabilizers. In fact, the antidepressants are sometimes associated with switches into mania or more rapid cycling. There has also been some debate about the overall efficacy of antidepressants in unipolar depression, with some meta-analyses showing large effects and others showing more modest effects. Although this debate is not likely to be settled immediately, there is little debate that antidepressants have important benefits for most patients.

Psychotherapeutic interventions such as cognitive behavior therapy appear to be as effective as antidepressant treatment for mild to moderate forms of depression. However, cognitive behavior therapy tends to take longer to be effective and is generally more expensive than antidepressant treatment. Psychotherapy is often combined with antidepressant treatment, and the combination appears more effective than either strategy alone.

### B. Anxiety Disorders

After major depression, anxiety disorders represent the most common application of antidepressants. A number of SSRIs and SNRIs have been approved for all the major anxiety disorders, including PTSD, OCD, social anxiety disorder, GAD, and panic disorder. Panic disorder is characterized by recurrent episodes of brief overwhelming anxiety, which often occur without precipitant. Patients may begin to fear having an attack, or they avoid situations in which they might have an attack. In contrast, GAD is characterized by a chronic, free-floating anxiety and undue worry that tends to be chronic in nature. Although older antidepressants and drugs of the sedative-hypnotic class are still occasionally used for the treatment of anxiety disorders, SSRIs and SNRIs have largely replaced them.

The benzodiazepines (see Chapter 22) provide much more rapid relief of both generalized anxiety and panic than do any of the antidepressants. However, the antidepressants appear to be at least as effective and perhaps more effective than benzodiazepines in the long-term treatment of these anxiety disorders. Furthermore, antidepressants do not carry the risks of dependence and tolerance that may occur with the benzodiazepines.

OCD is known to respond to serotonergic antidepressants. It is characterized by repetitive anxiety-provoking thoughts (obsessions) or repetitive behaviors aimed at reducing anxiety (compulsions). Clomipramine and several of the SSRIs are approved for the treatment of OCD, and they are moderately effective. Behavior therapy is usually combined with the antidepressant for additional benefits.

Social anxiety disorder is an uncommonly diagnosed but a fairly common condition in which the patient experiences severe anxiety in social interactions. This anxiety may limit their ability to function adequately in their jobs or interpersonal relationships. Several SSRIs and venlafaxine are approved for the treatment of social anxiety. The efficacy of the SSRIs in the treatment of social anxiety is greater in some studies than their efficacy in the treatment of MDD.

PTSD is manifested when a traumatic or life-threatening event results in intrusive anxiety-provoking thoughts or imagery, hypervigilance, nightmares, and avoidance of situations that remind the patient of the trauma. SSRIs are considered first-line treatment for PTSD and can benefit a number of symptoms including anxious thoughts and hypervigilance. Other treatments, including psychotherapeutic interventions, are usually required in addition to antidepressants.

### C. Pain Disorders

It has been known for over 40 years that antidepressants possess analgesic properties independent of their mood effects. TCAs have been used in the treatment of neuropathic and other pain conditions since the 1960s. Medications that possess both norepinephrine and 5-HT reuptake blocking properties are often useful in treating pain disorders. Ascending corticospinal monoamine pathways appear to be important in the endogenous analgesic system. In addition, chronic pain conditions are commonly associated with major depression. TCAs continue to be commonly used for some of these conditions, and SNRIs are increasingly used. In 2010, duloxetine was approved for the treatment of chronic joint and muscle pain. As mentioned earlier, milnacipran has been approved for the treatment of fibromyalgia. Other SNRIs, eg, desvenlafaxine, are being investigated for a variety of pain conditions from postherpetic neuralgia to chronic back pain.

### D. Premenstrual Dysphoric Disorder

Approximately 5% of women in the child-bearing years will have prominent mood and physical symptoms during the late luteal phase of almost every cycle; these may include anxiety, depressed mood, irritability, insomnia, fatigue, and a variety of other physical symptoms. These symptoms are more severe than those typically seen in premenstrual syndrome (PMS) and can be quite disruptive to vocational and interpersonal activities. The SSRIs are known to be beneficial to many women with PMDD, and fluoxetine and sertraline have been approved for this indication. Treating for 2 weeks out of the month in the luteal phase may be as effective as continuous treatment. The rapid effects of SSRIs in PMDD may be associated with rapid increases in pregnenolone levels.

### E. Smoking Cessation

Bupropion was approved in 1997 as a treatment for smoking cessation. Approximately twice as many people treated with bupropion as with placebo have a reduced urge to smoke. In addition, patients taking bupropion appear to experience fewer mood symptoms and possibly less weight gain while withdrawing from nicotine dependence. Bupropion appears to be about as effective as nicotine patches in smoking cessation. The mechanism by which bupropion is helpful in this application is unknown, but the drug may mimic nicotine's effects on dopamine and norepinephrine and may antagonize nicotinic receptors. Nicotine is also known to have antidepressant effects in some people, and bupropion may substitute for this effect.

Other antidepressants may also have a role in the treatment of smoking cessation. Nortriptyline has been shown to be helpful in smoking cessation, but the effects have not been as consistent as those seen with bupropion.

### F. Eating Disorders

Bulimia nervosa and anorexia nervosa are potentially devastating disorders. Bulimia is characterized by episodic intake of large amounts of food (binges) followed by ritualistic purging through emesis, the use of laxatives, or other methods. Medical complications of the purging, such as hypokalemia, are common and dangerous. Anorexia is a disorder in which reduced food intake results in a loss of weight of 15% or more of ideal body weight, and the person has a morbid fear of gaining weight and a highly distorted body image. Anorexia is often chronic and may be fatal in 10% or more of cases.

Antidepressants appear to be helpful in the treatment of bulimia but not anorexia. Fluoxetine was approved for the treatment of bulimia in 1996, and other antidepressants have shown benefit in reducing the binge-purge cycle. The primary treatment for anorexia at this time is refeeding, family therapy, and cognitive behavioral therapy.

Bupropion may have some benefits in treating obesity. Nondepressed, obese patients treated with bupropion were able to lose somewhat more weight and maintain the loss relative to a similar population treated with placebo. However, the weight loss was not robust, and there appear to be more effective options for weight loss.

### G. Other Uses for Antidepressants

Antidepressants are used for many other on- and off-label applications. Enuresis in children is an older labeled use for some TCAs, but they are less commonly used now because of their side effects. The SNRI duloxetine is approved in Europe for the treatment of urinary stress incontinence. Many of the serotonergic antidepressants appear to be helpful for treating vasomotor symptoms in perimenopause. Desvenlafaxine is under consideration for FDA approval for the treatment of these vasomotor symptoms, and studies have suggested that SSRIs, venlafaxine, and nefazodone may also provide benefit. Although serotonergic antidepressants are commonly associated with inducing sexual adverse effects, some of these effects might prove useful for some sexual disorders. For example, SSRIs are known to delay orgasm in some patients. For this reason, SSRIs are sometimes used to treat premature ejaculation. In addition, bupropion has been used to treat sexual adverse effects associated with SSRI use, although its efficacy for this use has not been consistently demonstrated in controlled trials.

## Choosing an Antidepressant

The choice of an antidepressant depends first on the indication. Not all conditions are equally responsive to all antidepressants. However, in the treatment of MDD, it is difficult to demonstrate that one antidepressant is consistently more effective than another.

Thus, the choice of an antidepressant for the treatment of depression rests primarily on practical considerations such as cost, availability, adverse effects, potential drug interactions, the patient's history of response or lack thereof, and patient preference. Other factors such as the patient's age, gender, and medical status may also guide antidepressant selection. For example, older patients are particularly sensitive to the anticholinergic effects of the TCAs. On the other hand, the CYP3A4-inhibiting effects of the SSRI fluvoxamine may make this a problematic choice in some older patients because fluvoxamine may interact with many other medications that an older patient may require. There is some suggestion that female patients may respond to and tolerate serotonergic better than noradrenergic or TCA antidepressants, but the data supporting this gender difference have not been consistent. Patients with narrow-angle glaucoma may have an exacerbation with noradrenergic antidepressants, whereas bupropion and other antidepressants are known to lower the seizure threshold in epilepsy patients.

At present, SSRIs are the most commonly prescribed first-line agents in the treatment of both MDD and anxiety disorders. Their popularity comes from their ease of use, tolerability, and safety in overdose. The starting dose of the SSRIs is usually the same as the therapeutic dose for most patients, and so titration may not be required. In addition, most SSRIs are now generically available and inexpensive. Other agents, including the SNRIs, bupropion, and mirtazapine, are also reasonable first-line agents for the treatment of MDD. Bupropion, mirtazapine, and nefazodone are the antidepressants with the least association with sexual side effects and are often prescribed for this reason. However, bupropion is not thought to be effective in the treatment of the anxiety disorders and may be poorly tolerated in anxious patients. The primary indication for bupropion is in the treatment of major depression, including seasonal (winter) depression. Off-label uses of bupropion include the treatment of attention deficit hyperkinetic disorder (ADHD), and bupropion is commonly combined with other antidepressants to augment therapeutic response. The primary indication for mirtazapine is in the treatment of major depression. However, its strong antihistamine properties have contributed to its occasional use as a hypnotic and as an adjunctive treatment to more activating antidepressants.

The TCAs and MAOIs are now relegated to second- or third-line treatments for MDD. Both the TCAs and the MAOIs are potentially lethal in overdose, require titration to achieve a therapeutic dose, have serious drug interactions, and have many troublesome adverse effects. As a consequence, their use in the treatment of MDD or anxiety is now reserved for patients who have been unresponsive to other agents. Clearly, there are patients whose depression responds only to MAOIs or TCAs. Thus, TCAs and MAOIs are probably underused in treatment-resistant depressed patients.

The use of antidepressants outside the treatment of MDD tends to require specific agents. For example, the TCAs and SNRIs appear to be useful in the treatment of pain conditions, but other antidepressant classes appear to be far less effective. SSRIs and the highly serotonergic TCA, clomipramine, are effective in the treatment of OCD, but noradrenergic antidepressants have not proved to be as helpful for this condition. Bupropion and nortriptyline have usefulness in the treatment of smoking cessation, but SSRIs have not been proven useful. Thus, outside the treatment of depression, the choice of antidepressant is primarily dependent on the known benefit of a particular antidepressant or class for a particular indication.

## Dosing

The optimal dose of an antidepressant depends on the indication and on the patient. For SSRIs, SNRIs, and a number of newer agents, the starting dose for the treatment of depression is usually a therapeutic dose (Table 30–3). Patients who show little or no benefit after at least 4 weeks of treatment may benefit from a higher dose even though it has been difficult to show a clear advantage for higher doses with SSRIs, SNRIs, and other newer antidepressants. The dose is generally titrated to the maximum dosage recommended or to the highest dosage tolerated if the patient is not responsive to lower doses. Some patients may benefit from doses lower than the usual minimum recommended therapeutic dose. TCAs and MAOIs typically require titration to a therapeutic dosage over several weeks. Dosing of the TCAs may be guided by monitoring TCA serum levels.

Some anxiety disorders may require higher doses of antidepressants than are used in the treatment of major depression. For example, patients treated for OCD often require maximum or somewhat higher than maximum recommended MDD doses to achieve optimal benefits. Likewise, the minimum dose of paroxetine for the effective treatment of panic disorder is higher than the minimum dose required for the effective treatment of depression.

In the treatment of pain disorders, modest doses of TCAs are often sufficient. For example, 25–50 mg/d of imipramine might be beneficial in the treatment of pain associated with a neuropathy, but this would be a subtherapeutic dose in the treatment of MDD. In contrast, SNRIs are usually prescribed in pain disorders at the same doses used in the treatment of depression.

## Adverse Effects

Although some potential adverse effects are common to all antidepressants, most of their adverse effects are specific to a subclass of agents and to their pharmacodynamic effects. An FDA warning applied to all antidepressants is the risk of increased suicidality in patients under the age 25. The warning suggests that use of antidepressants is associated with suicidal ideation and gestures, but not completed suicides, in up to 4% of patients under 25 years who were prescribed antidepressant in clinical trials. This rate is about twice the rate seen with placebo treatment. For those over 25, there is either no increased risk or a reduced risk of suicidal thoughts and gestures on antidepressants, particularly after age 65. Although a small minority of patients may experience a treatment-emergent increase in suicidal ideation with antidepressants, the absence of treatment of a major depressive episode in all age groups is a particularly important risk factor in completed suicides.

**TABLE 30–3 Antidepressant dose ranges.**

| Drug | Usual Therapeutic Dosage (mg/d) |
|---|---|
| **SSRIs** | |
| Citalopram | 20–60 |
| Escitalopram | 10–30 |
| Fluoxetine | 20–60 |
| Fluvoxamine | 100–300 |
| Paroxetine | 20–60 |
| Sertraline | 50–200 |
| **SNRIs** | |
| Venlafaxine | 75–375 |
| Desvenlafaxine | 50–200 |
| Duloxetine | 40–120 |
| Milnacipran | 100–200 |
| **Tricyclics** | |
| Amitriptyline | 150–300 |
| Clomipramine | 100–250 |
| Desipramine | 150–300 |
| Doxepin | 150–300 |
| Imipramine | 150–300 |
| Nortriptyline | 50–150 |
| Protriptyline | 15–60 |
| Trimipramine maleate | 150–300 |
| **5-$HT_2$ antagonists** | |
| Nefazodone | 300–500 |
| Trazodone | 150–300 |
| **Tetracyclics and unicyclics** | |
| Amoxapine | 150–400 |
| Bupropion | 200–450 |
| Maprotiline | 150–225 |
| Mirtazapine | 15–45 |
| **MAOIs** | |
| Isocarboxazid | 30–60 |
| Phenelzine | 45–90 |
| Selegiline | 20–50 |
| Tranylcypromine | 30–60 |

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

### A. Selective Serotonin Reuptake Inhibitors

The adverse effects of the most commonly prescribed antidepressants—the SSRIs—can be predicted from their potent inhibition of SERT. SSRIs enhance serotonergic tone, not just in the brain but throughout the body. Increased serotonergic activity in the gut is commonly associated with nausea, gastrointestinal upset, diarrhea, and other gastrointestinal symptoms. Gastrointestinal adverse effects usually emerge early in the course of treatment and tend to improve after the first week. Increasing serotonergic tone at the level of the spinal cord and above is associated with diminished sexual function and interest. As a result, at least 30–40% of patients treated with SSRIs report loss of libido, delayed orgasm, or diminished arousal. The sexual effects often persist as long as the patient remains on the antidepressant but may diminish with time.

Other adverse effects related to the serotonergic effects of SSRIs include an increase in headaches and insomnia or hypersomnia. Some patients gain weight while taking SSRIs, particularly paroxetine. Sudden discontinuation of short half-life SSRIs such as paroxetine and sertraline is associated with a *discontinuation syndrome* in some patients characterized by dizziness, paresthesias, and other symptoms beginning 1 or 2 days after stopping the drug and persisting for 1 week or longer.

Most antidepressants are category C agents by the FDA teratogen classification system. There is an association of paroxetine with cardiac septal defects in first trimester exposures. Thus, paroxetine is a category D agent. Other possible associations of SSRIs with post-birth complications, including pulmonary hypertension, have not been clearly established.

### B. Serotonin-Norepinephrine Reuptake Inhibitors and Tricyclic Antidepressants

SNRIs have many of the serotonergic adverse effects associated with SSRIs. In addition, SNRIs may also have noradrenergic effects, including increased blood pressure and heart rate, and CNS activation, such as insomnia, anxiety, and agitation. The hemodynamic effects of SNRIs tend not to be problematic in most patients. A dose-related increase in blood pressure has been seen more commonly with the immediate-release form of venlafaxine than with other SNRIs. Likewise, there are more reports of cardiac toxicity with venlafaxine overdose than with either the other SNRIs or SSRIs. Duloxetine is rarely associated with hepatic toxicity in patients with a history of liver damage. All the SNRIs have been associated with a discontinuation syndrome resembling that seen with SSRI discontinuation.

The primary adverse effects of TCAs have been described in the previous text. Anticholinergic effects are perhaps the most common. These effects result in dry mouth, constipation, urinary retention, blurred vision, and confusion. They are more common with tertiary amine TCAs such as amitriptyline and imipramine than with the secondary amine TCAs desipramine and nortriptyline. The potent α-blocking property of TCAs often results in orthostatic hypotension. $H_1$ antagonism by the TCAs is associated with weight gain and sedation. The TCAs are class 1A antiarrhythmic agents (see Chapter 14) and are arrhythmogenic at higher doses. Sexual effects are common, particularly with highly serotonergic TCAs such as clomipramine. The TCAs have a prominent discontinuation syndrome characterized by cholinergic rebound and flulike symptoms.

### C. 5-HT$_2$ Antagonists

The most common adverse effects associated with the 5-HT$_2$ antagonists are sedation and gastrointestinal disturbances. Sedative effects, particularly with trazodone, can be quite pronounced. Thus, it is not surprising that the treatment of insomnia is currently the primary application of trazodone. The gastrointestinal effects appear to be dose-related and are less pronounced than those seen with SNRIs or SSRIs. Sexual effects are uncommon with nefazodone or trazodone treatment as a result of the relatively selective serotonergic effects of these drugs on the 5-HT$_2$ receptor rather than on SERT. However, trazodone has rarely been associated with inducing priapism. Both nefazodone and trazodone are α-blocking agents and may result in a dose-related orthostatic hypotension in some patients. Nefazodone has been associated with hepatotoxicity, including rare fatalities and cases of fulminant hepatic failure requiring transplantation. The rate of serious hepatoxicity with nefazodone has been estimated at 1 in 250,000 to 1 in 300,000 patient-years of nefazodone treatment.

### D. Tetracyclics and Unicyclics

Amoxapine is sometimes associated with a parkinsonian syndrome due to its D$_2$-blocking action. Mirtazapine has significant sedative effect. Maprotiline has a moderately high affinity for NET and may cause TCA-like adverse effects and, rarely, seizures. Bupropion is occasionally associated with agitation, insomnia, and anorexia.

### E. Monoamine Oxidase Inhibitors

The most common adverse effects of the MAOIs leading to discontinuation of these drugs are orthostatic hypotension and weight gain. In addition, the irreversible nonselective MAOIs are associated with the highest rates of sexual effects of all the antidepressants. Anorgasmia is fairly common with therapeutic doses of some MAOIs. The amphetamine-like properties of some MAOIs contributes to activation, insomnia, and restlessness in some patients. Phenelzine tends to be more sedating than either selegiline or tranylcypromine. Confusion is also sometimes associated with higher doses of MAOIs. Because they block metabolism of tyramine and similar ingested amines, MAOIs may cause dangerous interactions with certain foods and with serotonergic drugs (see Interactions). Finally, MAOIs have been associated with a sudden discontinuation syndrome manifested in a delirium-like presentation with psychosis, excitement, and confusion.

## Overdose

Suicide attempts are a common and unfortunate consequence of major depression. The lifetime risk of completing suicide in patients previously hospitalized with MDD may be as high as 15%. Overdose is the most common method used in suicide attempts, and antidepressants, especially the TCAs, are frequently involved. Overdose can induce lethal arrhythmias, including ventricular tachycardia and fibrillation. In addition, blood pressure changes and anticholinergic effects including altered mental status and seizures are sometimes seen in TCA overdoses. A 1500 mg dose of imipramine or amitriptyline (less than 7 days' supply at antidepressant doses) is enough to be lethal in many patients. Toddlers taking 100 mg will likely show evidence of toxicity. Treatment typically involves cardiac monitoring, airway support, and gastric lavage. Sodium bicarbonate is often administered to uncouple the TCA from cardiac sodium channels.

An overdose with an MAOI can produce a variety of effects including autonomic instability, hyperadrenergic symptoms, psychotic symptoms, confusion, delirium, fever, and seizures. Management of MAOI overdoses usually involves cardiac monitoring, vital signs support, and lavage.

Compared with TCAs and MAOIs, the other antidepressants are generally much safer in overdose. Fatalities with SSRI overdose alone are extremely uncommon. Similarly, SNRIs tend to be much safer in overdose than the TCAs. However, venlafaxine has been associated with some cardiac toxicity in overdose and appears to be less safe than SSRIs. Bupropion is associated with seizures in overdose, and mirtazapine may be associated with sedation, disorientation, and tachycardia. With the newer agents, fatal overdoses often involve the combination of the antidepressant with other drugs, including alcohol. Management of overdose with the newer antidepressants usually involves emptying of gastric contents and vital sign support as the initial intervention.

## Drug Interactions

Antidepressants are commonly prescribed with other psychotropic and nonpsychotropic agents. There is potential for drug interactions with all antidepressants, but the most serious of these involve the MAOIs and to a lesser extent the TCAs.

### A. Selective Serotonin Reuptake Inhibitors

The most common interactions with SSRIs are pharmacokinetic interactions. For example, paroxetine and fluoxetine are potent CYP2D6 inhibitors (Table 30–4). Thus, administration with 2D6 substrates such as TCAs can lead to dramatic and sometimes unpredictable elevations in the tricyclic drug concentration. The result may be toxicity from the TCA. Similarly, fluvoxamine, a CYP3A4 inhibitor, may elevate the levels of concurrently administered substrates for this enzyme such as diltiazem and induce bradycardia or hypotension. Other SSRIs, such as citalopram and escitalopram, are relatively free of pharmacokinetic interactions. The most serious interaction with the SSRIs are pharmacodynamic interactions with MAOIs that produce a serotonin syndrome (see below).

### B. Selective Serotonin-Norepinephrine Reuptake Inhibitors and Tricyclic Antidepressants

The SNRIs have relatively fewer CYP450 interactions than the SSRIs. Venlafaxine is a substrate but not an inhibitor of CYP2D6 or other isoenzymes, whereas desvenlafaxine is a minor substrate for CYP3A4. Duloxetine is a moderate inhibitor of CYP2D6 and so may elevate TCA and levels of other CYP2D6 substrates. Like all serotonergic antidepressants, SNRIs are contraindicated in combination with MAOIs.

Elevations of TCA levels may occur when combined with CYP2D6 inhibitors or from constitutional factors. About 7% of the Caucasian population in the USA has a CYP2D6

**TABLE 30–4 Some antidepressant–CYP450 drug interactions.**

| Enzyme | Substrates | Inhibitors | Inducers |
|---|---|---|---|
| 1A2 | Tertiary amine tricyclic antidepressants (TCAs), duloxetine, theophylline, phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine | Fluvoxamine, fluoxetine, moclobemide, ramelteon | Tobacco, omeprazole |
| 2C19 | TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam | Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconozole, omeprazole | Rifampin |
| 2D6 | TCAs, benztropine, perphenazine, clozapine, haloperidol, codeine/oxycodone, risperidone, class Ic antiarrhythmics, β blockers, trazodone, paroxetine, maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine, bupropion | Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone, cimetidine, haloperidol, quinidine, ritonavir | Phenobarbital, rifampin |
| 3A4 | Citalopram, escitalopram, TCAs, glucocorticoids, androgens/estrogens, carbamazepine, erythromycin, $Ca^{2+}$ channel blockers, protease inhibitors, sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen, zolpidem | Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine, fluconazole, erythromycin, protease inhibitors, ketoconazole, verapamil | Barbiturates, glucocorticoids, rifampin, modafinil, carbamazepine |

polymorphism that is associated with slow metabolism of TCAs and other 2D6 substrates. Combination of a known CYP2D6 inhibitor and a TCA in a patient who is a slow metabolizer may result in additive effects. Such an interaction has been implicated, though rarely, in cases of TCA toxicity. There may also be additive TCA effects such as anticholinergic or antihistamine effects when combined with other agents that share these properties such as benztropine or diphenhydramine. Similarly, antihypertensive drugs may exacerbate the orthostatic hypotension induced by TCAs.

### C. 5-$HT_2$ Antagonists

Nefazodone is an inhibitor of the CYP3A4 isoenzyme, so it can raise the level and thus exacerbate adverse effects of many 3A4-dependent drugs. For example, triazolam levels are increased by concurrent administration of nefazodone such that a reduction in triazolam dosage by 75% is recommended. Likewise, administration of nefazodone with simvastatin has been associated with 20-fold increase in plasma levels of simvastatin.

Trazodone is a substrate but not a potent inhibitor of CYP3A4. As a result, combining trazodone with potent inhibitors of CYP3A4, such as ritonavir or ketoconazole, may lead to substantial increases in trazodone levels.

### D. Tetracyclic and Unicyclic Antidepressants

Bupropion is metabolized primarily by CYP2B6, and its metabolism may be altered by drugs such as cyclophosphamide, which is a substrate of 2B6. The major metabolite of bupropion, hydroxybupropion, is a moderate inhibitor of CYP2D6 and so can raise desipramine levels. Bupropion should be avoided in patients taking MAOIs.

Mirtazapine is a substrate for several CYP450 enzymes including 2D6, 3A4, and 1A2. Consequently, drugs that inhibit these isozymes may raise mirtazapine levels. However, mirtazapine is not an inhibitor of these enzymes. The sedating effects of mirtazapine may be additive with those of CNS depressants such as alcohol and benzodiazepines.

Amoxapine and maprotiline share most drug interactions common to the TCA group. Both are CYP2D6 substrates and should be used with caution in combination with inhibitors such as fluoxetine. Amoxapine and maprotiline also both have anticholinergic and antihistaminic properties that may be additive with drugs that share a similar profile.

### E. Monoamine Oxidase Inhibitors

MAOIs are associated with two classes of serious drug interactions. The first of these is the pharmacodynamic interaction of MAOIs with serotonergic agents including SSRIs, SNRIs, and most TCAs along with some analgesic agents such as meperidine. These combinations of an MAOI with a serotonergic agent may result in a life-threatening **serotonin syndrome** (see Chapter 16). The serotonin syndrome is thought to be caused by overstimulation of 5-HT receptors in the central gray nuclei and the medulla. Symptoms range from mild to lethal and include a triad of cognitive (delirium, coma), autonomic (hypertension, tachycardia, diaphoreses), and somatic (myoclonus, hyperreflexia, tremor) effects. Most serotonergic antidepressants should be discontinued at least 2 weeks before starting an MAOI. Fluoxetine, because of its long half-life, should be discontinued for 4–5 weeks before an MAOI is initiated. Conversely, an MAOI must be discontinued for at least 2 weeks before starting a serotonergic agent.

The second serious interaction with MAOIs occurs when an MAOI is combined with tyramine in the diet or with sympathomimetic substrates of MAO. An MAOI prevents the breakdown of tyramine in the gut, and this results in high serum levels that enhance peripheral noradrenergic effects, including raising blood pressure dramatically. Patients on an MAOI who ingest large amounts of dietary tyramine may experience malignant hypertension and subsequently a stroke or myocardial infarction. Thus, patients taking MAOIs require a low-tyramine diet and should avoid foods such as aged cheeses, tap beer, soy products, and dried sausages, which contain high amounts of tyramine (see Chapter 9). Similar sympathomimetics also may cause significant hypertension when combined with MAOIs. Thus, over-the-counter cold preparations that contain pseudoephedrine and phenylpropanolamine are contraindicated in patients taking MAOIs.

## SUMMARY Antidepressants

| Subclass | Mechanism of Action | Effects | Clinical Applications | Pharmacokinetics, Toxicities, Interactions |
|---|---|---|---|---|
| **SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)** | | | | |
| • Fluoxetine<br>• Citalopram<br>• Escitalopram<br>• Paroxetine<br>• Sertraline | Highly selective blockade of serotonin transporter (SERT) • little effect on norepinephrine transporter (NET) | Acute increase of serotonergic synaptic activity • slower changes in several signaling pathways and neurotrophic activity | Major depression, anxiety disorders • panic disorder • obsessive-compulsive disorder • post-traumatic stress disorder • perimenopausal vasomotor symptoms • eating disorder (bulimia) | Half-lives from 15–75 h • oral activity • *Toxicity:* Well tolerated but cause sexual dysfunction • risk of serotonin syndrome with MAOIs • *Interactions:* Some CYP inhibition (fluoxetine 2D6, 3A4; fluvoxamine 1A2; paroxetine 2D6) |
| • *Fluvoxamine: Similar to above but approved only for obsessive-compulsive behavior* | | | | |
| **SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)** | | | | |
| • Duloxetine<br>• Venlafaxine | Moderately selective blockade of NET and SERT | Acute increase in serotonergic and adrenergic synaptic activity • otherwise like SSRIs | Major depression, chronic pain disorders • fibromyalgia, perimenopausal symptoms | *Toxicity:* Anticholinergic, sedation, hypertension (venlafaxine) • *Interactions:* Some CYP2D6 inhibition (duloxetine, desvenlafaxine) |
| • *Desvenlafaxine: Desmethyl metabolite of venlafaxine, metabolism is by phase II rather than CYP phase I*<br>• *Milnacipran: Significantly more selective for NET than SERT; little effect on DAT* | | | | |
| **TRICYCLIC ANTIDEPRESSANTS (TCAs)** | | | | |
| • Imipramine<br>• Many others | Mixed and variable blockade of NET and SERT | Like SNRIs plus significant blockade of autonomic nervous system and histamine receptors | Major depression not responsive to other drugs • chronic pain disorders • incontinence • obsessive-compulsive disorder (clomipramine) | Long half-lives • CYP substrates • active metabolites • *Toxicity:* Anticholinergic, α-blocking effects, sedation, weight gain, arrhythmias, and seizures in overdose • *Interactions:* CYP inducers and inhibitors |
| **5-$HT_2$ ANTAGONISTS** | | | | |
| • Nefazodone<br>• Trazodone | Inhibition of 5-$HT_{2A}$ receptor • nefazodone also blocks SERT weakly | Trazodone forms a metabolite (m-cpp) that blocks 5-$HT_{2A,2C}$ receptors | Major depression • sedation and hypnosis (trazodone) | Relatively short half-lives • active metabolites • *Toxicity:* Modest α- and $H_1$-receptor blockade (trazodone) • *Interactions:* Nefazodone inhibits CYP3A4 |
| **TETRACYCLICS, UNICYCLIC** | | | | |
| • Bupropion<br>• Amoxapine<br>• Maprotiline<br>• Mirtazapine | Increased norepinephrine and dopamine activity (bupropion) • NET > SERT inhibition (amoxapine, maprotiline) • increased release of norepinephrine, 5-HT (mirtazapine) | Presynaptic release of catecholamines but no effect on 5-HT (bupropion) • amoxapine and maprotiline resemble TCAs | Major depression • smoking cessation (bupropion) • sedation (mirtazapine) • amoxapine and maprotiline rarely used | Extensive metabolism in liver • *Toxicity:* Lowers seizure threshold (amoxapine, bupropion); sedation and weight gain (mirtazepine) • *Interactions:* CYP2D6 inhibitor (bupropion) |
| **MONOAMINE OXIDASE INHIBITORS (MAOIs)** | | | | |
| • Phenelzine<br>• Tranylcypromine<br>• Selegiline | Blockade of MAO-A and MAO-B (phenelzine, nonselective) • MAO-B irreversible selective MAO-B inhibition (low-dose selegiline) | Transdermal absorption of selegiline achieves levels that inhibit MAO-A | Major depression unresponsive to other drugs | Very slow elimination • *Toxicity:* Hypotension, insomnia • *Interactions:* Hypertensive crisis with tyramine, other indirect sympathomimetics • serotonin syndrome with serotonergic agents, meperidine |

# PREPARATIONS AVAILABLE

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS

**Citalopram (generic, Celexa)**
Oral: 10, 20, 40 mg tablets; 10 mg/5 mL solution

**Escitalopram (Lexapro)**
Oral: 5, 10, 20 mg tablets; 5 mg/5 mL solution

**Fluoxetine (generic, Prozac)**
Oral: 10, 20, 40 mg capsules; 10, 20 mg tablets; 20 mg/5 mL liquid
Oral delayed-release (Prozac Weekly): 90 mg capsules

**Fluvoxamine (generic, labeled only for obsessive-compulsive disorder)**
Oral: 25, 50, 100 mg tablets

**Paroxetine (generic, Paxil)**
Oral: 10, 20, 30, 40 mg tablets; 10 mg/5 mL suspension; 12.5, 25, 37.5 mg controlled-release tablets

**Sertraline (generic, Zoloft)**
Oral: 25, 50, 100 mg tablets; 20 mg/mL oral concentrate

**Vilazodone (Viibryd)**
Oral: 10, 20, 40 mg tablets

## SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

**Desvenlafaxine (Pristiq)**
Oral: 50, 100 mg capsules

**Duloxetine (Cymbalta)**
Oral: 20, 30, 50 mg capsules

**Milnacipran (Savella; labeled only for fibromyalgia)**
Oral: 12.5, 25, 50, 100 mg tablets

**Venlafaxine (Effexor)**
Oral: 25, 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg extended-release capsules

## 5-HT$_2$ ANTAGONISTS

**Nefazodone (generic)**
Oral: 50, 100, 150, 200, 250 mg tablets

**Trazodone (generic, Desyrel)**
Oral: 50, 100, 150, 300 mg tablets

## TRICYCLICS

**Amitriptyline (generic, Elavil)**
Oral: 10, 25, 50, 75, 100, 150 mg tablets
Parenteral: 10 mg/mL for IM injection

**Amoxapine (generic)**
Oral: 25, 50, 100, 150 mg tablets

**Clomipramine (generic, Anafranil; labeled only for obsessive-compulsive disorder)**
Oral: 25, 50, 75 mg capsules

**Desipramine (generic, Norpramin)**
Oral: 10, 25, 50, 75, 100, 150 mg tablets

**Doxepin (generic, Sinequan)**
Oral: 10, 25, 50, 75, 100, 150 mg capsules; 10 mg/mL concentrate

**Imipramine (generic, Tofranil)**
Oral: 10, 25, 50 mg tablets (as hydrochloride); 75, 100, 125, 150 mg capsules (as pamoate)

**Nortriptyline (generic, Pamelor)**
Oral: 10, 25,50, 75 mg capsules; 2 mg/mL solution

**Protriptyline (generic, Vivactil)**
Oral: 5, 10 mg tablets

**Trimipramine (Surmontil)**
Oral: 25, 50, 100 mg capsules

## TETRACYCLIC AND UNICYCLIC AGENTS

**Amoxipine (generic)**
Oral: 25, 50, 100, 150 mg tablets

**Bupropion (generic, Wellbutrin)**
Oral: 75, 100 mg tablets; 100, 150, 200 mg 12-hour sustained-release tablets; 150, 300 mg 24-hour sustained-release tablets
Oral: 25, 50, 75 mg tablets

**Maprotiline (generic)**
Oral: 7.5, 15, 30, 45 mg tablets; 15, 30, 45 mg oral disintegrating tablets

**Mirtazapine (generic, Remeron)**
Oral: 7.5, 15, 30, 45 mg tablets; 15, 30, 45 mg disintegrating tablets

## MONOAMINE OXIDASE INHIBITORS

**Isocarboxazid (generic, Marplan)**
Oral: 10 mg tablets

**Phenelzine (generic, Nardil)**
Oral: 15 mg tablets

**Selegiline**
Oral (generic, Eldepryl): 5 mg tablets, capsules; 1.25 oral disintegrating tablets

**Tranylcypromine (generic, Parnate)**
Oral: 10 mg tablets

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## CASE STUDY ANSWER

Fluoxetine, the prototype SSRI, has a number of pharmacokinetic and pharmacodynamic interactions. Fluoxetine is a CYP450 2D6 inhibitor and thus can inhibit the metabolism of 2D6 substrates such as propranolol and other β blockers, tricyclic antidepressants, tramadol, opioids such as methadone, codeine, and oxycodone, antipsychotics such as haloperidol and thioridazine, and many other drugs. This inhibition of metabolism can result in significantly higher plasma levels of the concurrent drug, and this may lead to an increase in adverse reactions associated with that drug.

As a potent inhibitor of the serotonin transporter, fluoxetine is associated with a number of pharmacodynamic interactions involving serotonergic neurotransmission. The combination of tramadol with fluoxetine has occasionally been associated with a serotonin syndrome, characterized by diaphoreses, autonomic instability, myoclonus, seizures, and coma. The combination of fluoxetine with an MAOI is contraindicated because of the risk of a fatal serotonin syndrome. In addition, meperidine is specifically contraindicated in combination with an MAOI.