Lippincott's Illustrated Reviews:

Pharmacology

You will have learned within, those are

Chapter no. **6** to **10**

SL	Chapter No.	Title / Chapter Name
1	Chapter 6	Adrenergic Agonists
2	Chapter 7	Adrenergic Antagonists
3	Chapter 8	Neurodegenerative Diseases
4	Chapter 9	Anxiolytic and Hypnotic Drugs
5	Chapter 10	CNS Stimulants

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 6

Adrenergic Agonists

I. Overview

The adrenergic drugs affect receptors that are stimulated by norepinephrine or *epinephrine*. Some adrenergic drugs act directly on the adrenergic receptor (adrenoceptor) by activating it and are said to be sympathomimetic. Others, which will be dealt with in Chapter 7, block the action of the neurotransmitters at the receptors (sympatholytics), whereas still other drugs affect adrenergic function by interrupting the release of norepinephrine from adrenergic neurons. This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1).

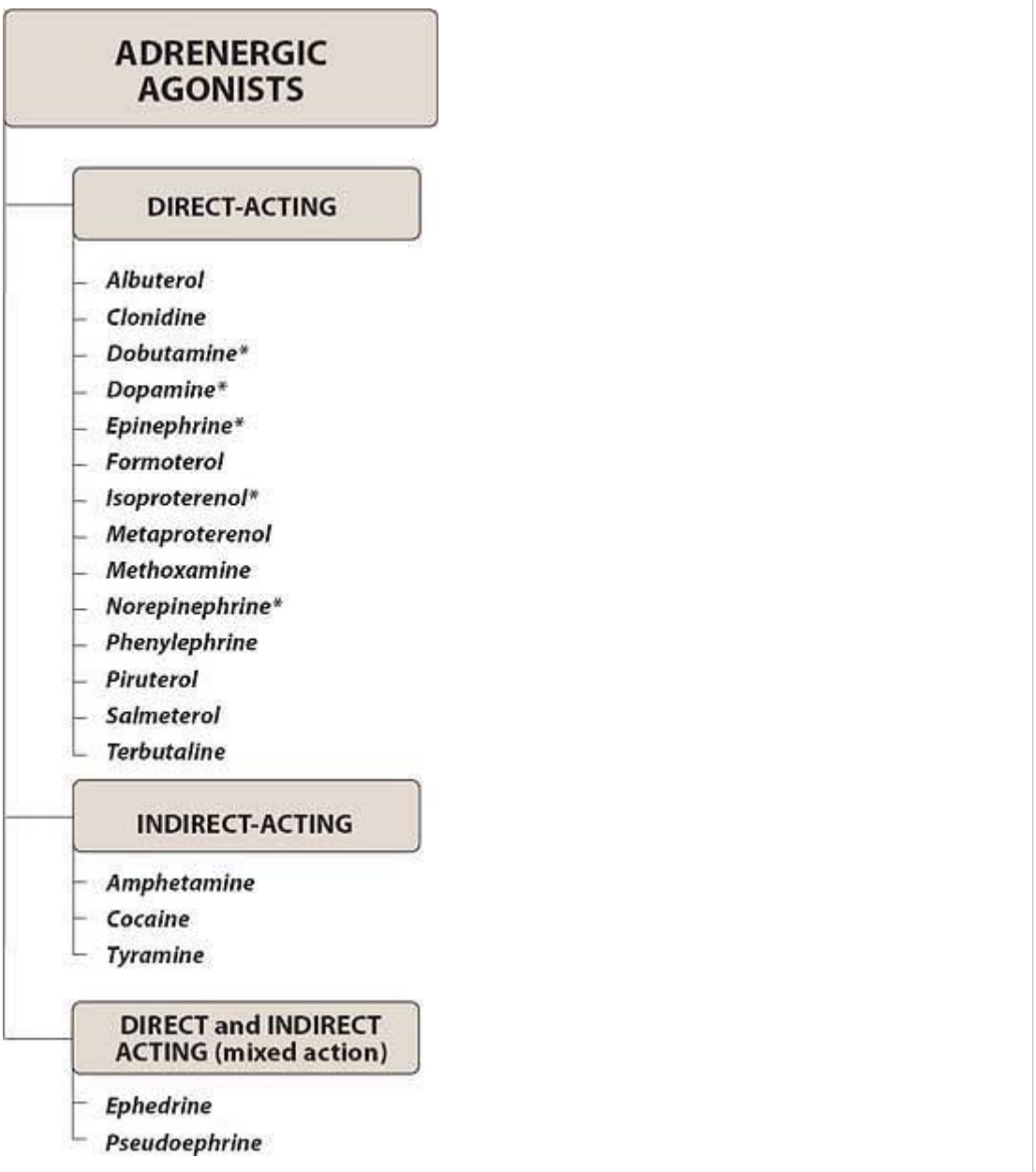


Figure 6.1 Summary of adrenergic agonists. Agents marked with an asterisk (*) are catecholamines.

II. The Adrenergic Neuron

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. The adrenergic neurons and receptors, located either presynaptically on the neuron or postsynaptically on the effector organ, are the sites of action of the adrenergic drugs (Figure 6.2).

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons (see p. 43), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission takes place

at numerous bead-like enlargements called varicosities. The process involves five steps:synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a Na^+-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase.[1] This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme dopa decarboxylase (aromatic l-amino acid decarboxylase) to form *dopamine* in the cytoplasm of the presynaptic neuron.

2. **Storage of norepinephrine in vesicles:** *Dopamine* is then trans-ported into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine. This carrier system is blocked by *reserpine* (see p. 90). *Dopamine* is hydroxylated to form norepinephrine by the enzyme, dopamine Î²-hydroxylase. [Note: Synaptic vesicles contain *dopamine* or norepinephrine plus adenosine triphosphate (ATP), and Î²-hydroxylase, as well as other cotransmitters.] In the adrenal medulla, norepinephrine is methylated to yield *epinephrine*, both of which are stored in chromaffin cells. On stimulation, the adrenal medulla releases about 80 percent *epinephrine* and 20 percent norepinephrine directly into the circulation.

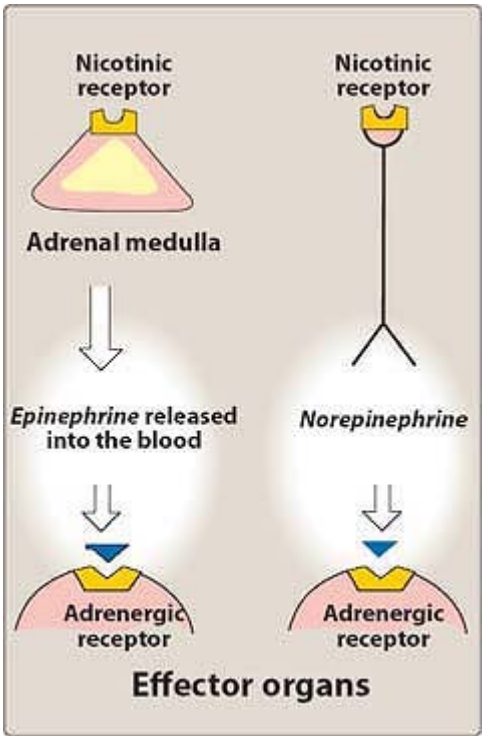


Figure 6.2 Sites of actions of adrenergic agonists.

3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes vesicles inside the neuron to fuse with the cell membrane and expel (exocytose) their contents into the synapse. This release is blocked by drugs such as *guanethidine* (see p. 91).

4. **Binding to** a **receptor:** Norepinephrine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending.

The recognition of norepinephrine by the membrane receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second-messenger system,[2] and the phosphatidylinositol cycle,[3] to transduce the signal into an effect.

5. **Removal of norepinephrine:** Norepinephrine may 1) diffuse out of the synaptic space and enter the general circulation, 2) be metabolized to O-methylated derivatives by postsynaptic cell membraneâ€“associated catechol O-methyltransferase (COMT) in the synaptic space, or 3) be recaptured by an uptake system that pumps the norepinephrine back into the neuron. The uptake by the neuronal membrane involves a sodium/potassium-activated ATPase that can be inhibited by tricyclic antidepressants, such as *imipramine*, or by *cocaine* (see Figure 6.3). Uptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of norepinephrine's effects.

6. **Potential fates of recaptured norepinephrine:** Once norepinephrine reenters the cytoplasm of the adrenergic neuron, it may be taken up into adrenergic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. The inactive products of norepinephrine metabolism are excreted in the urine as vanillylmandelic acid, metanephrine, and normetanephrine.

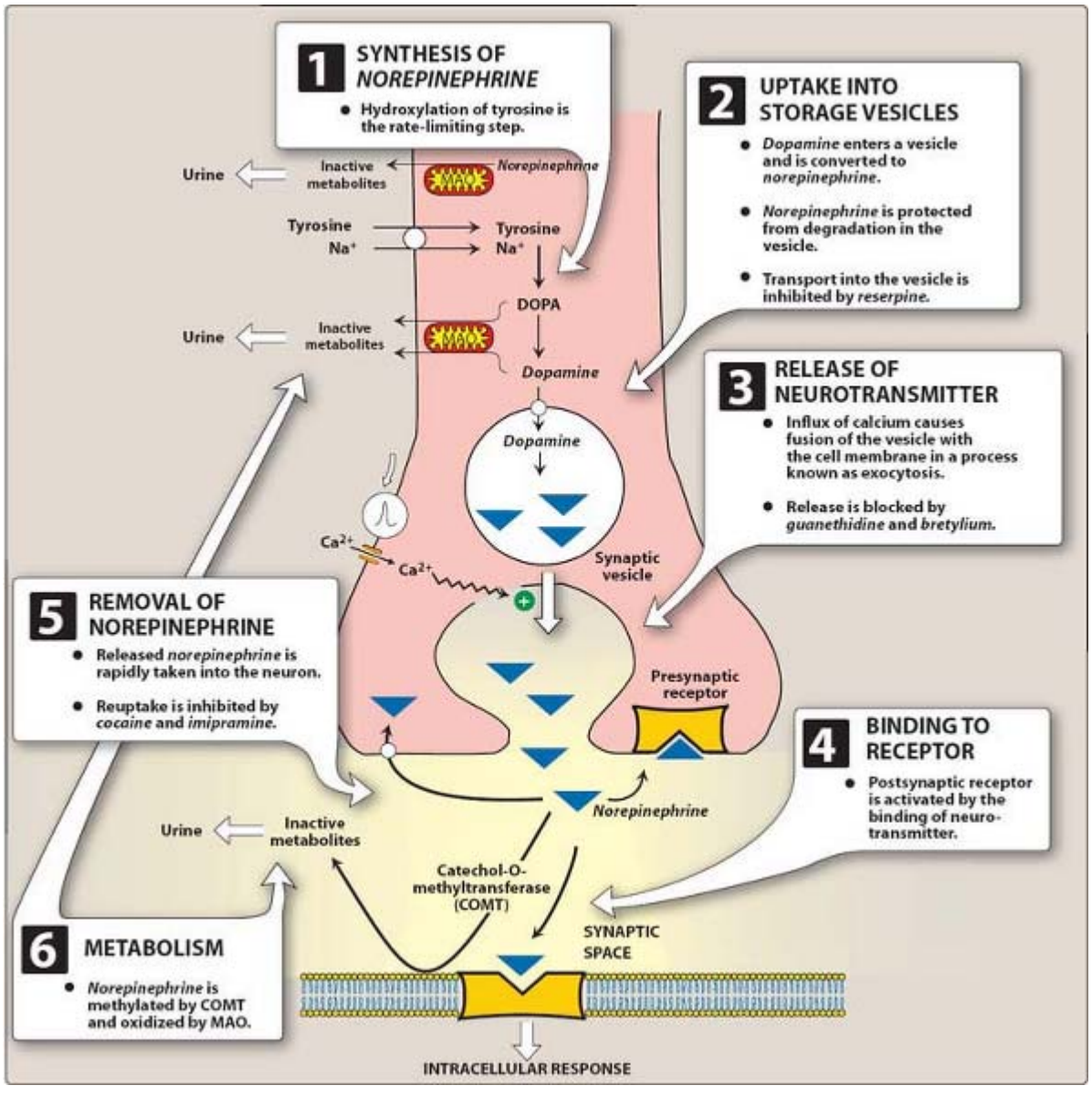


Figure 6.3 Synthesis and release of *norepinephrine* from the adrenergic neuron. (MAO = monoamine oxidase.)

B. Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two families of receptors, designated Î± and Î², were initially identified on the basis of their responses to the adrenergic agonists *epinephrine*, norepinephrine, and *isoproterenol*. The use of specific blocking drugs and the cloning of genes have revealed the molecular identities of a number of receptor subtypes. These proteins belong to a multigene family. Alterations in the primary structure of the receptors influence their affinity for various agents.

1. **Î±$_1$ and Î±$_2$ Receptors:** The Î±-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and norepinephrine (Figure 6.4). For

Î± receptors, the rank order of potency is *epinephrine* â‰¥ norepinephrine >> *isoproterenol*. The Î±-adrenoceptors are subdivided into two subgroups, $Î±_1$ and $Î±_2$, based on their affinities for Î± agonists and blocking drugs. For example, the $Î±_1$ receptors have a higher affinity for *phenylephrine* than do the $Î±_2$ receptors. Conversely, the drug *clonidine* selectively binds to $Î±_2$ receptors and has less effect on $Î±_1$ receptors.

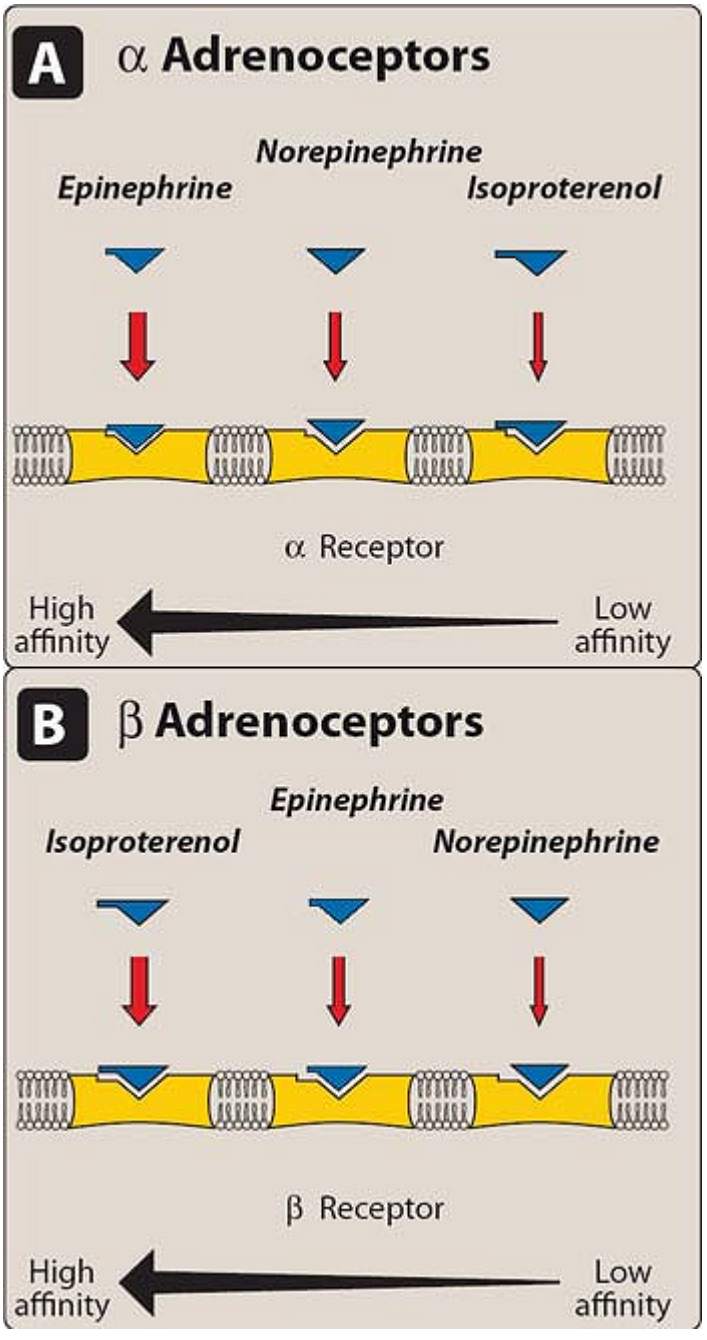


Figure 6.4 Types of adrenergic receptors.

a. **$Î±_1$ Receptors:** These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effectsâ€"originally designated as Î±-adrenergicâ€"involving constriction of smooth muscle. Activation of $Î±_1$ receptors initiates a series of reactions through a G protein activation of phospholipase C, resulting in the generation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG)

from phosphatidylinositol. IP_3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 6.5).

b. **Î±$_2$ Receptors:** These receptors, located primarily on presynaptic nerve endings and on other cells, such as the Î² cell of the pancreas, and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released norepinephrine traverses the synaptic cleft and interacts with the Î±$_1$ receptors. A portion of the released norepinephrine â€œcircles backâ€ and reacts with Î±$_2$ receptors on the neuronal membrane (see Figure 6.5). The stimulation of the Î±$_2$ receptor causes feedback inhibition of the ongoing release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuromediator output when there is high sympathetic activity. [Note: In this instance these receptors are acting as inhibitory autoreceptors.] Î±$_2$ Receptors are also found on presynpatic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release [Note: In these instances these receptors are behaving as inhibitory heteroreceptors.] This is another local modulating mechanism to control autonomic activity in a given area. In contrast to Î±$_1$ receptors, the effects of binding at Î±$_2$ receptors are mediated by inhibition of adenylyl cyclase and a fall in the levels of intracellular cAMP.

c. **Further subdivisions:** The Î±$_1$ and Î±$_2$ receptors are further divided into Î±$_{1A}$, Î±$_{1B}$, Î±$_{1C}$, and Î±$_{1D}$ and into Î±$_{2A}$, Î±$_{2B}$, Î±$_{2C}$, and Î±$_{2D}$. This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective Î±$_{1A}$ antagonist that is used to treat benign prostate hyperplasia. The drug is clinically useful because it targets Î±$_{1A}$ receptors found primarily in the urinary tract and prostate gland.

2. **Î² Receptors:** Î² Receptors exhibit a set of responses different from those of the Î± receptors. These are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and norepinephrine (see Figure 6.4). For Î² receptors, the rank order of potency is *isoproterenol* > *epinephrine* > norepinephrine. The Î²-adrenoceptors can be subdivided into three major subgroups, Î²$_1$, Î²$_2$, and Î²$_3$, based on their affinities for adrenergic agonists and antagonists, although several others have been identified by gene cloning. [It is known that Î²$_3$ receptors are involved in lipolysis but their role in other specific reactions are not known] . Î²$_1$ Receptors have approximately equal affinities for *epinephrine* and norepinephrine, whereas Î²$_2$ receptors have a higher affinity for *epinephrine* than for norepinephrine. Thus, tissues with a predominance of Î²$_2$ receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating *epinephrine* released by the adrenal medulla. Binding of a neurotransmitter at any of the three Î² receptors results in activation of adenylyl cyclase and, therefore, increased concentrations of cAMP within the cell.

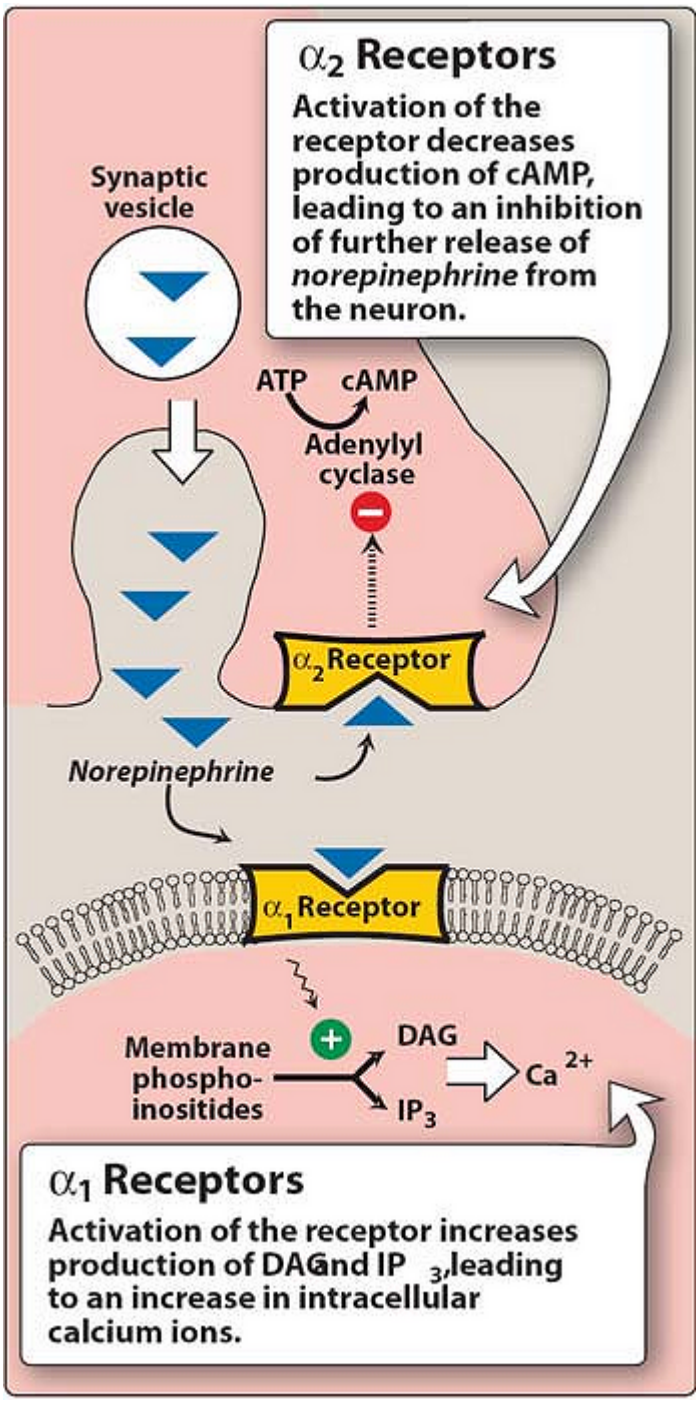


Figure 6.5 Second messengers mediate the effects of Î± receptors. DAG = diacylglycerol; IP_3 = inositol trisphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate.

3. **Distribution of receptors:** Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor. For example, tissues such as the vasculature to skeletal muscle have both $Î±_1$ and $Î²_2$ receptors, but the $Î²_2$ receptors predominate. Other tissues may have one type of receptor exclusively, with practically no significant numbers of other types of adrenergic receptors. For example, the heart contains predominantly $Î²_1$ receptors.

4. **Characteristic responses mediated by adrenoceptors:** It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of Î±$_1$ receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Conversely, stimulation of Î²$_1$ receptors characteristically causes cardiac stimulation, whereas stimulation of Î²$_2$ receptors produces vasodilation (in skeletal vascular beds) and bronchiolar relaxation.

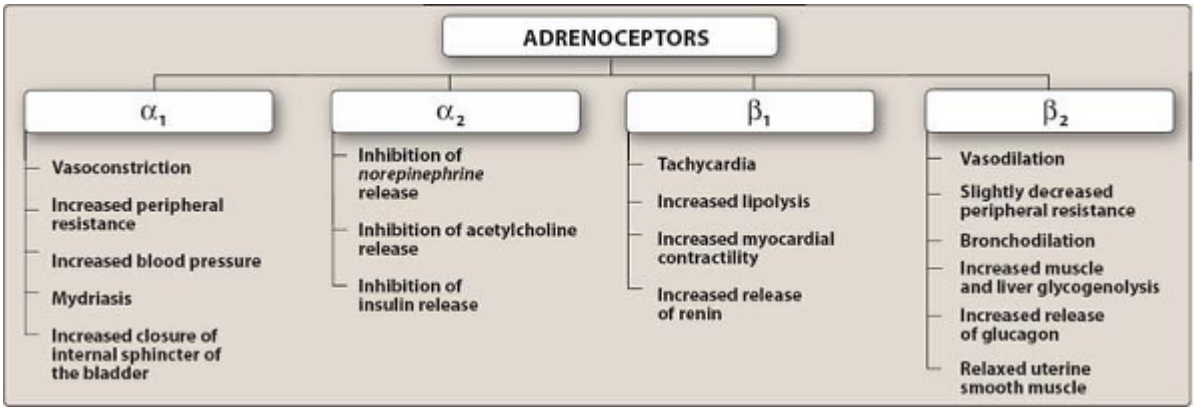


Figure 6.6 Major effects mediated by Î± and Î² adrenoceptors.

5. **Desensitization of receptors:** Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase A or Î²-adrenergic receptor kinase.

III. Characteristics of Adrenergic Agonists

Most of the adrenergic drugs are derivatives of Î²-phenylethylamine (Figure 6.7). Substitutions on the benzene ring or on the ethylamine side chains produce a great variety of compounds with varying abilities to differentiate between Î± and Î² receptors and to penetrate the CNS. Two important structural features of these drugs are the number and location of OH substitutions on the benzene ring and the nature of the substituent on the amino nitrogen.

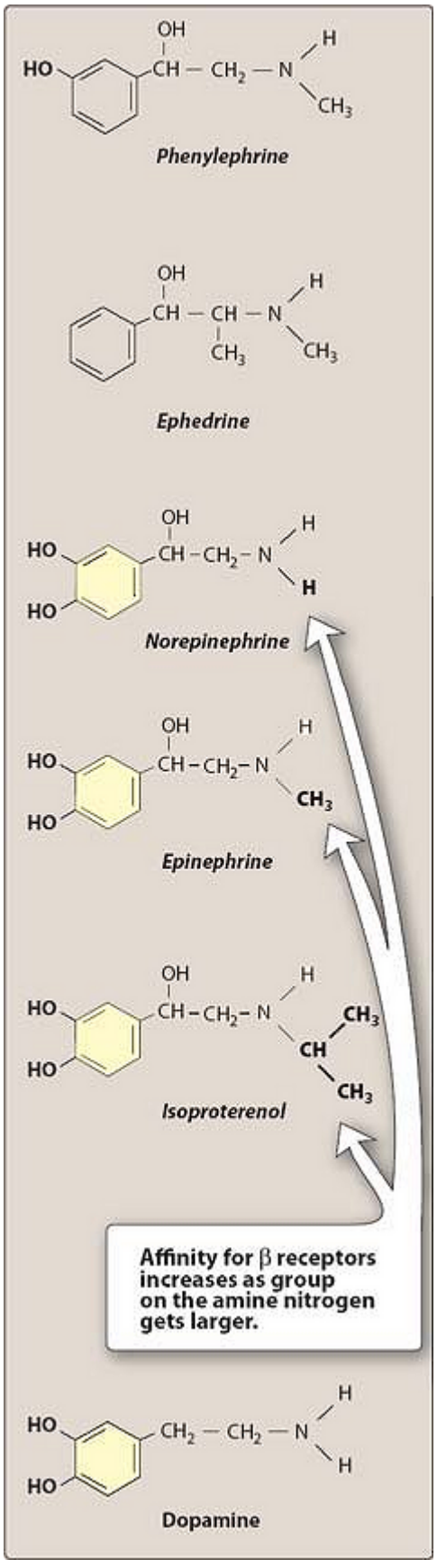

Phenylephrine
Ephedrine
Norepinephrine
Epinephrine
Isoproterenol
Affinity for β receptors increases as group on the amine nitrogen gets larger.
Dopamine

Figure 6.7 Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as *epinephrine*, norepinephrine, *isoproterenol*, and *dopamine*) are called catecholamines. These compounds share the following properties:

1. **High potency:** Drugs that are catechol derivatives (with â€“OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating Î± or Î² receptors.
2. **Rapid inactivation:** Not only are the catecholamines metabolized by COMT postsynaptically and by MAO intraneuronally, they are also metabolized in other tissues. For example, COMT is in the gut wall, and MAO is in the liver and gut wall. Thus, catecholamines have only a brief period of action when given parenterally, and they are ineffective when administered orally because of inactivation.
3. **Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most of these drugs have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrin*e, *ephedrine*, and *amphetamine*. *Phenylephrine*, an analog of *epinephrine*, has only a single â€“OH at position 3 on the benzene ring, whereas *ephedrine* lacks hydroxyls on the ring but has a methyl substitution at the Î±-carbon. These are poor substrates for MAO and, thus, show a prolonged duration of action, because MAO is an important route of detoxification. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS. [Note: *Ephedrine* and *amphetamine* may act indirectly by causing the release of stored catecholamines.]

C. Substitutions on the amine nitrogen

The nature and bulk of the substituent on the amine nitrogen is important in determining the Î² selectivity of the adrenergic agonist. For example, *epinephrine*, with a â€“CH_3 substituent on the amine nitrogen, is more potent at Î² receptors than norepinephrine, which has an unsubstituted amine. Similarly, *isoproterenol*, with an isopropyl substituent â€“$CH(CH_3)_2$ on the amine nitrogen (see Figure 6.7), is a strong Î² agonist with little Î± activity (see Figure 6.4).

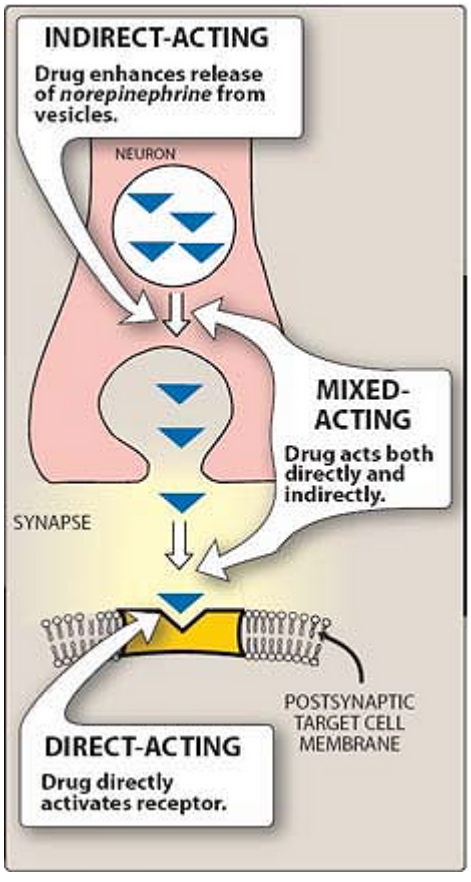


Figure 6.8 Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

D. Mechanism of action of the adrenergic agonists

1. **Direct-acting agonists:** These drugs act directly on Î± or Î² receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone *epinephrine* from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include *epinephrine*, norepinephrine, *isoproterenol*, and *phenylephrine*.

2. **Indirect-acting agonists:** These agents, which include *amphetamine,* cocaine and tyramine, may block the uptake of norepinephrine (uptake blockers) or are taken up into the presynaptic neuron and cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (see Figure 6.8). As with neuronal stimulation, the norepinephrine then traverses the synapse and binds to the Î± or Î² receptors. Examples of uptake blockers and agents that cause norepinephrine release include *cocaine* and amphetamines, respectively.

3. **Mixed-action agonists:** Some agonists, such as *ephedrine, pseudoephedrine* and *metaraminol*, have the capacity both to stimulate adrenoceptors directly and to release norepinephrine from the adrenergic neuron (see Figure 6.8).

IV. Direct-Acting Adrenergic Agonists

Direct-acting agonists bind to adrenergic receptors without interacting with the presynaptic neuron. The activated receptor initiates synthesis of second messengers and subsequent intracellular signals. As a group, these agents are

widely used clinically.

A. Epinephrine

Epinephrine [ep-i-NEF-rin] is one of four catecholaminesâ€"*epinephrine*, norepinephrine, *dopamine*, and *dobutamine*â€"commonly used in therapy. The first three catecholamines occur naturally in the body as neurotransmitters; the latter is a synthetic compound. *Epinephrine* is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of norepinephrine, into the bloodstream. *Epinephrine* interacts with both Î± and Î² receptors. At low doses, Î² effects (vasodilation) on the vascular system predominate, whereas at high doses, Î± effects (vasoconstriction) are strongest.

1. **Actions:**

   a. **Cardiovascular:** The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotropic: $\hat{I}^2_1$ action) and increases its rate of contraction (positive chronotropic: $\hat{I}^2_1$ action). Cardiac

   output therefore increases. With these effects comes increased oxygen demands on the myocardium. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera (Î± effects), and it dilates vessels going to the liver and skeletal muscle ($\hat{I}^2_2$ effects). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure (Figure 6.9).

   b. **Respiratory:** *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle ($\hat{I}^2_2$ action). This action relieves all known allergic- or histamine-induced bronchoconstriction. In the case of anaphylactic shock, this can be lifesaving. In individuals suffering from an acute asthmatic attack, *epinephrine* rapidly relieves the dyspnea (labored breathing) and increases the tidal volume (volume of gases inspired and expired). *Epinephrine* also inhibits the release of allergy mediators such as histamines from mast cells.

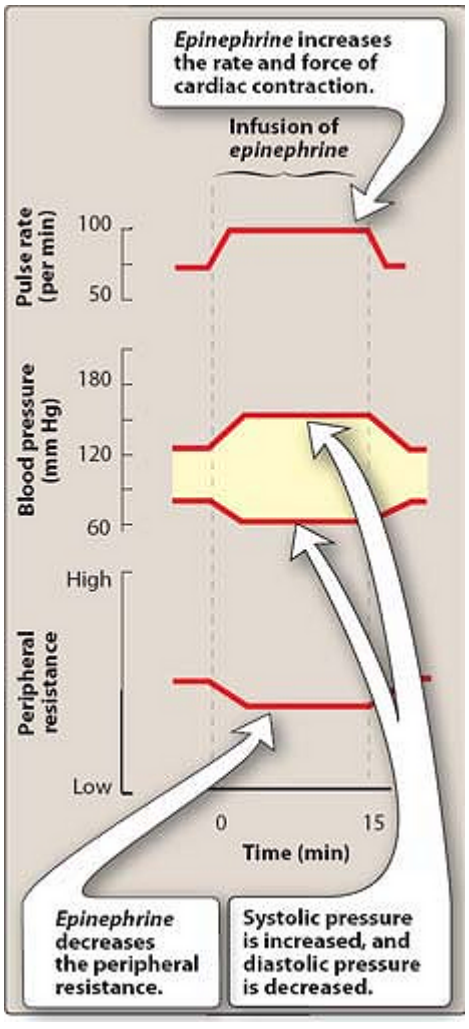


Figure 6.9 Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

c. **Hyperglycemia:** *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (Î²$_2$ effect), increased release of glucagon (Î²$_2$ effect), and a decreased release of insulin (Î±$_2$ effect). These effects are mediated via the cAMP mechanism.

d. **Lipolysis:** *Epinephrine* initiates lipolysis through its agonist activity on the Î² receptors of adipose tissue, which upon stimulation activate adenylyl cyclase to increase cAMP levels. Cyclic AMP stimulates a hormone-sensitive lipase, which hydrolyzes triacylglycerols to free fatty acids and glycerol.[4]

2. **Biotransformations:** *Epinephrine*, like the other catecholamines, is metabolized by two enzymatic pathways: MAO, and COMT, which has S-adenosylmethionine as a cofactor (see Figure 6.3). The final metabolites found in the urine are metanephrine and vanillylmandelic acid. [Note: Urine also contains normetanephrine, a product of norepinephrine metabolism.]

3. **Therapeutic uses**

a. **Bronchospasm:** *Epinephrine* is the primary drug used in the emergency treatment of any condition of the respiratory tract when bronchoconstriction has resulted in diminished respiratory exchange. Thus, in treatment of acute asthma and anaphylactic shock, *epinephrine* is the drug of choice; within a few minutes

after subcutaneous administration, greatly improved respiratory exchange is observed. Administration may be repeated after a few hours. However, selective $\hat{I}^2_2$ agonists, such as *albuterol*, are presently favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effect.

b. **Glaucoma:** In ophthalmology, a two-percent *epinephrine* solution may be used topically to reduce intraocular pressure in open-angle glaucoma. It reduces the production of aqueous humor by vasoconstriction of the ciliary body blood vessels.

c. **Anaphylactic shock:** *Epinephrine* is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.

d. **Cardiac arrest:** *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest regardless of the cause.

e. **Anesthetics:** Local anesthetic solutions usually contain 1:100,000 parts *epinephrine*. The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection, thereby allowing the local anesthetic to persist at the injection site before being absorbed into the circulation and metabolized. Very weak solutions of *epinephrine* (1:100,000) can also be used topically to vasoconstrict mucous membranes to control oozing of capillary blood.

4. **Pharmacokinetics:** *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation). In emergency situations, *epinephrine* is given intravenously for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, by inhalation, or topically to the eye (Figure 6.10). Oral administration is ineffective, because *epinephrine* and the other catecholamines are inactivated by intestinal enzymes. Only metabolites are excreted in the urine.

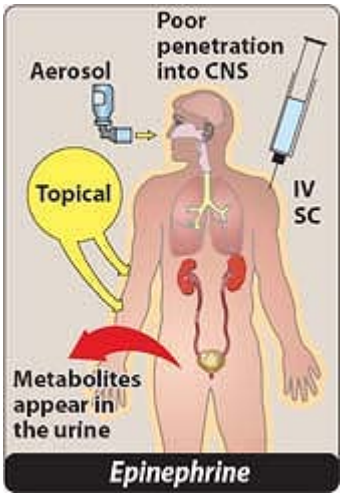


Figure 6.10 Pharmacokinetics of *epinephrine*.

5. **Adverse effects:**

a. **CNS disturbances:** *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor.

b. **Hemorrhage:** The drug may induce cerebral hemorrhage as a result of a marked elevation of blood pressure.

c. **Cardiac arrhythmias:** *Epinephrine* can trigger cardiac arrhythmias, particularly if the patient is receiving

digitalis.

d. **Pulmonary edema:** *Epinephrine* can induce pulmonary edema.

6. **Interactions:**

a. **Hyperthyroidism:** *Epinephrine* may have enhanced cardio-vascular actions in patients with hyperthyroidism. If *epinephrine* is required in such an individual, the dose must be reduced. The mechanism appears to involve increased production of adrenergic receptors on the vasculature of the hyperthyroid individual, leading to a hypersensitive response.

b. **Cocaine:** In the presence of *cocaine, epinephrine* produces exaggerated cardiovascular actions. This is due to the ability of cocaine to prevent reuptake of catecholamines into the adrenergic neuron; thus, like norepinephrine, *epinephrine* remains at the receptor site for longer periods of time (see Figure 6.3).

c. **Diabetes:** *Epinephrine* increases the release of endogenous stores of glucose. In the diabetic, dosages of insulin may have to be increased.

d. **Î²-Blockers:** These agents prevent *epinephrine*'s effects on b receptors, leaving Î±-receptor stimulation unopposed. This may lead to an increase in peripheral resistance and an increase in blood pressure.

e. **Inhalation anesthetics:** Inhalational anesthetics sensitizethe heart to the effects of *epinephrine,* which may lead to tachycardia.

B. Norepinephrine

Because norepinephrine [nor-ep-i-NEF-rin] is the neuromediator of adrenergic nerves, it should theoretically stimulate all types of adrenergic receptors. In practice, when the drug is given in therapeutic doses to humans, the Î±-adrenergic receptor is most affected.

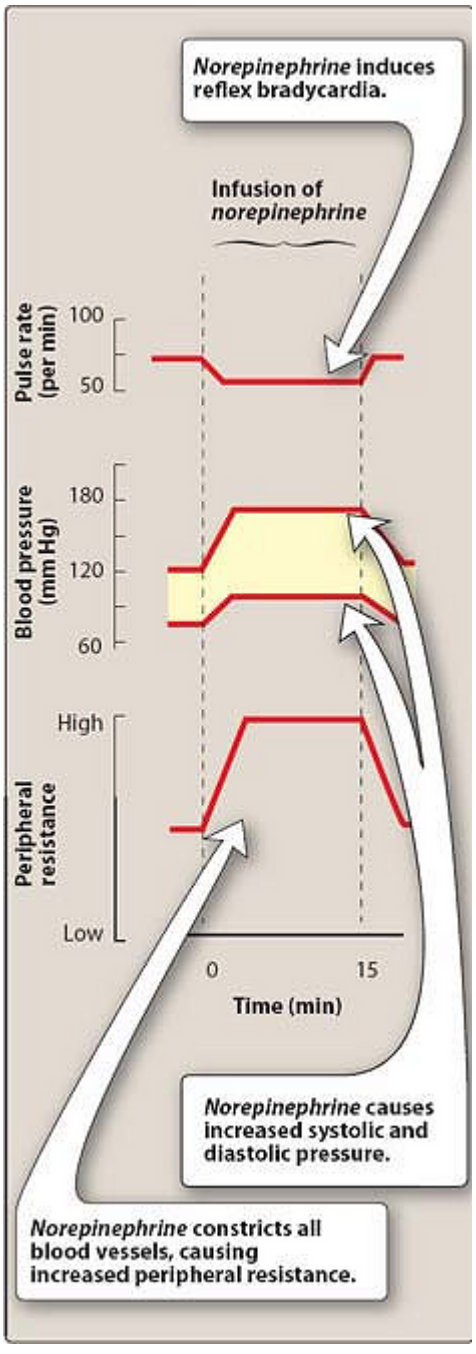


Figure 6.11 Cardiovascular effects of intravenous infusion of *norepinephrine*.

1. **Cardiovascular actions:**

   a. **Vasoconstriction:** Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (Î±$_1$ effect). Both systolic and diastolic blood pressures increase (Figure 6.11). [Note: Norepinephrine causes greater vasoconstriction than does *epinephrine,* because it does not induce compensatory vasodilation via Î²$_2$ receptors on blood vessels supplying skeletal muscles, etc. The weak Î²$_2$ activity of norepinephrine also explains why it is not useful in the treatment of asthma.]

   b. **Baroreceptor reflex:** In isolated cardiac tissue, norepinephrine stimulates cardiac contractility; however, in

vivo, little if any cardiac stimulation is noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This reflex bradycardia is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (see Figure 6.11).

c. **Effect of atropine pretreatment:** If *atropine*, which blocks the transmission of vagal effects, is given before norepinephrine, then norepinephrine stimulation of the heart is evident as tachycardia.

2. **Therapeutic uses:** Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. However, *metaraminol* is favored, because it does not reduce blood flow to the kidney, as does norepinephrine. Other actions of norepinephrine are not considered to be clinically significant. It is never used for asthma or in combination with local anesthetics. Norepinephrine is a potent vasoconstrictor and will cause extravasation (discharge of blood from vessel into tissues) along the injection site. [Note: When norepinephrine is used as a drug, it is sometimes called *levarterenol* [leev-are-TER-a-nole].]

3. **Pharmacokinetics:** Norepinephrine may be given IV for rapid onset of action. The duration of action is 1 to 2 minutes following the end of the infusion period. It is poorly absorbed after subcutaneous injection

and is destroyed in the gut if administered orally. Metabolism is similar to that of *epinephrine*.

4. **Adverse effects:** These are similar to those of *epinephrine*. In addition, norepinephrine may cause blanching and sloughing of skin along injected vein (due to extreme vasoconstriction).

C. Isoproterenol

Isoproterenol [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that predominantly stimulates both Î²$_1$- and Î²$_2$-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on Îœ receptors is insignificant.

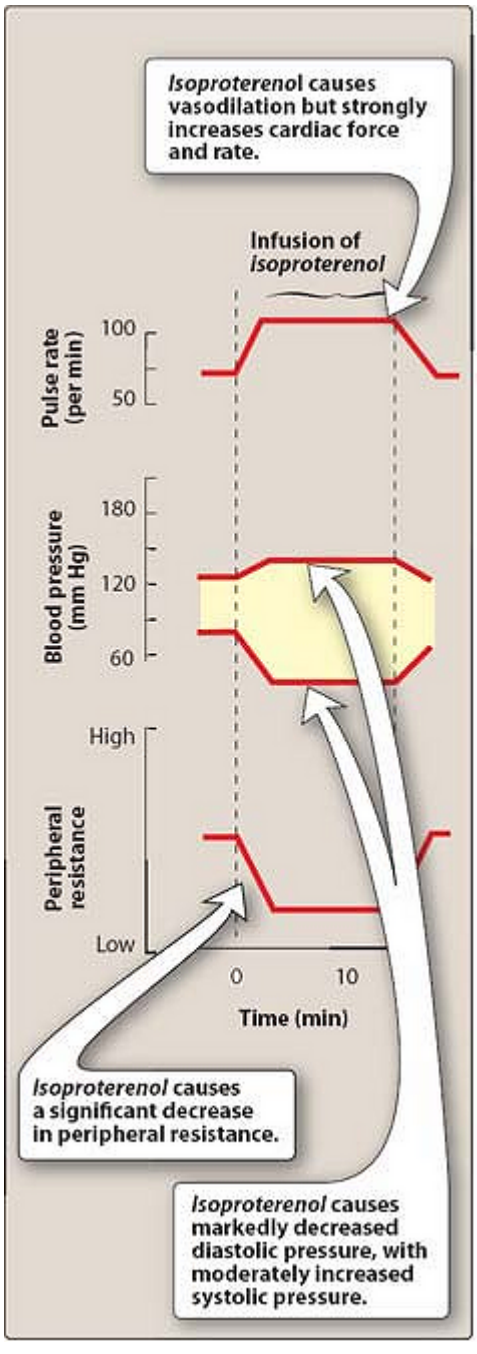


Figure 6.12 Cardiovascular effects of intravenous infusion of *isoproterenol*.

1. **Actions:**

   a. **Cardiovascular:** *Isoproterenol* produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output (Figure 6.12). It is as active as *epinephrine* in this action and, therefore, is useful in the treatment of atrioventricular block or cardiac arrest. *Isoproterenol* also dilates the arterioles of skeletal muscle ($\hat{I}^2_2$ effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure (see Figure 6.12).

b. **Pulmonary:** A profound and rapid bronchodilation is produced by the drug (Î²$_2$ action, Figure 6.13). *Isoproterenol* is as active as *epinephrine* and rapidly alleviates an acute attack of asthma when taken by inhalation (which is the recommended route). This action lasts about 1 hour and may be repeated by subsequent doses.

c. **Other effects:** Other actions on Î² receptors, such as increased blood sugar and increased lipolysis, can be demonstrated but are not clinically significant.

2. **Therapeutic uses:** *Isoproterenol* is now rarely used as a broncho-dilator in asthma. It can be employed to stimulate the heart in emergency situations.

3. **Pharmacokinetics:** *Isoproterenol* can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as an inhaled aerosol. It is a marginal substrate for COMT and is stable to MAO action.

4. **Adverse effects:** The adverse effects of *isoproterenol* are similar to those of *epinephrine*.

D. Dopamine

Dopamine [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate Î±- and Î²-adrenergic receptors. For example, at higher doses, it can cause vasoconstriction by activating Î±$_1$ receptors, whereas at lower doses, it stimulates Î²$_1$ cardiac receptors. In addition, D_1 and D_2 dopaminergic receptors, distinct from the Î±- and Î²-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D_2 receptors are

also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

1. **Actions:**

a. **Cardiovascular:** *Dopamine* exerts a stimulatory effect on the Î²$_1$ receptors of the heart, having both inotropic and chronotropic effects (see Figure 6.13). At very high doses, *dopamine* activates Î±$_1$ receptors on the vasculature, resulting in vasoconstriction.

b. **Renal and visceral:** *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thus increasing blood flow to the kidneys and other viscera (see Figure 6.13). These receptors are not affected by Î±- or Î²-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function. [Note: Similar *dopamine* receptors are found in the autonomic ganglia and in the CNS.]

2. **Therapeutic uses:** *Dopamine* is the drug of choice for shock and is given by continuous infusion. It raises the blood pressure by stimulating the Î²$_1$ receptors on the heart to increase cardiac output, and Î±$_1$ receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. An increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis. In this regard, *dopamine* is far superior to norepinephrine, which diminishes the blood supply to the kidney and may cause renal shutdown.

3. **Adverse effects:** An overdose of *dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized to homovanillic acid by MAO or COMT, and its adverse effects (nausea, hypertension, arrhythmias) are therefore short-lived.

E. Dobutamine

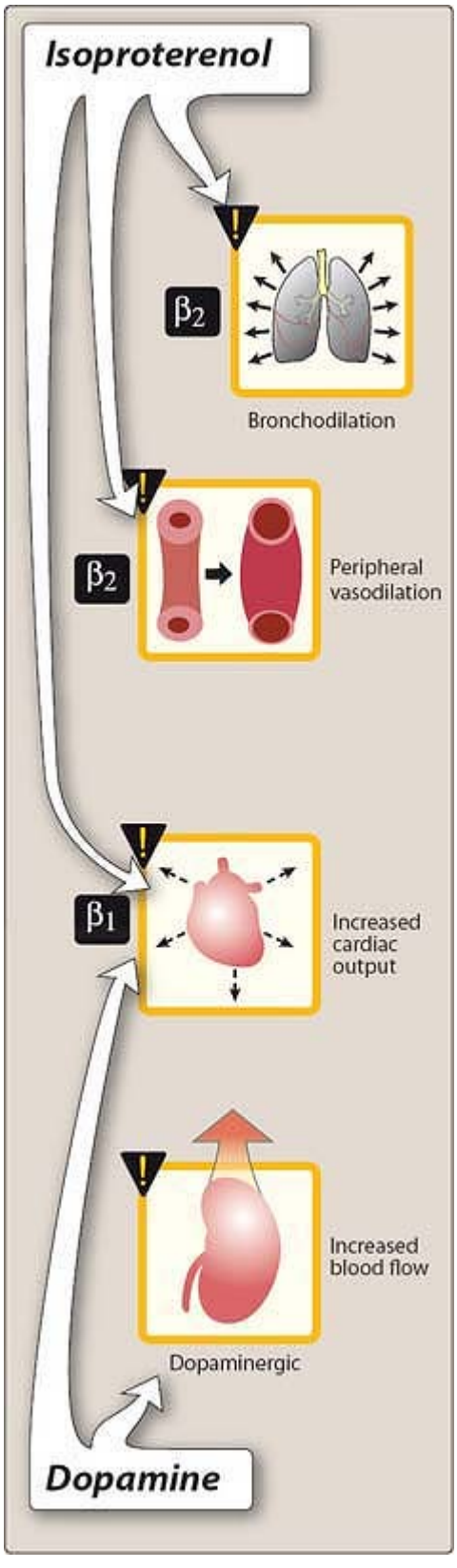


Figure 6.13 Clinically important actions of *isoproterenol* and *dopamine*.

1. **Actions:** *Dobutamine* [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is a Î²$_1$-receptor agonist. It is available as a racemic mixture. One of the stereoisomers has a stimulatory activity. It increases cardiac rate and output with few vascular effects.
2. **Therapeutic uses:** *Dobutamine* is used to increase cardiac output in congestive heart failure (see p. 194) as well as for inotropic support after cardiac surgery. The drug increases cardiac output with little change in heart rate, and it does not significantly elevate oxygen demands of the myocardiumâ€"a major advantage over other sympathomimetic drugs.
3. **Adverse effects:** *Dobutamine* should be used with caution in atrial fibrillation, because the drug increases atrioventricular conduction. Other adverse effects are the same as those for *epinephrine*. Tolerance may develop on prolonged use.

F. Oxymetazoline

Oxymetazoline [ok-see-met-AZ-of-leen] is a direct-acting synthetic adrenergic agonist that stimulates both Î±$_1$- and Î±$_2$-adrenergic receptors. It is primarily used locally in the eye or the nose as a vasoconstrictor. *Oxymetazoline* is found in many over-the-counter short-term nasal spray

decongestant products as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, or contact lens. The mechanism of action of *oxymetazoline* is direct stimulation of Î± receptors on blood vessels supplying the nasal mucosa and the conjunctiva to reduce blood flow and decrease congestion. *Oxymetazolin*e is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. When administered in the nose, burning of the nasal mucosa and sneezing may occur. Rebound congestion is observed with long-term use.

G. Phenylephrine

Phenylephrine [fen-ill-EF-rin] is a direct-acting, synthetic adrenergic drug that binds primarily to Î± receptors and favors Î±$_1$ receptors over Î±$_2$ receptors. It is not a catechol derivative and, therefore, not a substrate for COMT. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. *Phenylephrine* acts as a nasal decongestant and produces prolonged vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the atrioventricular junction and atria). Large doses can cause hypertensive headache and cardiac irregularities.

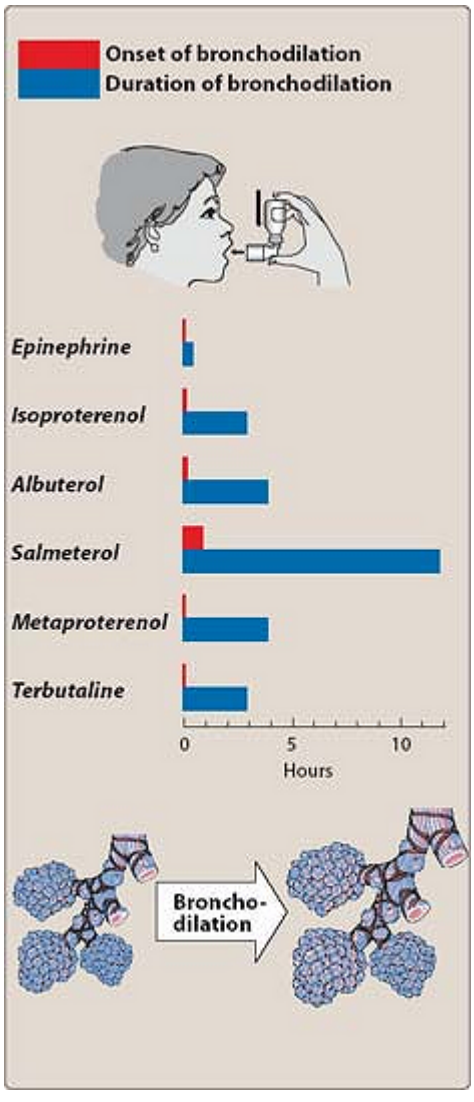


Figure 6.14 Onset and duration of bronchodilation effects of inhaled adrenergic agonists.

H. Methoxamine

Methoxamine [meth-OX-a-meen] is a direct-acting, synthetic adrenergic drug that binds primarily to Î± receptors, with $Î±_1$ receptors favored over $Î±_2$ receptors. *Methoxamine* raises blood pressure by stimulating $Î±_1$ receptors in the arterioles, causing vasoconstriction. This causes an increase in total peripheral resistance. Because of its effects on the vagus nerve, *methoxamine* is used clinically to relieve attacks of paroxysmal supraventricular tachycardia. It is also used to overcome hypotension during surgery involving *halothane* anesthetics. In contrast to most other adrenergic drugs, *methoxamine* does not tend to trigger cardiac arrhythmias in the heart, which is sensitized by these general anesthetics. Adverse effects include hypertensive headache and vomiting.

I. Clonidine

Clonidine [KLOE-ni-deen] is an $Î±_2$ agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS (see p. 225). It can be used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines. *Clonidine* acts centrally to produce inhibition of sympathetic vasomotor centers, decreasing

sympathetic outflow to the periphery.

J. Metaproterenol

Metaproterenol [met-a-proe-TER-a-nole], although chemically similar to *isoproterenol*, is not a catecholamine, and it is resistant to methylation by COMT. It can be administered orally or by inhalation. The drug acts primarily at Î²$_2$ receptors, producing little effect on the heart. *Metaproterenol* produces dilation of the bronchioles and improves airway function. The drug is useful as a bronchodilator in the treatment of asthma and to reverse bronchospasm (Figure 6.14).

K. Albuterol, pirbuterol, and terbutaline

Albuterol [al-BYOO-ter-ole], *pirbuterol* [peer-BYOO-ter-ole], and *terbutaline* [ter-BYOO-te-leen] are short-acting Î²$_2$ agonists used primarily as bronchodilators and administered by a metered-dose inhaler (see Figure 6.14). Compared with the nonselective Î²-adrenergic agonists, such as *metaproterenol*, these drugs produce equivalent bronchodilation with less cardiac stimulation.

L. Salmeterol and formoterol

Salmeterol [sal-ME-ter-ole] and *formoterol* [for-MOH-ter-ole] are Î²$_2$-adrenergic selective, long-acting bronchodilators. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol*. Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action (see Figure 6.14). These agents are not recommended as monotherapy and are highly efficacious when combined with a corticorsteroid. *Salmeterol* and *formoterol* are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

V. Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause norepinephrine release from presynaptic terminals or inhibit the uptake of norepinephrine (see Figure 6.8). They potentiate the effects of norepinephrine produced endogenously, but these agents do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of *amphetamin*e [am-FET-a-meen] is often mistaken by drug abusers as its only action. However, the drug can increase blood pressure significantly by Î±-agonist action on the vasculature as well as Î²-stimulatory effects on the heart. Its peripheral actions are mediated primarily through the blockade of norepinephrine uptake and cellular release of stored catecholamines; thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and uses of amphetamines are discussed under stimulants of the CNS (see p. 121). The CNS stimulant effects of *amphetamine* and its derivatives have led to their use for treating hyperactivity in children, narcolepsy, and appetite control. Its use in pregnancy should be avoided because of adverse effects on development of the fetus.

B. Tyramine

Tyramine [TIE-ra-meen] is not a clinically useful drug, but it is important because it is found in fermented foods, such as ripe cheese and Chianti wine (see MAO inhibitors, p. 145). It is a normal byproduct of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient is taking MAO inhibitors, it can precipitate serious vasopressor episodes. Like amphetamines, tyramine can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

C. Cocaine

Cocaine [koe-KANE] is unique among local anesthetics in having the ability to block the Na^+/K^+-activated ATPase

(required for cellular uptake of norepinephrine) on the cell membrane of the adrenergic neuron.

Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of *epinephrine* and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocain*e as compared to those in one who is not. In addition, the duration of action of *epinephrine* and norepinephrine is increased. Like amphetamines, it can increase blood pressure by Î±-agonist actions and Î²-stimulatory effects. [Note: *Cocaine* as a CNS stimulant and drug of abuse is discussed on p. 118.]

VI. Mixed-Action Adrenergic Agonists

Mixed-action drugs induce the release of norepinephrine from presynaptic terminals, and they activate adrenergic receptors on the postsynaptic membrane (see Figure 6.8).

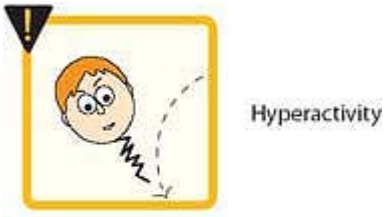


Figure 6.15 Some adverse effects observed with adrenergic agonists.

A. Ephedrine and pseudoephedrine

Ephedrine [e-FED-rin], and *pseudoephedrine* [soo-doe-e-FED-rin] are plant alkaloids, that are now made synthetically. These drugs are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings (see Figure 6.8) but also directly stimulate both Î± and Î² receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent. *Ephedrine* and

pseudoephedrine are not catechols and are poor substrates for COMT and MAO; thus, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS; however, *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in the urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in the urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. *Ephedrine* produces bronchodilation, but it is less potent than *epinephrine* or *isoproterenol* in this regard and produces its action more slowly. It is therefore sometimes used prophylactically in chronic treatment of asthma to prevent attacks rather than to treat the acute attack. *Ephedrine* enhances contractility and improves motor function in myasthenia gravis, particularly when used in conjunction with anticholinesterases (see p. 50). *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. *Ephedrine* has been used to treat asthma, as a nasal decongestant (due to its local vasoconstrictor action), and to raise blood pressure. *Pseudoephedrine* is primarily used to treat nasal and sinus congestion or congestion of the eustachian tubes. [Note: The clinical use of *ephedrine* is declining due to the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) were banned by the U.S. Food and Drug Administration in April 2004 because of life-threatening cardiovascular reactions. *Pseudoephedrine* has been illegally converted to *methamphetamine*. Thus, products containing *pseudoephedrine* have certain restrictions and must be kept behind the sales counter.]

Important characteristics of the adrenergic agonists are summarized in Figures 6.15, 6.16 and 6.17.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2	↑ Glucose metabolism, lipolysis	α_1-Adrenergic receptors
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Potassium uptake, glycogenolysis Dilates arteries to skeletal muscle	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Figure 6.16 Summary of Î²-adrenergic receptors

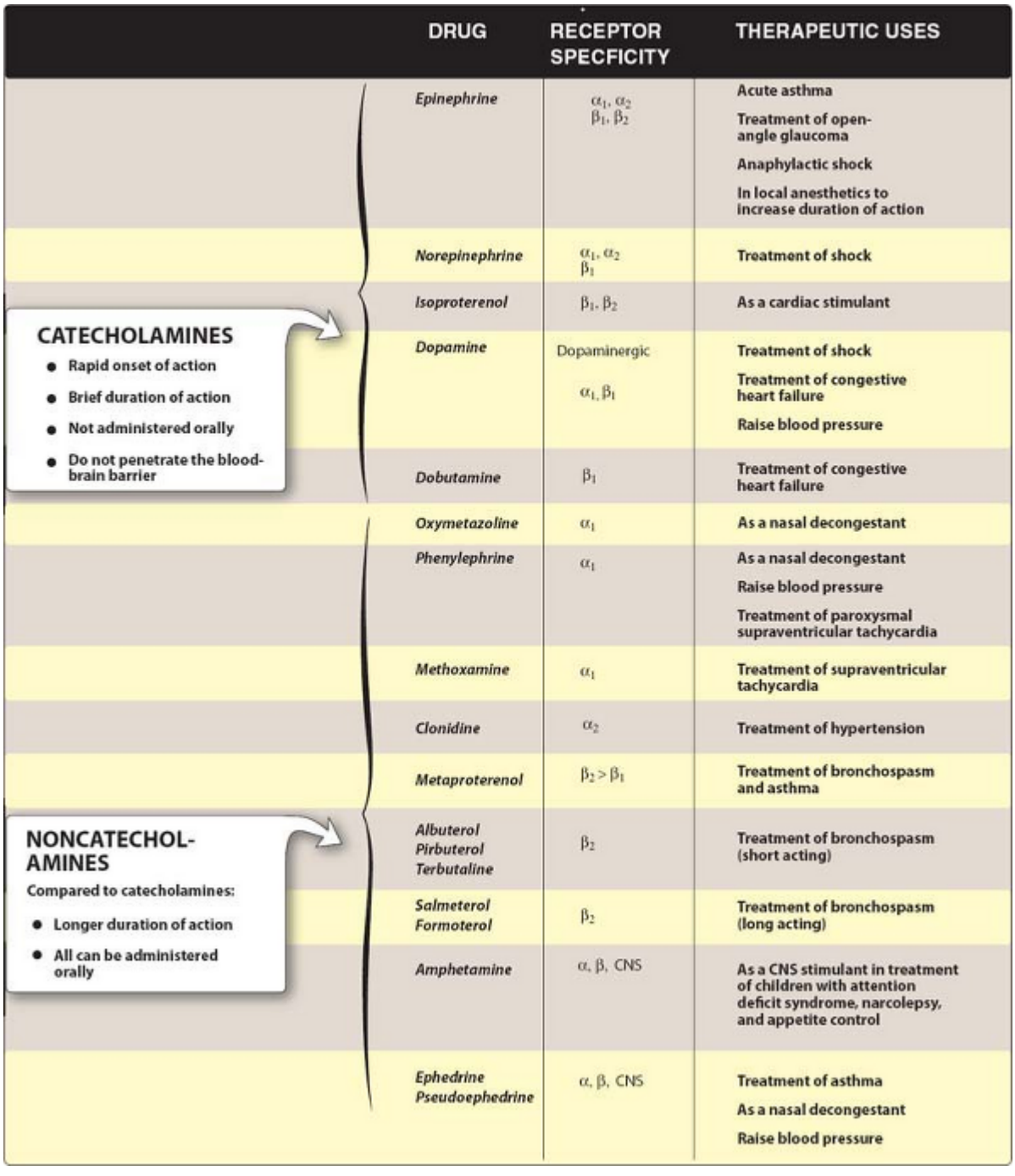


Figure 6.17 Summary of the therapeutic uses of adrenergic agonists.

Study Questions

Choose the ONE best answer.

6.1 A 68-year-old man presents to the emergency department with acute heart failure. You decide that this patient requires immediate drug therapy to improve his cardiac function. Which one of the following drugs

would be most beneficial?

A. Albuterol.

B. Dobutamine.

C. Epinephrine.

D. Norepinephrine.

E. Phenylephrine.

View Answer

6.2 Remedies for nasal stuffiness often contain which one of the following drugs?

A. Albuterol.

B. Atropine.

C. Epinephrine.

D. Norepinephrine.

E. Phenylephrine.

View Answer

6.3 Which one of the following drugs, when administered intravenously, can decrease blood flow to the skin, increase blood flow to skeletal muscle, and increase the force and rate of cardiac contraction?

A. Epinephrine.

B. Isoproterenol.

C. Norepinephrine.

D. Phenylephrine.

E. Terbutaline.

View Answer

6.4 The following circles represent pupillary diameter in one eye prior to and following the topical application of Drug X:

A. Physostigmine.

B. Acetylcholine.

C. Terbutaline.

D. Phenylephrine.

E. Isoproterenol.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 7

Adrenergic Antagonists

I. Overview

The adrenergic antagonists (also called blockers or sympatholytic agents) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for Î± or Î² receptors in the peripheral nervous system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are therefore considered in that section (see p. 151).] The receptor-blocking drugs discussed in this chapter are summarized in Figure 7.1.

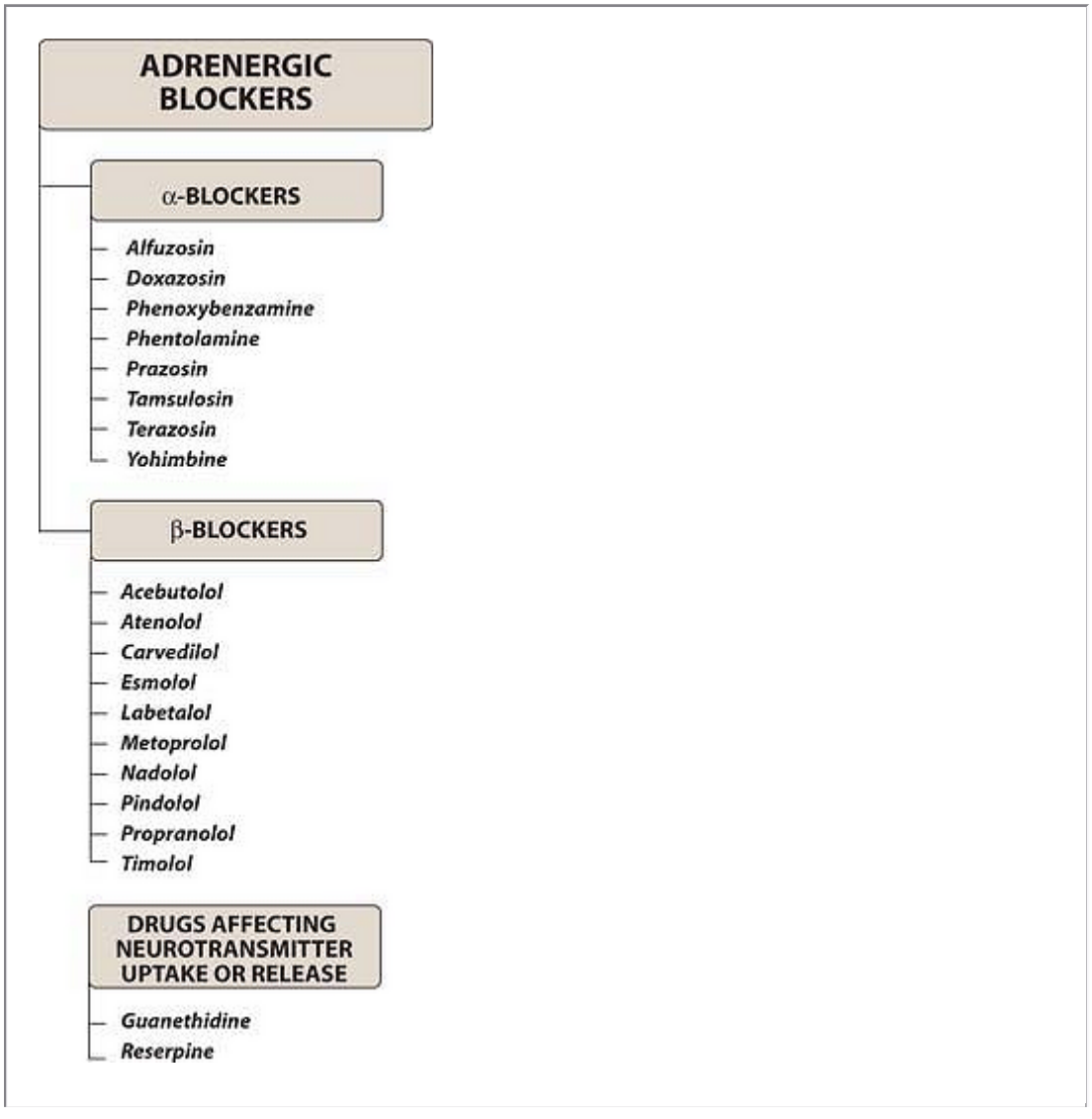


Figure 7.1 Summary of blocking agents and drugs affecting neurotransmitter uptake or release.

II. Î±-Adrenergic Blocking Agents

Drugs that block Î±-adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on Î±-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. [Note: Î² receptors, including $Î²_1$-adrenoceptors on the heart, are not affected by Î± blockade.] The Î±-adrenergic blocking agents, *phenoxybenzamine* and *phentolamine*, have limited clinical applications.

A. Phenoxybenzamine

Phenoxybenzamine [fen-ox-ee-BEN-za-meen] is nonselective, linking covalently to both $Î±_1$-postsynaptic and $Î±_2$-presynaptic receptors (Figure 7.2). The block is irreversible and noncompetitive, and the only mechanism the body has for overcoming the block is to synthesize new adrenoceptors, which requires a day or more. Therefore, the actions of *phenoxybenzamine* last about 24 hours after a single administration. After the drug is injected, a delay of a few hours occurs before a blockade develops, because the molecule must undergo biotransformation to the active form.

1. **Actions:**

   a. **Cardiovascular effects:** By blocking Î± receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the

   ability to block presynaptic inhibitory $Î±_2$ receptors in the heart can contribute to an increased cardiac output. [Note: These receptors when blocked will result in more norepinephrine release, which stimulates Î² receptors on the heart to increase cardiac output]. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension and has been discontinued for this purpose.

   b. **Epinephrine reversal:** All Î±-adrenergic blockers reverse the Î±-agonist actions of *epinephrine.* For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of Î² receptors is not blocked. Therefore, the systemic blood pressure decreases in response to *epinephrine* given in the presence of *phenoxybenzamine* (Figure 7.3). [Note: The actions of norepinephrine are not reversed but are diminished, because norepinephrine lacks significant Î²-agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure Î² agonist (see Figure 7.3).

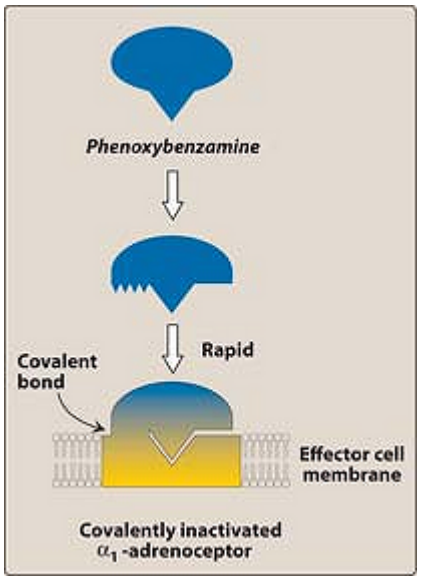


Figure 7.2 Covalent inactivation of Î±$_1$ adrenoceptor by *phenoxybenzamine*.

2. **Therapeutic uses:** *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with *phenoxybenzamine* to preclude the hypertensive crisis that can result from manipulation of the tissue. This drug is also useful in the chronic management of these tumors, particularly when the catecholamine-secreting cells are diffuse and, therefore, inoperable. *Phenoxybenzamine* or *phentolamine* are sometimes effective in treating Raynaud's disease. Autonomic hyperreflexia, which predisposes paraplegics to strokes, can be managed with *phenoxybenzamine.*
3. **Adverse effects:** *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It can inhibit ejaculation. The drug also may induce reflex tachycardia, mediated by the baroreceptor reflex, and is contraindicated in patients with decreased coronary perfusion.

B. Phentolamine

In contrast to *phenoxybenzamine, phentolamine* [fen-TOLE-a-meen] produces a competitive block of Î±$_1$ and Î±$_2$ receptors. The drug's action lasts for approximately 4 hours after a single administration. Like *phenoxybenzamine*, it produces postural hypotension and causes *epinephrine* reversal. *Phentolamine*-induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the Î±$_2$ receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain, and it is contraindicated in patients with decreased coronary perfusion. *Phentolamine* is also used for the short-term management of pheochromocytoma. *Phentolamine* is now rarely used for the treatment of impotence (it can be injected intracavernosally to produce vasodilation of penile arteries).

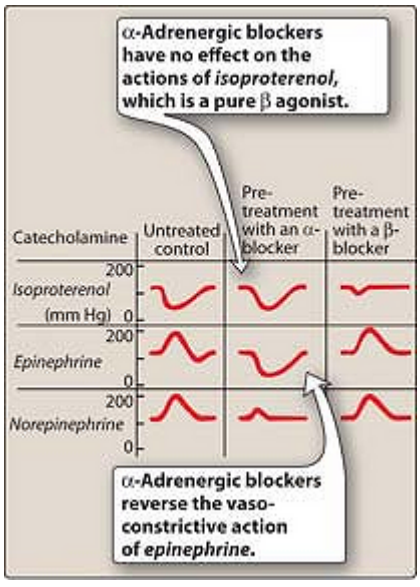


Figure 7.3 Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol, epinephrine*, and *norepinephrine*.

C. Prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin

Prazosin [PRAY-zoe-sin], *terazosin* [ter-AY-zoe-sin], *doxazosin* [dox-AY-zoe-sin], and *tamsulosin* [tam-SUE-loh-sin] are selective competitive blockers of the Î±$_1$ receptor. In contrast to *phenoxybenzamine* and *phentolamine*,

the first three drugs are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* [al-FYOO-zoe-sin] are indicated for the treatment of benign prostatic hypertrophy (also known as benign prostatic hyperplasia or BPH). Metabolism leads to inactive products that are excreted in the urine except for those of *doxazosin*, which appear in the feces. *Doxazosin* is the longest acting of these drugs.

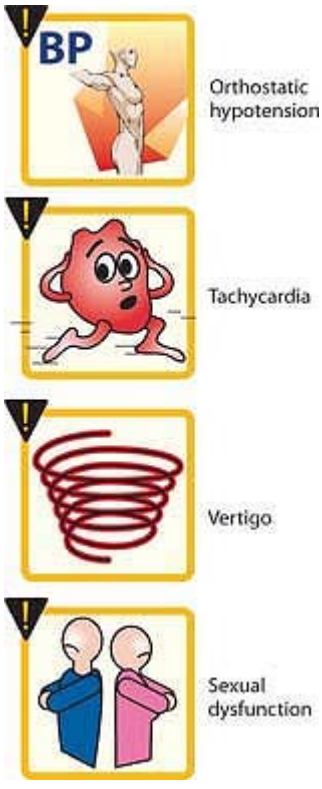


Figure 7.4 Some adverse effects commonly observed with nonselective Î±-adrenergic blocking agents.

1. **Cardiovascular effects:** All of these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. *Tamsulosin* has the least effect on blood pressure. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and the glomerular filtration rate.

2. **Therapeutic uses:** Individuals with elevated blood pressure who have been treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs produces an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a â€œfirst-doseâ€ effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. An increase in the risk of congestive heart failure has been reported when $\hat{I}\pm_1$-receptor blockers have been used as monotherapy in hypertension. The $\hat{I}\pm_1$-receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH. Blockade of the Î± receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. *Tamsulosin* is a more potent inhibitor of the $\hat{I}\pm_{1A}$ receptors found on the smooth muscle of the prostate. This selectivity accounts for *tamsulosin*'s minimal effect on blood pressure. [Note: *Finasteride* and *dutasteride* inhibit 5Î±-reductase, preventing the conversion of testosterone to dihydrotestosterone. These drugs are approved for the treatment of BPH by reducing prostate volume in selected patients (see. p. 309)]

3. **Adverse effects:** $\hat{I}\pm_1$ Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). An additive antihypertensive effect occurs when *prazosin* is given with either a diuretic or a Î²-blocker, thereby necessitating a reduction in its dose. Due to a tendency to retain sodium and fluid, *prazosin* is frequently used along with a diuretic. Male sexual function is not as severely affected by these drugs as it is by *phenoxybenzamine* and *phentolamine*; however, by blocking a receptors in the ejaculatory ducts and impairing

smooth muscle contraction, inhibition of ejaculation and retrograde ejaculation have been reported. Figure 7.4 summarizes some adverse effects observed with Î±-blockers.

D. Yohimbine

Yohimbine [yo-HIM-bean] is a selective competitive $\hat{I}\pm_2$ blocker. It is found as a component of the bark of the yohimbe tree and is sometimes used as a sexual stimulant. *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery. It directly blocks $\hat{I}\pm_2$ receptors and has been used to relieve vasoconstriction associated with Raynaud's disease. *Yohimbine* is contraindicated in CNS and cardiovascular conditions because it is a CNS and cardiovascular stimulant.

III. Î²-Adrenergic Blocking Agents

All the clinically available Î²-blockers are competitive antagonists. Nonselective Î²-blockers act at both $\hat{I}^2_1$ and $\hat{I}^2_2$ receptors, whereas cardioselective Î² antagonists primarily block $\hat{I}^2_1$ receptors [Note: There are no clinically useful $\hat{I}^2_2$ antagonists]. These drugs also differ in intrinsic sympathomimetic activity, in CNS effects, and in pharmacokinetics (Figure 7.5). Although all Î²-blockers lower blood pressure in hypertension, they do not induce postural hypotension, because the Î±-adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. Î²-Blockers are also effective in treating angina, cardiac arrhythmias, myocardial infarction, congestive heart failure, hyperthyroidism, and glaucoma, as well as serving in the prophylaxis of migraine headaches. [Note: The names of all Î²-blockers end in â€œ-ololâ€ except for *labetalol* and *carvedilol*.]

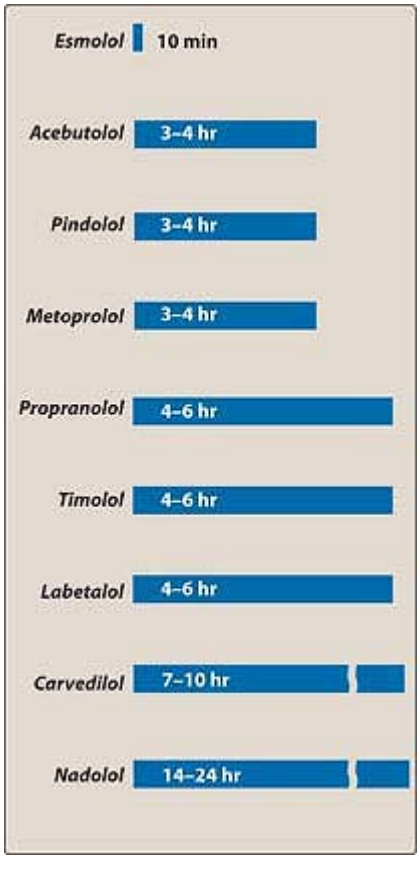


Figure 7.5 Elimination half-lives for some Î±-blockers.

A. Propranolol: A nonselective Î² antagonist

Propranolol [proe-PRAN-oh-lole] is the prototype Î²-adrenergic antagonist and blocks both $\hat{I}^2_1$ and $\hat{I}^2_2$ receptors. Sustained-release preparations for once-a-day dosing are available.

1. **Actions:**

   a. **Cardiovascular:** *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 7.6). It directly depresses sinoatrial and atrioventricular activity. The resulting bradycardia usually limits the dose of the drug. Cardiac output, work, and oxygen consumption are decreased by blockade of $\hat{I}^2_1$ receptors; these effects are useful in the treatment of angina (see p. 211). The Î²-blockers are effective in attenuating supraventricular cardiac arrhythmias but generally are not effective against ventricular arrhythmias (except those induced by exercise).

   b. **Peripheral vasoconstriction:** Blockade of Î² receptors prevents $\hat{I}^2_2$-mediated vasodilation (see Figure 7.6). The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. On balance, there is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, because the $\hat{I}\pm_1$-adrenergic receptors that control vascular resistance are unaffected.

   c. **Bronchoconstriction:** Blocking $\hat{I}^2_2$ receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (see Figure 7.6). This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease (COPD) or asthma. Î²-Blockers, and in particular nonselective ones, are thus contraindicated in patients with COPD or asthma.

   d. **Increased Na^+ retention:** Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume (see Figure 7.6). In some cases, this compensatory response tends to elevate the blood pressure. For these patients, Î²-blockers are often combined with a diuretic to prevent Na^+ retention. By inhibiting Î² receptors, renin production is also prevented, contributing to Na^+ retention.

   e. **Disturbances in glucose metabolism:** Î²-blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if a Type I (formerly insulin-dependent) diabetic is to be given *propranolol*, very careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection. Î²-Blockers also attenuate the normal physiologic response to hypoglycemia.

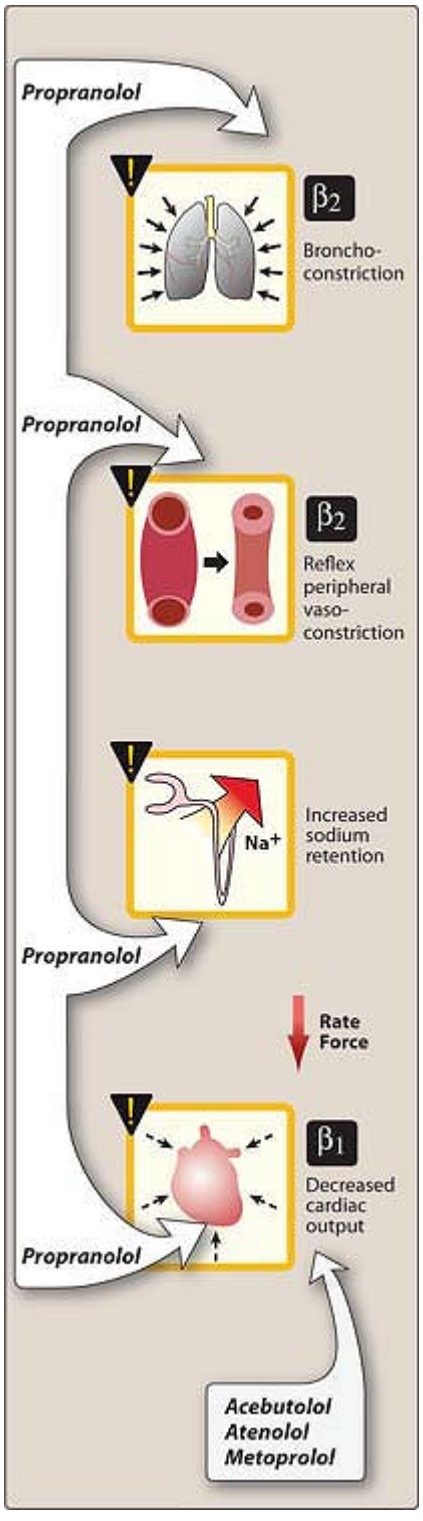


Figure 7.6 Actions of *propranolol* and other Î²-blockers.

f. **Blocked action of isoproterenol:** All Î²-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* on the cardiovascular system. Thus, in the presence of a Î²-blocker, *isoproterenol* does not produce either the typical cardiac stimulation or reductions in mean arterial pressure and diastolic pressure

(see Figure 7.3). [Note: In the presence of a Î²-blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by Î± receptors) remains unimpaired. The actions of norepinephrine on the cardiovascular system are mediated primarily by Î± receptors and are, therefore, unaffected.]

2. **Therapeutic effects:**

   a. **Hypertension:** *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney and decreased sympathetic outflow from the CNS also contribute to *propranolol's* antihypertensive effects (see p. 220).

   b. **Glaucoma:** Î²-Blockers, particularly topically applied *timolol*, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Many patients with glaucoma have been maintained with these drugs for years. They neither affect the ability of the eye to focus for near vision nor change pupil size, as do the cholinergic drugs. However, in an acute attack of glaucoma, *pilocarpine* is still the drug of choice. The Î²-blockers are only used to treat this disease chronically.

   c. **Migraine:** *Propranolol* is also effective in reducing migraine episodes when used prophylactically (see p. 526). Î²-Blockers are valuable in the treatment of chronic migraine, in which they decrease the incidence and severity of the attacks. The mechanism may depend on the blockade of catecholamine-induced vasodilation in the brain vasculature. [Note: During an attack, the usual therapy with *sumatriptan* or other drugs is used.]

   d. **Hyperthyroidism:** *Propranolol* and other Î²-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), Î²-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

   e. **Angina pectoris:** *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing the chest pain on exertion that is common in angina. *Propranolol* is therefore

   useful in the chronic management of stable angina, but not for acute treatment. Tolerance to moderate exercise is increased, and this is measurable by improvement in the electrocardiogram. However, treatment with *propranolol* does not allow strenuous physical exercise, such as tennis.

   f. **Myocardial infarction:** *Propranolol* and other Î²-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of Î²-blockers. In addition, administration of a Î²-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery. The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

3. **Adverse effects:**

   a. **Bronchoconstriction:** *Propranolol* has a serious and potentially lethal side effect when administered to an asthmatic (Figure 7.7). An immediate contraction of the bronchiolar smooth muscle prevents air from entering the lungs. Deaths by asphyxiation have been reported for asthmatics who were inadvertently administered the drug. Therefore, *propranolol* must never be used in treating any individual with COPD or asthma.

   b. **Arrhythmias:** Treatment with Î²-blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The Î²-blockers must be tapered off gradually for 1 week. Long-term treatment with a Î² antagonist leads to up-regulation of the Î²-receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

c. **Sexual impairment:** Because sexual function in the male occurs through Î±-adrenergic activation, Î²-blockers do not affect normal ejaculation or the internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear, and they may be independent of Î²-receptor blockade.

d. **Disturbances in metabolism:** Î²-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. [Note: Cardioselective Î²-blockers are preferred in treating asthmatic patients who use insulin (see $Î²_1$-selective antagonists).]

e. **Drug interactions:** Drugs that interfere with the metabolism of *propranolol*, such as *cimetidine, fluoxetine, paroxetine*, and *ritonavir*, may potentiate its antihypertensive effects. Conversely, those that stimulate its metabolism, such as barbiturates, *phenytoin,* and *rifampin*, can decrease its effects.

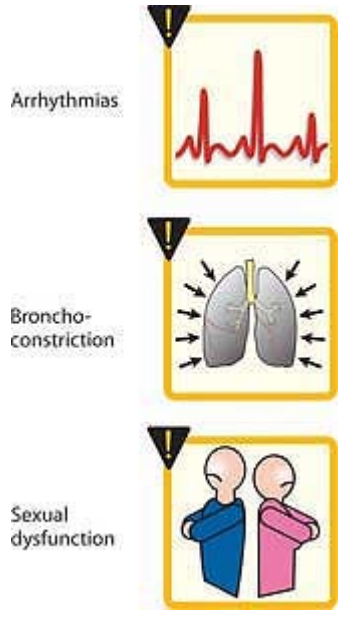


Figure 7.7 Adverse effects commonly observed in individuals treated with *propranolol*.

B. Timolol and nadolol: Nonselective Î² antagonists

Timolol [TIM-o-lole] and *nadolol* [NAH-doh-lole] also block $Î²_1$- and $Î²_2$- adrenoceptors and are more potent than *propranolol*. *Nadolol* has a

very long duration of action (see Figure 7.5). *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

C. Acebutolol, atenolol, metoprolol, and esmolol: Selective $Î²_1$ antagonists

Drugs that preferentially block the $Î²_1$ receptors have been developed to eliminate the unwanted bronchoconstrictor effect ($Î²_2$ effect) of *propranolol* seen among asthmatic patients. Cardioselective Î²-blockers, such as *acebutolol* [a-se-BYOO-toe-lole], *atenolol* [a-TEN-oh-lole], and *metoprolol* [me-TOE-proe-lole], antagonize $Î²_1$ receptors at doses 50- to 100-fold less than those required to block $Î²_2$ receptors. This

cardioselectivity is thus most pronounced at low doses and is lost at high doses. [Note: *Acebutolol* has some intrinsic agonist activity.]

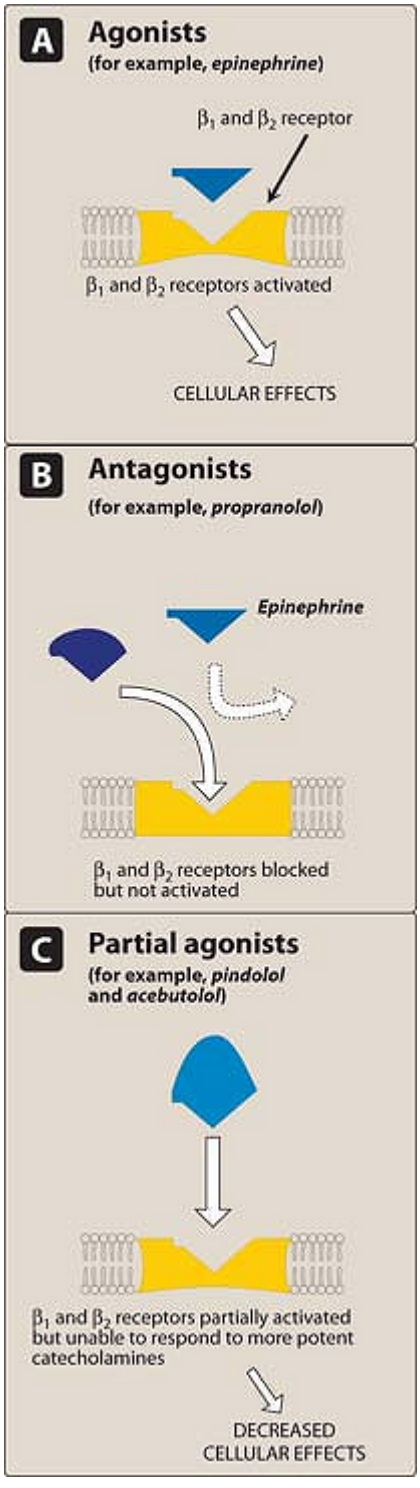


Figure 7.8 Comparison of agonists, antagonists, and partial agonists of Î² adrenoceptors.

1. **Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (see Figure

7.6). *Esmolol* [EZ-moe-lole] has a very short lifetime (see Figure 7.5) due to metabolism of an ester linkage. It is only given intravenously if required during surgery or diagnostic procedures (for example, cystoscopy). In contrast to *propranolol*, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthmatics treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised.

2. **Therapeutic use in hypertension:** The cardioselective Î²-blockers are useful in hypertensive patients with impaired pulmonary function. Because these drugs have less effect on peripheral vascular $Î²_2$ receptors, coldness of extremities, a common side effect of Î²-blocker therapy, is less frequent. Cardioselective Î²-blockers are useful in diabetic hypertensive patients who are receiving insulin or oral hypoglycemic agents.

D. Pindolol and acebutolol: Antagonists with partial agonist activity

1. **Actions:**

   a. **Cardiovascular:** *Acebutolol* and *pindolol* [PIN-doe-lole] are not pure antagonists; instead, they have the ability to weakly stimulate both $Î²_1$ and $Î²_2$ receptors (Figure 7.8) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the Î² receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, *epinephrine* and norepinephrine. The result of these opposing actions is a much diminished effect on cardiac rate and cardiac output compared to that of Î²-blockers without ISA.

   b. **Decreased metabolic effects:** Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other Î²-blockers.

2. **Therapeutic use in hypertension:** Î²-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with *acebutolol* and *pindolol*

than it is with *propranolol*, making them valuable in the treatment of diabetics. [Note: The b blockers with ISA are not used as antiarrhythmic agents due to their partial agonist effect.] Figure 7.9 summarizes some of the indications for Î²-blockers.

E. Labetalol and carvedilol: Antagonists of both Î±- and Î²-adrenoceptors

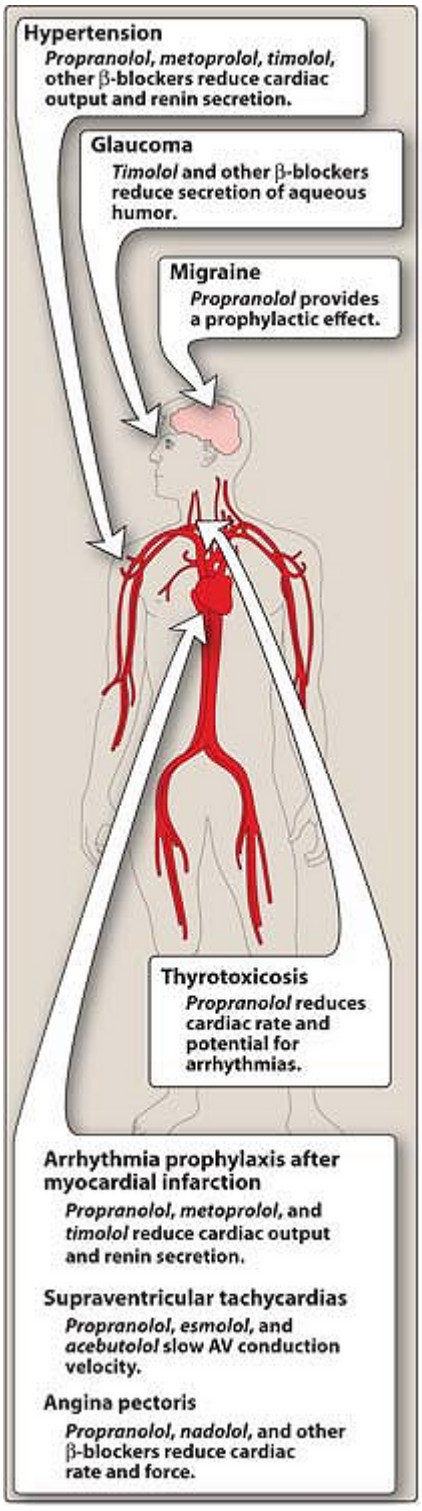


Figure 7.9 Some clinical applications of Î²-blockers. AV = atrioventricular.

1. **Actions:** *Labetalol* [lah-BET-a-lole] and *carvedilol* [CAR-ve-dil-ol] are reversible Î²-blockers with concurrent Î±$_1$-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other Î²-blockers that produce peripheral vasoconstriction, and they are therefore useful in treating

hypertensive patients for whom increased peripheral vascular resistance is undesirable. They do not alter serum lipid or blood glucose levels. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2. **Therapeutic use in hypertension:** *Labetalol* is useful for treating the elderly or black hypertensive patient in whom increased peripheral vascular resistance is undesirable. [Note: In general, black hypertensive patients are not well controlled with Î²-blockers.] *Labetalol* may be employed as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure (see p. 227).
3. **Adverse effects:** Orthostatic hypotension and dizziness are associated with $\hat{I}\pm_1$ blockade. Figure 7.10 summarizes the receptor specificities and uses of the Î²-adrenergic antagonists.

IV. Drugs Affecting Neurotransmitter Release or Uptake

As noted on p. 119, some agonists, such as *amphetamine* and *tyramine*, do not act directly on the adrenoceptor. Instead, they exert their effects indirectly on the adrenergic neuron by causing the release of neurotransmitter from storage vesicles. Similarly, some agents act on the adrenergic neuron, either to interfere with neurotransmitter release or to alter the uptake of the neurotransmitter into the adrenergic nerve. However, due to the advent of newer and more effective agents, with fewer side effects, these agents are rarely used therapeutically. These agents are included in this chapter due to their unique mechanisms of action and historical value.

A. Reserpine

Reserpine [re-SER-peen], a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphateâ€“dependent transport of biogenic amines, norepinephrine, *dopamine*, and *serotonin* from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. The drug has a slow onset, a long duration of action, and effects that persist for many days after discontinuation.

B. Guanethidine

Guanethidine [gwahn-ETH-i-deen] blocks the release of stored norepinephrine as well as displaces norepinephrine from storage vesicles (thus producing a transient increase in blood pressure). This leads to gradual depletion of norepinephrine in nerve endings except for those in the CNS. *Guanethidine* commonly causes orthostatic hypotension and interferes with male sexual function. Supersensitivity to norepinephrine due to depletion of the amine can result in hypertensive crisis in patients with pheochromocytoma.

C. Cocaine

Although cocaine inhibits norepinephrine uptake, it is an adrenergic agonist. See page 78 for discussion.

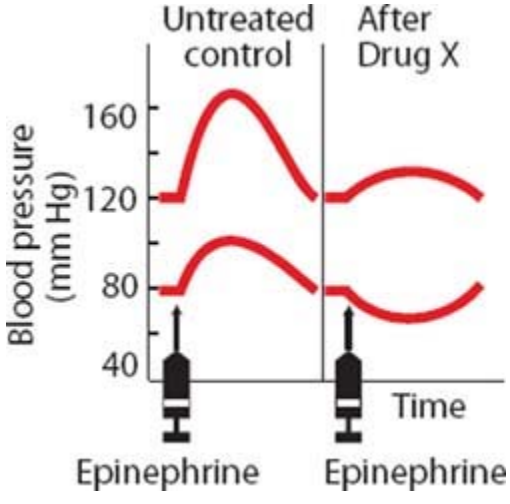
DRUG	RECEPTOR SPECFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Glaucoma Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Timolol*	β_1, β_2	Glaucoma Hypertension
Acebutolol[1] *Atenolol* *Esmolol* *Metoprolol*	β_1	Hypertension
Pindolol[1]	β_1, β_2	Hypertension
Carvedilol *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension Congestive heart failure

Figure 7.10 Summary of Î²-adrenergic antagonists. [1]*Acebutolol* and *pindolol* are partial agonists.

Study Questions

Choose the ONE best answer.

7.1 The graphs below depict the changes in blood pressure caused by the intravenous administration of epinephrine before and after an unknown Drug X.



Which of the following drugs is most likely Drug X?

A. Atropine.

B. Phenylephrine.

C. Physostigmine.

D. Prazosin.

E. Propranolol.

View Answer

7.2 A 38-year-old male has recently started monotherapy for mild hypertension. At his most recent office visit, he complains of tiredness and not being able to complete three sets of tennis. Which one of the following drugs is he most likely to be taking for hypertension?

A. Albuterol.

B. Atenolol.

C. Ephedrine.

D. Phentolamine.

E. Prazosin.

View Answer

7.3 A 60-year-old asthmatic man comes in for a checkup and complains that he is having some difficulty in â€œstarting to urinate.â€ Physical examination indicates that the man has a blood pressure of 160/100 mm Hg and a slightly enlarged prostate. Which of the following medications would be useful in treating both of these conditions?

A. Doxazosin.

B. Labetalol.

C. Phentolamine.

D. Propranolol.

E. Isoproterenol.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 8

Neurodegenerative Diseases

I. Overview

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs. These concepts are useful in understanding the etiology and treatment strategies of Parkinson's and Alzheimer's diseasesâ€"the two neurodegenerative disorders that respond to drug therapy (Figure 8.1).

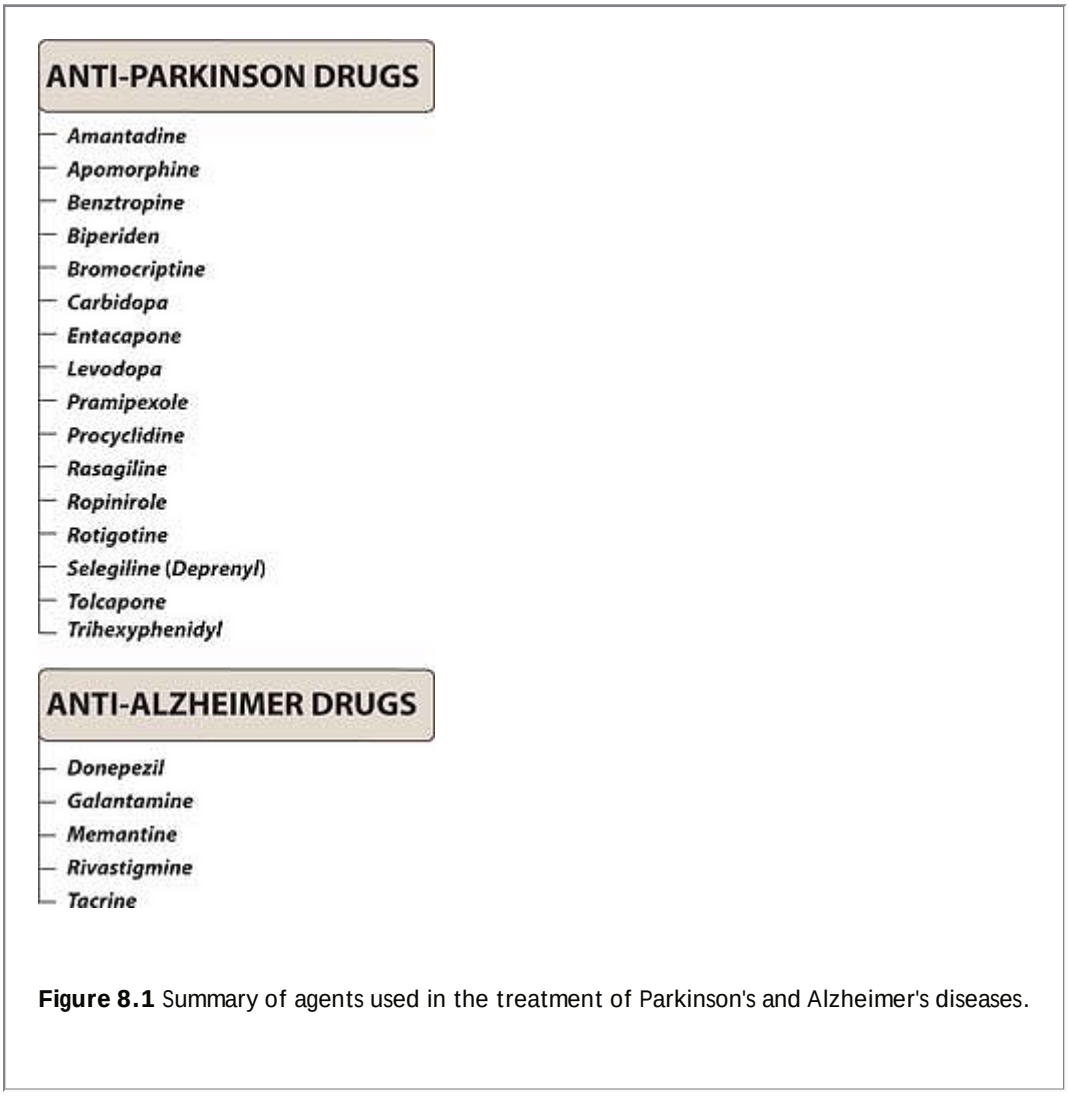


Figure 8.1 Summary of agents used in the treatment of Parkinson's and Alzheimer's diseases.

II. Neurotransmission in the CNS

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system described in Chapter 3. For example, transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral autonomic nervous system and those in the CNS. The circuitry of the CNS is much more complex than that of the autonomic nervous system, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral autonomic nervous system, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 10 (and perhaps as many as 50) different neurotransmitters. In contrast, the autonomic nervous system uses only two primary neurotransmitters, acetylcholine and norepinephrine. Figure 8.2 describes some of the more important neurotransmitters in the CNS.

NEUROTRANSMITTER		POSTSYNAPTIC EFFECTS
	Acetylcholine	Excitatory: Involved in arousal, short-term memory, learning and movement.
BIOGENIC AMINES	Norepinephrine	Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation.
	Dopamine	Excitatory: Involved in emotion, reward systems and motor control.
	Serotonin	Excitatory/Inhibitory: Feeding behavior, control of body temperature, modulation of sensory pathways including nociception (stimulation of pain nerve sensors), regulation of mood and emotion, and sleep/wakefulness.
AMINO ACIDS	GABA	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization. Mediates the majority of inhibitory postsynaptic potentials.
	Glycine	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization.
	Glutamate	Excitatory: Mediates excitatory Na^+ influx into the postsynaptic neuron.
NEURO-PEPTIDES	Substance P	Excitatory: Mediates nociception (pain) within the spinal cord.
	Met-enkephalin	Generally inhibitory: Mediates analgesia as well as other central nervous system effects.

Figure 8.2 Summary of some neurotransmitters of the central nervous system. GABA = Î»-aminobutyric acid.

III. Synaptic Potentials

In the CNS, receptors at most synapses are coupled to ion channels; that is, binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.

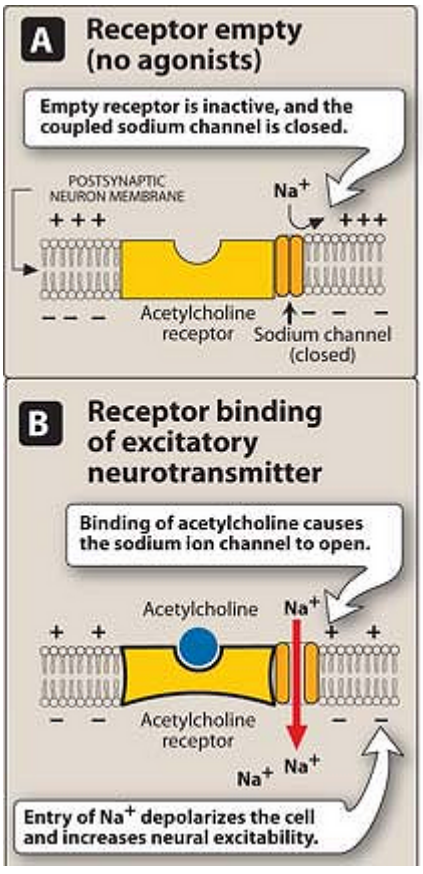


Figure 8.3 Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. 2) The influx of Na^+ causes a weak depolarization or EPSP that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] (See Figure 8.3 for an example of an excitatory pathway.)

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: 1)

Stimulation of inhibitory neurons releases neurotransmitter molecules, such as Î³-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the

permeability of specific ions, such as potassium (K^+) and chloride (Cl^-) ions. 2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization or IPSP that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. (See Figure 8.4 for an example of an inhibitory pathway.)

C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall resultant action is due to the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts thus seem to be chemically coded, and this may offer greater opportunity for selective modulation of certain neuronal pathways.

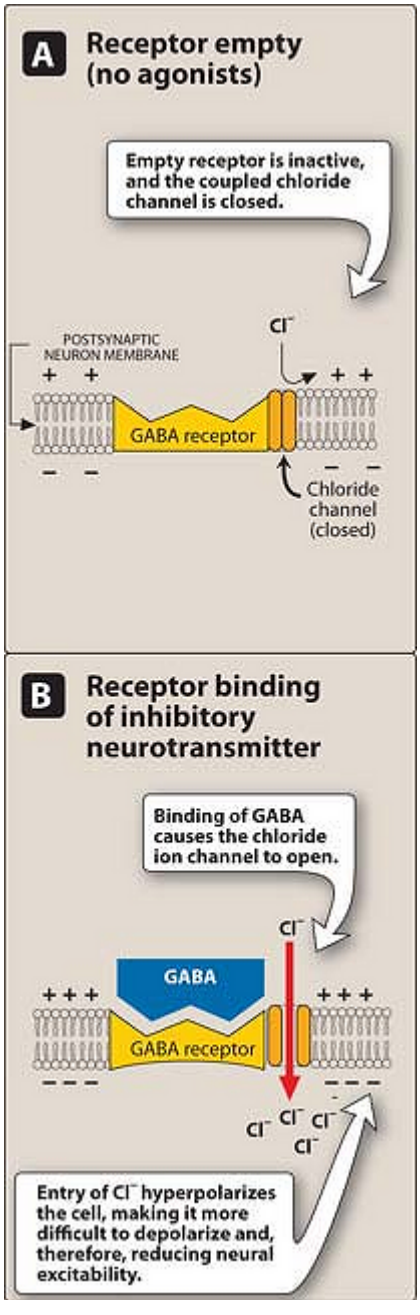


Figure 8.4 Binding of the inhibitory neurotransmitter, Î»-aminobutyric acid (GABA), causes hyperpolarization of the neuron.

IV. Neurodegenerative Diseases

Neurodegenerative diseases of the CNS include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both. For example, Alzheimer's disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson's disease is associated with a loss of dopaminergic neurons in the substantia nigra. The most prevalent of these disorders is Alzheimer's disease, estimated to have affected some 4 million people in 2000. The number of cases is expected to increase as the proportion of elderly in the population increases.

V. Overview of Parkinson's Disease

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities. Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.

A. Etiology

The cause of Parkinson's disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatumâ€"parts of the brain's basal ganglia system that are involved in motor control. The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region, which can be visualized using positron-emission tomography and the dopamine analog *fluorodopa* (Figure 8.5). Genetic factors do not play a dominant role in the etiology of Parkinson's disease, although they may exert some influence on an individual's susceptibility to the disease. It appears increasingly likely that an as-yet-unidentified environmental factor may play a role in the loss of dopaminergic neurons.

1. **Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum (shown as red neurons in Figure 8.6). Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and, therefore, modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity rather than participating in specific movements.

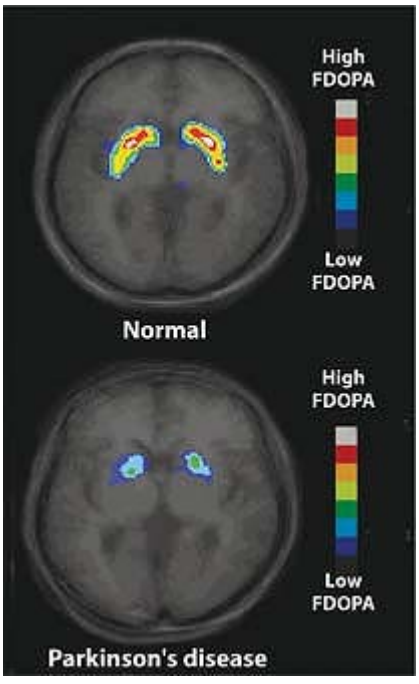


Figure 8.5 Positron-emission tomographic scan of the brain showing the difference in fluorodopa (FDOPA) levels between those with and without Parkinson's disease.

2. **Neostriatum:** Normally, the neostriatum is connected to the substantia nigra by neurons (shown as orange in Figure 8.6) that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia nigra send neurons (show n red in Figure 8.6) back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas. In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals responsible for secreting dopamine in the neostriatum. Thus, the normal modulating inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons (shown as green in Figure 8.6). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.
3. **Secondary parkinsonism:** Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as the phenothiazines and *haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms. These drugs should not be used in parkinsonian patients.

B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (see Figure 8.6). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance. Because long-term treatment with *levodopa* is limited by fluctuations in therapeutic responses, strategies to maintain CNS dopamine levels as constant as possible have been devised.

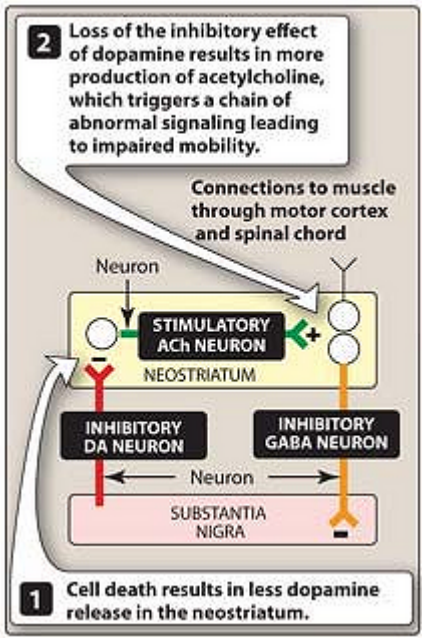


Figure 8.6 Role of substantia nigra in Parkinson's disease. DA = dopamine; GABA = Î»-aminobutyric acid; ACh = acetylcholine.

VI. Drugs Used in Parkinson's Disease

Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

A. Levodopa and carbidopa

Levodopa [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 8.7). It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the

substantia nigra. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20 percent of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects â€œwear off.â€ Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.

1. **Mechanism of action:**

   a. **Levodopa:** Because parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, *levodopa*, is actively transported into the CNS and is converted to dopamine in the brain (see Figure 8.7). Large doses of *levodopa* are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

   b. **Carbidopa:** The effects of *levodopa* on the CNS can be greatly enhanced by coadministering *carbidopa*

[kar-bi-DOE-pa], a dopa decarboxylase inhibitor that does not cross the blood-brain barrier. *Carbidopa* diminishes the metabolism of *levodopa* in the gastrointestinal tract and peripheral tissues; thus, it increases the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to five-fold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

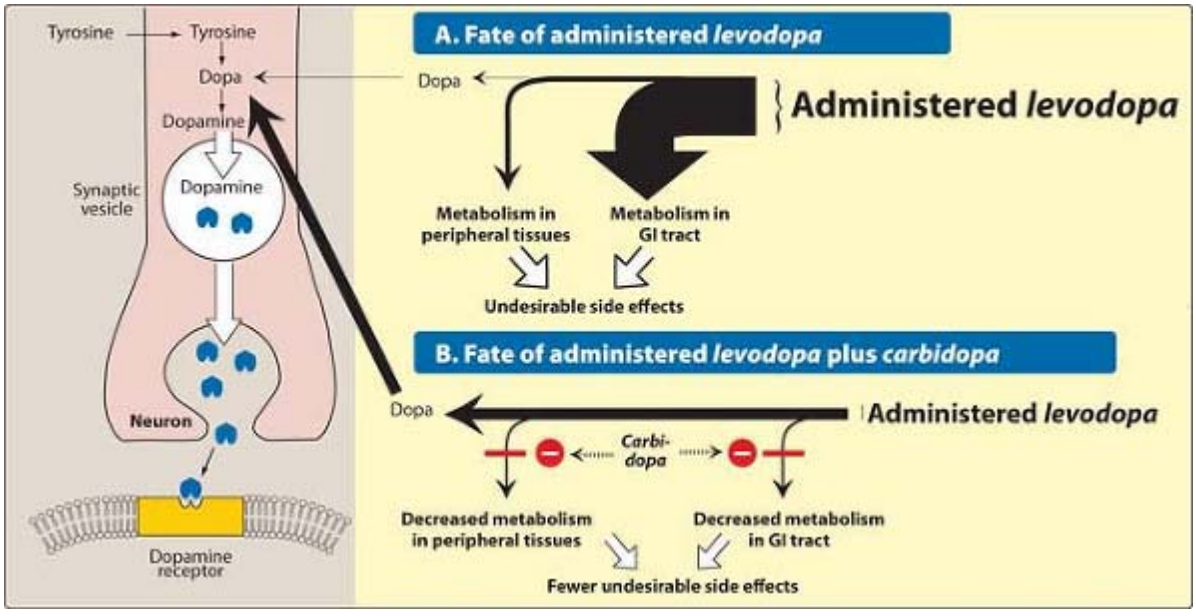


Figure 8.7 Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.

2. **Actions:** *Levodopa* decreases the rigidity, tremors, and other symptoms of parkinsonism.

3. **Therapeutic uses:** *Levodopa* in combination with *carbidopa* is a potent and efficacious drug regimen currently available to treat Parkinson's disease. In approximately two-thirds of patients with Parkinson's disease, *levodopa*â€"*carbidopa* treatment substantially reduces the severity of the disease for the first few years of treatment. Patients then typically experience a decline in response during the third to fifth year of therapy.

4. **Absorption and metabolism:** The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentrations of levodopa, or perhaps give rise to the more troublesome â€œon-offâ€ phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of *levodopa* into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with *levodopa* for absorption from the gut and for transport across the blood-brain barrier. Thus, *levodopa* should be taken on an empty stomach, typically 45 minutes before a meal. Withdrawal from the drug must be gradual.

5. **Adverse effects:**

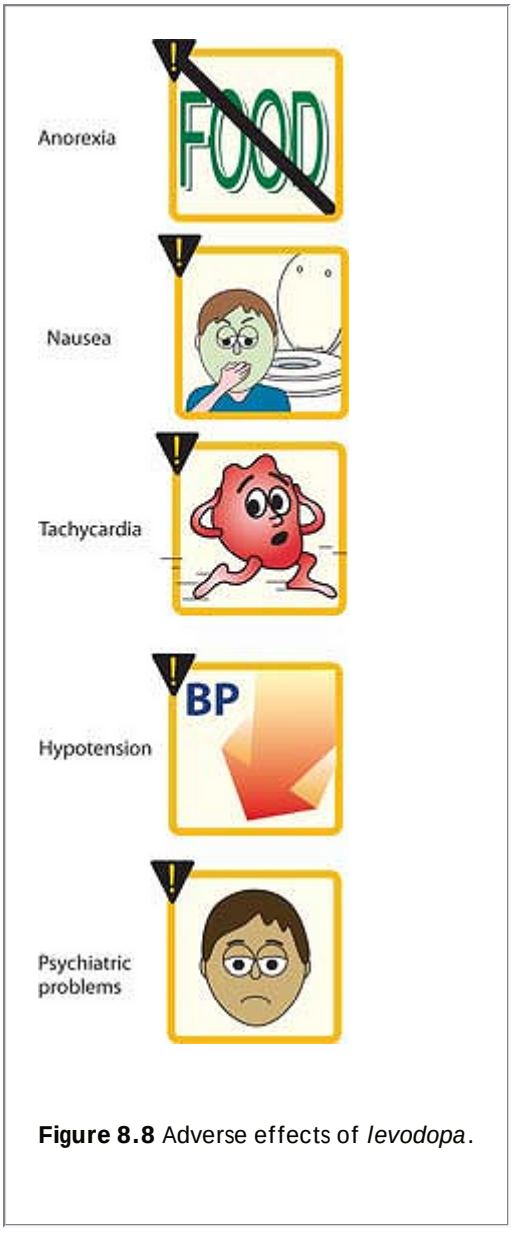


Figure 8.8 Adverse effects of *levodopa*.

a. **Peripheral effects:** Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla. (Figure 8.8). Tachycardia and ventricular extra systoles result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis, and in some individuals, blood dyscrasias and a positive reaction to the Coombs' test are seen. Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.

b. **CNS effects:** Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia. *Levodopa* can also cause mood changes, depression, psychosis, and anxiety.

6. **Interactions:** The vitamin pyridoxine (B_6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 8.9). Concomitant administration of *levodopa* and monoamine oxidase (MAO) inhibitors, such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production; therefore, caution is required when they are used simultaneously. In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines. In patients with glaucoma, the drug can cause an increase in intraocular pressure. Cardiac patients should be carefully monitored because of

generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves. However low doses of certain â€œatypicalâ€ antipsychotic agents are sometimes employed to treat levodopa-induced psychiatric symptoms.

B. Selegiline and rasagiline

Selegiline [seh-LEDGE-ah-leen], also called *deprenyl* [DE-pre-nill], selectively inhibits MAO Type B (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes norepinephrine and serotonin) unless given at above recommended doses, where it loses its selectivity. By thus decreasing the metabolism of dopamine, *selegiline* has been found to increase dopamine levels in the brain (Figure 8.10). Therefore, it enhances the actions of *levodopa* when these drugs are administered together. *Selegiline* substantially reduces the required dose of *levodopa*. Unlike nonselective MAO inhibitors, *selegiline* at recommended doses has little potential for causing hypertensive crises. However, if *selegiline* is administered at high doses, the selectivity of the drug is lost, and the patient is at risk for severe hypertension. [Note: Early reports of possible neuroprotective effects of *selegiline* have not been supported by long-term studies.] *Selegiline* is metabolized to methamphetamine and *amphetamine,* whose stimulating properties may produce insomnia if the drug is administered later than midafternoon. (See p. 148 for the use of *selegiline* in treating depression). *Rasagiline* [ra-SA-gi-leen], an irreversible and selective inhibitor of brain (MAO) Type B, has five times the potency of *selegiline*. Unlike *selegiline*, it is not metabolized to an amphetamine-like substance.

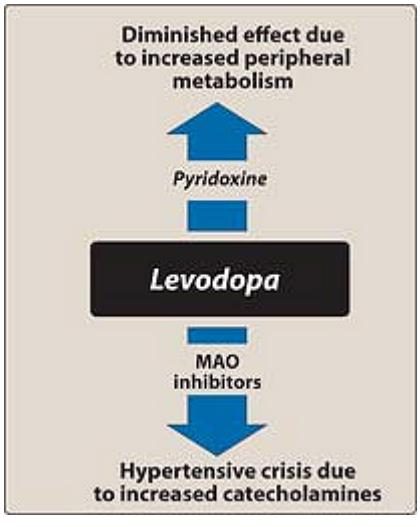


Figure 8.9 Some drug interactions observed with *levodopa*.

C. Catechol-O-methyltransferase inhibitors

Normally, the methylation of *levodopa* by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for *levodopa* metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed that competes with *levodopa* for active transport into the CNS (Figure 8.11). Inhibition of COMT by *entacapone* [en-TA-ka-pone] or *tolcapone* [TOLE-ka-pone] leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine. Both of these agents have been demonstrated to reduce the symptoms of â€œwearing-offâ€ phenomena seen in patients on *levodopa*â€“*carbidopa*. *Entacapone* and *tolcapone* are

nitrocatechol derivatives that selectively and reversibly inhibit COMT. The two drugs differ primarily in their pharmacokinetics and in some adverse effects.

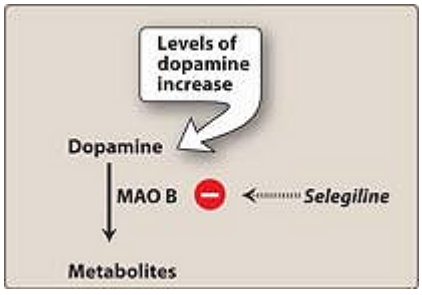


Figure 8.10 Action of *selegiline (deprenyl)* in dopamine metabolism. MAO = monoamine oxidase Type B.

1. **Pharmacokinetics:** Oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution. *Tolcapone* differs from *entacapone* in that the former penetrates the blood-brain barrier and inhibits COMT in the CNS. However, the inhibition of COMT in the periphery appears to be the primary therapeutic action. *Tolcapone* has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing. Both drugs are extensively metabolized and eliminated in the feces and urine. Dosage may need to be adjusted in patients with moderate or severe cirrhosis.

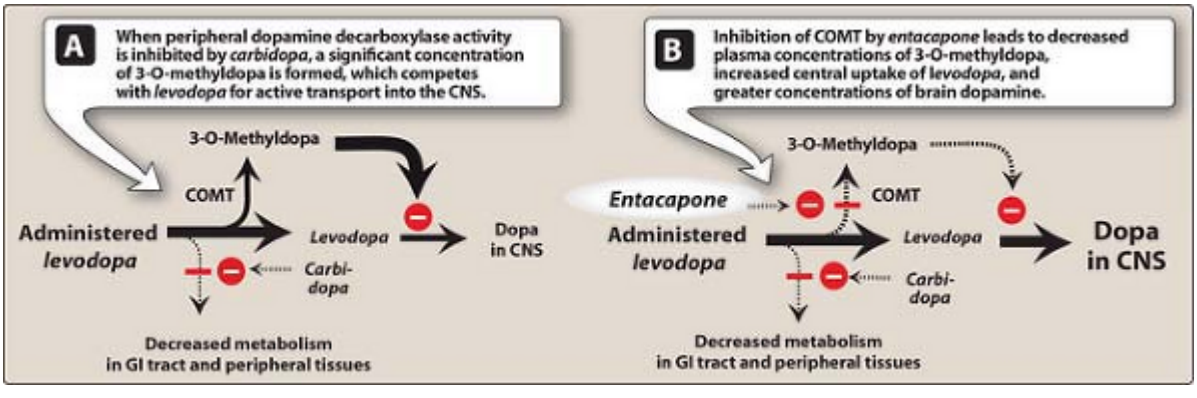


Figure 8.11 Effect of *entacapone* on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

2. **Adverse effects:** Both drugs exhibit adverse effects that are observed in patients taking *levodopa*â€“*carbidopa,* including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders.

Most seriously, fulminating hepatic necrosis is associated with *tolcapone* use. Therefore, it should be usedâ€"along with appropriate hepatic function monitoringâ€"only in patients in whom other modalities have failed. *Entacapone* does not exhibit this toxicity and has largely replaced *tolcapone*.

D. Dopamine-receptor agonists

This group of anti-Parkinson compounds includes *bromocriptine*, an ergot derivative, and two newer, nonergot drugs, *ropinirole, pramipexole* and *rotigotine.* These agents have durations of action longer than that of *levodopa* and, thus, have been effective in patients exhibiting fluctuations in their response to *levodopa*. Initial therapy with the newer drugs is associated particularly with less risk of developing dyskinesias and motor fluctuations when compared to patients started with *levodopa* therapy. *Bromocriptine, pramipexole*, and *ropinirole* are all effective in patients with advanced Parkinson's disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have shown no therapeutic response to *levodopa*. *Apomorphine* is also used in severe and advanced stages of the disease as an injectable dopamine agonist to supplement the oral medications commonly prescribed.

1. **Bromocriptine:** *Bromocriptine* [broe-moe-KRIP-teen], a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists (Figure 8.12). The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, *bromocriptine* and *levodopa* may cause the mental condition to worsen. Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction. In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a

worsening of the ulcer. Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.

2. **Apomorphine, pramipexole, ropinirole, and rotigotine:** These are nonergot dopamine agonists that have been approved for the treatment of Parkinson's disease. *Pramipexole* [pra-mi-PEX-ole] and *ropinirole* [roe-PIN-i-role] are agonists at dopamine receptors. *Apomorphine* [A-po-mor-feen] and *rotigotine* [ro-TI-go-teen] are newer dopamine agonists available in injectable and transdermal delivery systems, respectively. *Apomorphine* is meant to be used for the acute management of the hypomobility â€œoffâ€ phenomenon. These agents alleviate the motor deficits in both *levodopa*-naÃ¯ve patients (patients who have never been treated with *levodopa*) and patients with advanced Parkinson's disease who are taking *levodopa*. Dopamine agonists may delay the need to employ *levodopa* therapy in early Parkinson's disease and may decrease the dose of *levodopa* in advanced Parkinson's disease. Unlike the ergotamine derivatives, *pramipexole* and *ropinirole* do not exacerbate peripheral vasospasm, nor do they cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs; dyskinesias are less frequent than with *levodopa*. The dependence of *pramipexole* on renal function for its elimination cannot be overly stressed. For example, *cimetidine*, which inhibits renal tubular secretion of organic bases, increases the half-life of *pramipexole* by 40 percent. The fluoroquinolone antibiotics (see p. 387) and other inhibitors of the CYP450-1A2 hepatic enzyme have been shown to inhibit the metabolism of *ropinirole* and to enhance the AUC (area under the concentration vs. time curve) by some 80 percent. *Rotigotine* is a dopamine agonist used in the treatment of the signs and symptoms of early stage Parkinson's disease. It is administered as a once-daily transdermal patch that provides even pharmacokinetics over 24 hours. Figures 8.13 summarizes some properties of these dopamine agonists.

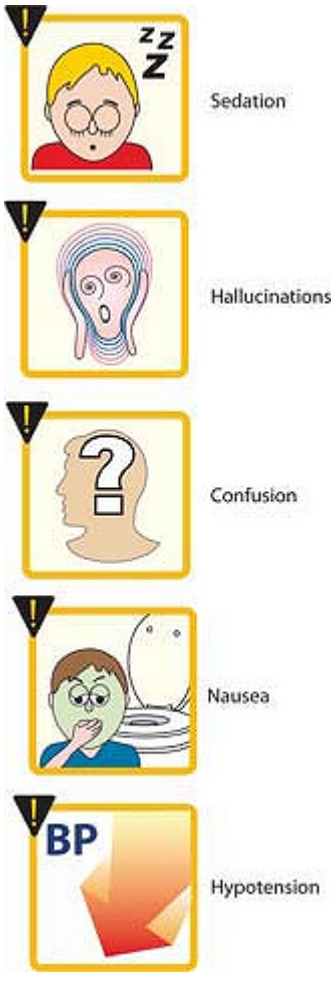


Figure 8.12 Some adverse effects of dopamine agonists.

E. Amantadine

It was accidentally discovered that the antiviral drug *amantadine* [a-MAN-ta-deen], which is effective in the treatment of influenza (see p. 437), has an antiparkinsonism action. *Amantadine* has several effects on a number of neurotransmitters implicated in causing parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors. Current evidence supports an action at NMDA receptors as the primary action at therapeutic concentrations. [Note: If

dopamine release is already at a maximum, *amantadine* has no effect.] The drug may cause restlessness, agitation, confusion, and hallucinations, and at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia.

	Pramipexole	Ropinirole	Rotigotine
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Figure 8.13 Pharmacokinetic properties of dopamine agonists of *pramipexole, ropinirole* and *rotigotine*. V_d = volume of distribution. [1]Increases to 12 hours in patients older than 65 years; [2]Less than 10 percent excreted unchanged; [3]Administered as a once-daily transdermal patch.

F. Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism therapy. The actions of *benztropine* [BENZ-tro-peen], *trihexyphenidyl* [tri-hex-ee FEN-i-dill], *procyclidine* [pro-CY-cli-deen], and *biperiden* [bi-PER-i den] are similar, although individual patients may respond more favorably to one drug. All of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis. Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission (again, because of the creation of an imbalance in the dopamine/acetylcholine ratio, see Figure 8.6). Adverse effects are similar to those caused by high doses of *atropine*â€"for example, pupillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

VII. Drugs Used in Alzheimer's Disease

Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit. None of the currently available therapeutic agents have been shown to alter the underlying neurodegenerative process. Dementia of the Alzheimer's type (versus the other forms of dementia that will not be addressed in this discussion, such as multi-infarct dementia or Lewy body dementia) has three distinguishing features: 1) accumulation of senile plaques (Î²-amyloid accumulations), 2) formation of numerous neurofibrillary tangles, and 3) loss of cortical neuronsâ€"particularly cholinergic neurons. Current therapies are aimed at either improving cholinergic transmission within the CNS or preventing excitotoxic actions resulting from overstimulation of N-methyl-D-aspartic acid (NMDA)-glutamate receptors in selected brain areas.

A. Acetylcholinesterase inhibitors

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer's disease. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least at those neurons that are still functioning. Currently, four reversible AChE inhibitors are approved for the treatment of mild to moderate Alzheimer's disease. They are *donepezil* [dah-NE-peh-zeel], *galantamine* [ga-LAN-ta-meen], *rivastigmine* [ri-va-STIG-meen], and *tacrine* [TAK-reen]. Except for *galantamine*, which is competitive, all are

uncompetitive inhibitors of AChE and appear to have some selectivity for AChE in the CNS as compared to the periphery. *Galantamine* may also be acting as an allosteric modulator of the nicotinic receptor in the CNS and, therefore, secondarily increase cholinergic neurotransmission through a separate mechanism. At best, these compounds

provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer's patients. *Rivastigmine* is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of P450-dependent enzymes. The other agents are substrates for P450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle crampsâ€"all of which are predicted by the actions of the drugs to enhance cholinergic neurotransmission (Figure 8.14). Unlike the others, *tacrine* is associated with hepatotoxicity.

B. NMDA-receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories; however, *overstimulation* of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an associated ion channel that allows Na^+ and, particularly, Ca^{2+} to enter the neuron. Unfortunately, *excess* intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis. Antagonists of the NMDA-glutamate receptor are often neuroprotective, preventing the loss of neurons following ischemic and other injuries. *Memantine* [MEM-an-teen] is a dimethyl adamantane derivative. *Memantine* acts by physically blocking the NMDA receptorâ€"associated ion channel, but at therapeutic doses, only a fraction of these channels are actually blocked. This partial blockade may allow *memantine* to limit Ca^{2+} influx into the neuron such that toxic intracellular levels are not achieved during NMDA receptor overstimulation, while still permitting sufficient Ca^{2+} flow through unblocked channels to preserve other vital processes that depend on Ca^{2+} (or Na^+) influx through these channels. This is in contrast to psychotoxic agents such as *phencyclidine,* which occupy and block nearly all of these channels. In short term studies, *memantine* has been shown to slow the rate of memory loss in both vascular-associated and Alzheimer's dementia in patients with moderate to severe cognitive losses. However, there is no evidence that *memantine* prevents or slows the neurodegeneration in patients with Alzheimer's disease or is more effective than the AChE inhibitors. *Memantine* is well tolerated, with few dose-dependent adverse events. Expected side effects, such as confusion, agitation, and restlessness, are indistinguishable from the symptoms of Alzheimer's disease. Given it's different mechanism of action and possible neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor. Long-term data showing a significant effect of this combination is not available.

Figure 8.14 Adverse efffects of acetylcholinesterase inhibitors.

VIII. Drugs Used in Amyotrophic Lateral Sclerosis

Though not indicated for the treatment of Alzheimer's disease, another NMDA-receptor antagonist is indicated for the management of amyotrophic lateral sclerosis (ALS). *Riluzole* [RI-lu-zole] blocks glutamate, sodium channels and calcium channels. It may improve the survival time and delay the need for ventilator support in patients suffering from ALS.

Study Questions

Choose the ONE best answer.

8.1 Which one of the following combinations of antiparkinson drugs is an appropriate therapy?

A. Amantadine, carbidopa, and entacapone.

B. Levodopa, carbidopa, and entacapone.

C. Pramipexole, carbidopa, and entacapone.

D. Ropinirole, selegiline, and entacapone.

E. Ropinirole, carbidopa, and selegiline.

View Answer

8.2 Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy?

A. Amantadine.

B. Bromocriptine.

C. Carbidopa.

D. Entacapone.

E. Ropinirole.

View Answer

8.3 Which of the following antiparkinson drugs may cause peripheral vasospasm?

A. Amantadine.

B. Bromocriptine.

C. Carbidopa.

D. Entacapone.

E. Ropinirole.

View Answer

8.4 Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

A. Adrenergic.

B. Cholinergic.

C. Dopaminergic.

D. GABAergic.

E. Serotonergic.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 9

Anxiolytic and Hypnotic Drugs

I. Overview

Anxiety is an unpleasant state of tension, apprehension, or uneasinessâ€”a fear that seems to arise from a sometimes unknown source. Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral or psychotherapy. Because many of the antianxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. In addition, some have anticonvulsant activity. Figure 9.1 summarizes the anxiolytic and hypnotic agents. Though also indicated for certain anxiety disorders, the selective serotonin reuptake inhibitors (SSRIs) will be presented in the chapter discussing antidepressants.

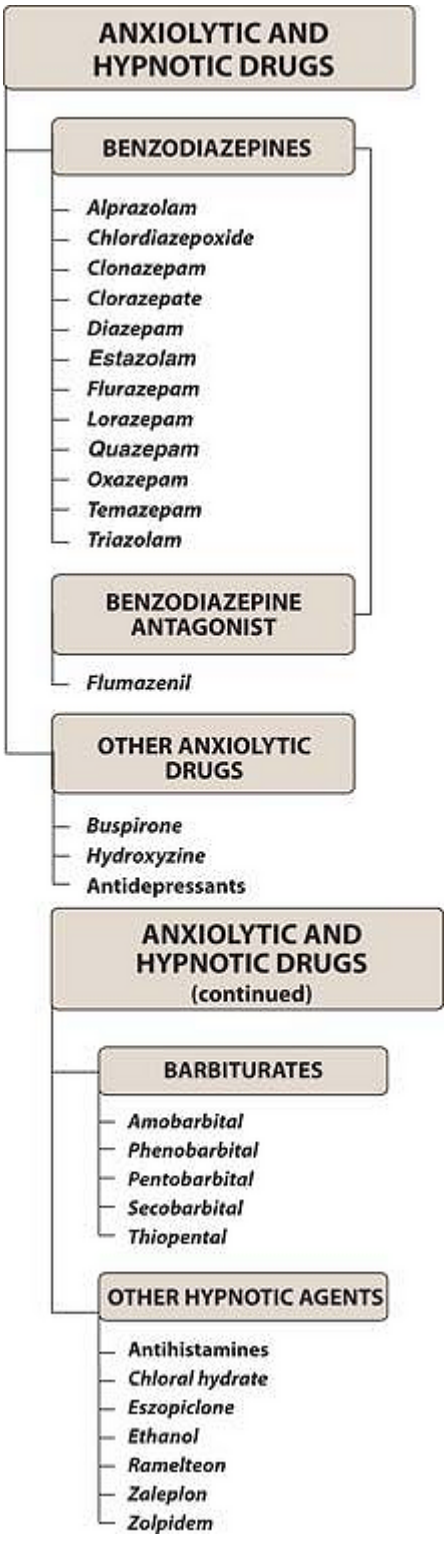


Figure 9.1 Summary of anxiolytic and hypnotic drugs.

II. Benzodiazepines

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and

meprobamate in the treatment of anxiety, because the benzodiazepines are safer and more effective (Figure 9.2).

A. Mechanism of action

The targets for benzodiazepine actions are the Î³-aminobutyric acid ($GABA_A$) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] These receptors are primarily composed of Î±, Î² and Î³ subunit families of which a combination of five or more span the postsynaptic membrane (Figure 9.3). Depending on the types, number of subunits, and brain region localization, the activation of the receptors results in different pharmacologic effects. Benzodiazepines modulate the GABA effects by binding to a specific, high-affinity site located at the interface of the Î± subunit and the $Î³_2$ subunit (see Figure 9.3). [Note: These binding sites are sometimes labeled benzodiazepine receptors. Two benzodiazepine receptor subtypes commonly found in the CNS have been designated as BZ_1 and BZ_2 receptor depending on whether their composition includes the $Î±_1$ subunit or the $Î±_2$ subunit, respectively. The benzodiazepine receptor locations in the CNS parallel those of the GABA neurons.

Binding of GABA to its receptor triggers an opening of a chloride channel, which leads to an increase in chloride conductance (see Figure 9.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and, thus, inhibits the formation of action potentials. [Note: Binding of a benzodiazepine to its receptor site will increase the affinity of GABA for the GABA-binding site (and vice versa) without actually changing the total number of sites.] The clinical effects of the various benzodiazepines correlate well with each drug's binding affinity for the GABA receptorâ€“chloride ion channel complex.

B. Actions

The benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not affect the autonomic nervous system. All benzodiazepines exhibit the following actions to a greater or lesser extent:

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the $Î±_2$ subunit in their $GABA_A$ receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

2. **Sedative and hypnotic actions:** All of the benzodiazepines used to treat anxiety have some sedative properties, and some can produce hypnosis (artificially produced sleep) at higher doses. Their effects have been shown to be mediated by the $Î±_1$-$GABA_A$ receptors.

3. **Anterograde amnesia:** The temporary impairment of memory with use of the benzodiazepines is also mediated by the $Î±_1$-$GABA_A$ receptors. This also impairs a person's ability to learn and form new memories.

4. **Anticonvulsant:** Several of the benzodiazepines have anticonvulsant activity and some are used to treat epilepsy (status epilepticus) and other seizure disorders. This effect is partially, although not completely, mediated by $Î±_1$-$GABA_A$ receptors.

5. **Muscle relaxant:** At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the $Î±_2$-$GABA_A$ receptors are largely located. *Baclofen* is a muscle relaxant that is believed to affect $GABA_b$ receptors at the level of the spinal cord.

C. Therapeutic uses

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

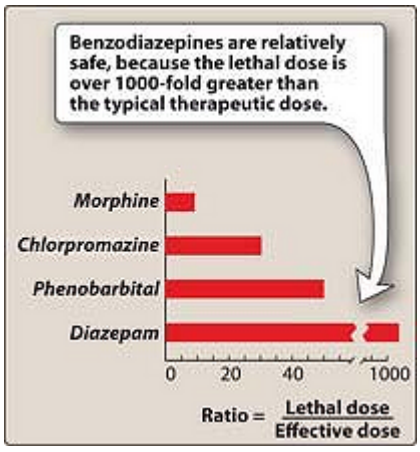


Figure 9.2 Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (a neuroleptic, see Chapter 13), and the anxiolytic, hypnotic drugs, *phenobarbital and diazepam*.

1. **Anxiety disorders:** Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder, social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and the extreme anxiety sometimes encountered with specific phobias, such as fear of flying. The benzodiazepines are also useful in treating

the anxiety that accompanies some forms of depression and schizophrenia. These drugs should not be used to alleviate the normal stress of everyday life. They should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential. The longer-acting agents, such as *clonazepam* [kloe-NAZ-e-pam], *lorazepam* [lor-AZ-e-pam], and *diazepam* [dye-AZ-e-pam], are often preferred in those patients with anxiety that may require treatment for prolonged periods of time. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Toleranceâ€"that is, decreased responsiveness to repeated doses of the drugâ€"occurs when used for more than one to two weeks. Cross-tolerance exists among this group of agents with ethanol. It has been shown that tolerance is associated with a decrease in GABA receptor density.] For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30 percent of sufferers.

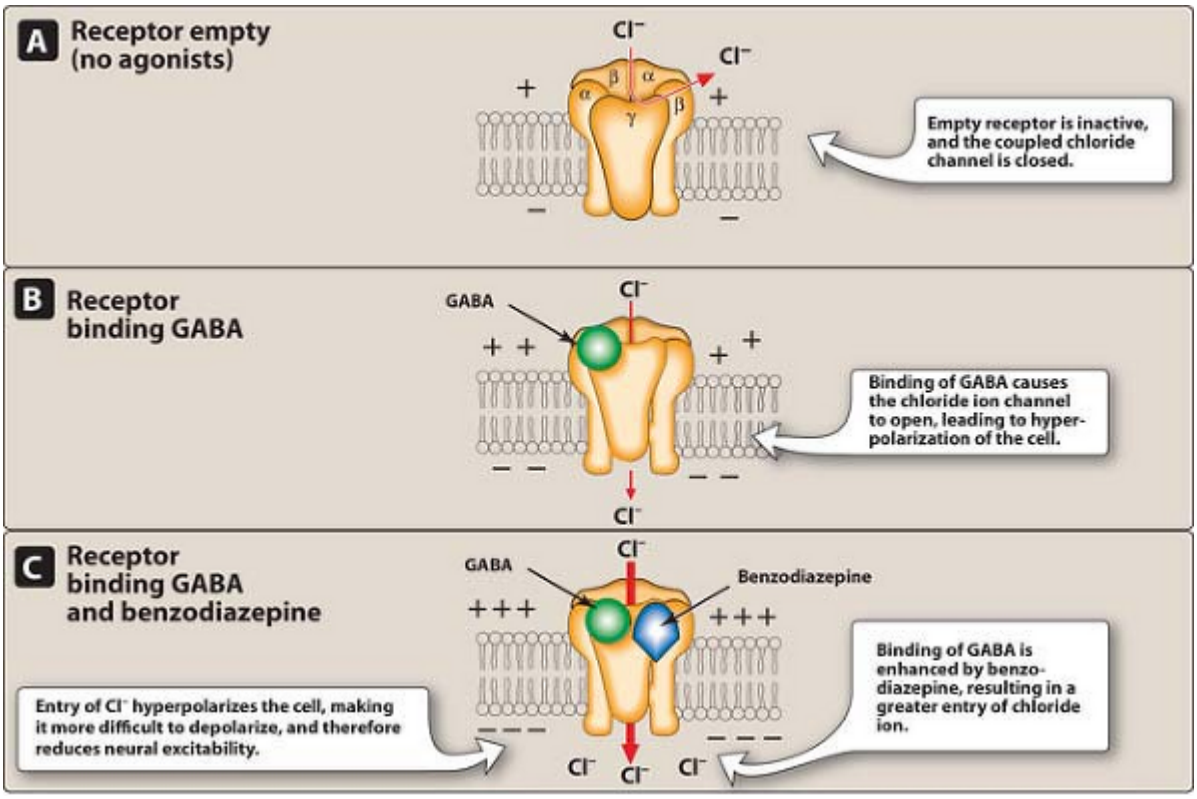


Figure 9.3 Schematic diagram of benzodiazepine-GABA-chloride ion channel complex. GABA = Î»-aminobutyric acid.

2. **Muscular disorders:** *Diazepam* is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

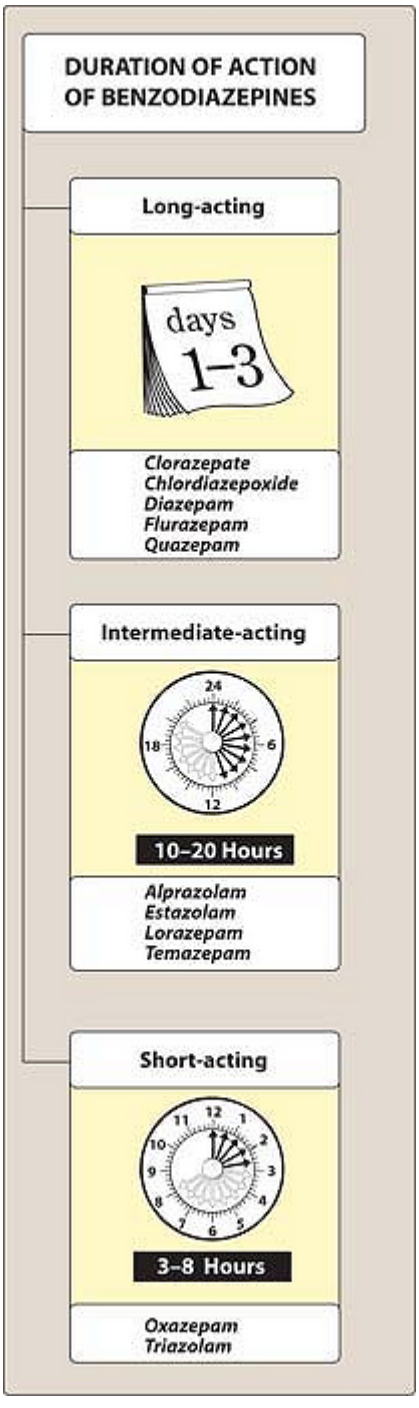


Figure 9.4 Comparison of the durations of action of the benzodiazepines.

3. **Amnesia:** The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. They also cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures. *Midazolam* [mi-DAY-zoe-lam] is an injectable-only benzodiazepine also used for the induction of anesthesia.

4. **Seizures:** *Clonazepam* is occasionally used in the treatment of certain types of epilepsy, whereas *diazepam* and *lorazepam* are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus (see p.

174). Due to cross-tolerance, *chlordiazepoxide* [klor-di-az-e-POX-ide], *clorazepate* [klor-AZ-e-pate], *diazepam*, and *oxazepam* [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures.

5. **Sleep disorders:** Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. They tend to decrease the latency to sleep onset and increase Stage II of non-rapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation (â€œhangoverâ€) upon awakening. Commonly prescribed benzodiazepines for sleep disorders include long-acting *flurazepam* [flure-AZ-e-pam], intermediate-acting *temazepam* [te-MAZ-e-pam], and short-acting *triazolam* [trye-AY-zoe-lam]. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, *zolpidem, zaleplon*, and *eszopiclone,* do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics (see p. 113). This may be due to their relative selectivity for the BZ_1 receptor.

   a. **Flurazepam:** This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakenings, and it increases the duration of sleep. *Flurazepam* has a long-acting effect (Figure 9.4) and causes little rebound insomnia. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. *Flurazepam* and its active metabolites have a half-life of approximately 85 hours, which may result in daytime sedation and accumulation of the drug.

   b. **Temazepam:** This drug is useful in patients who experience frequent wakening. However, the peak sedative effect occurs 1 to 3 hours after an oral dose; therefore, it should be given 1 to 2 hours before the desired bedtime.

   c. **Triazolam:** This benzodiazepine has a relatively short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia. Whereas *temazepam* is useful for insomnia caused by the inability to stay asleep, *triazolam* is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription or higher dose. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

D. Pharmacokinetics

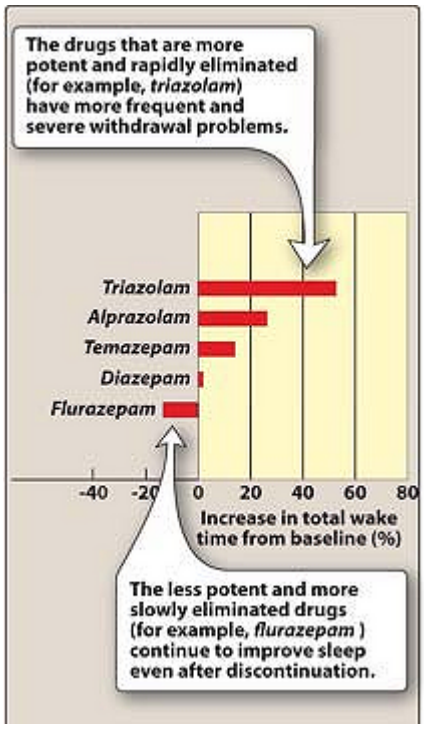


Figure 9.5 Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

1. **Absorption and distribution:** The benzodiazepines are lipophilic, and they are rapidly and completely absorbed after oral administration and distribute throughout the body.

2. **Duration of actions:** The half-lives of the benzodiazepines are very important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (see Figure 9.4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical durations of action do not always correlate with actual half-lives (otherwise we would, conceivably, give a dose of *diazepam* every other day or even less often given its active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution elsewhere.

3. **Fate:** Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by the hepatic microsomal system to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The drugs' effects are terminated not only by excretion but also by redistribution. The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites. All the benzodiazepines cross the placental barrier and may depress the CNS of the newborn if given before birth. Nursing infants may also become exposed to the drugs in breast milk.

E. Dependence

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and rarely, seizures. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated, such as *flurazepam* (Figure 9.5).

F. Adverse effects

1. **Drowsiness and confusion:** These effects are the two most common side effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased long-term recall and acquisition of new knowledge) can occur with use of benzodiazepines. *Triazolam*, one of the most potent oral benzodiazepines with the most rapid elimination, often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety, along with amnesia and confusion.

2. **Precautions:** Benzodiazepines should be used cautiously in treating patients with liver disease. They should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines. Benzodiazepines are, however, considerably less dangerous than the

   older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol, are taken concurrently.

III. Benzodiazepine Antagonist

Flumazenil [floo-MAZ-eh-nill] is a GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available for intravenous administration only. Onset is rapid but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient ingests tricyclic antidepressants. Dizziness, nausea, vomiting, and agitation are the most common side effects.

IV. Other Anxiolytic Agents

A. Buspirone

Buspirone [byoo-SPYE-rone] is useful in the treatment of generalized anxiety disorder and has an efficacy comparable to that of the benzodiazepines. The actions of *buspirone* appear to be mediated by serotonin ($5\text{-}HT_{1A}$) receptors, although other receptors could be involved, because *buspirone* displays some affinity for DA_2 dopamine receptors and $5\text{-}HT_{2A}$ serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. [Note: â€œ5-HTâ€ and not â€œSâ€ is the accepted abbreviation for serotonin (5-hydroxytryptamine) receptors.] In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. However, it causes hypothermia and can increase prolactin and growth hormone. *Buspirone* undergoes metabolism by CYP3A4; thus, its half-life is shortened if taken with *rifampin* and lengthened if taken with *erythromycin*â€”an inducer and an inhibitor of the enzyme, respectively. The frequency of adverse effects is low, with the most common effects being headaches, dizziness, nervousness, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. *Buspirone* has the disadvantage of a slow onset of action. Figure 9.6 compares some of the common adverse effects of *buspirone* and the benzodiazepine *alprazolam*.

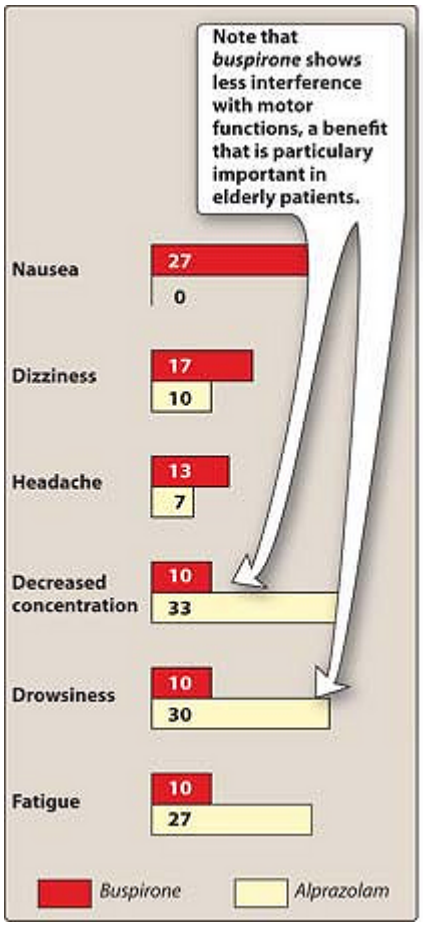


Figure 9.6 Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as the percentage of patients showing each symptom.

B. Hydroxyzine

Hydroxyzine [hye-DROX-i-zeen] is an antihistamine with antiemetic activity. It has a low tendency for habituation and, thus, is useful for patients with anxiety who have a history of drug abuse. It is also often used for sedation prior to dental procedures or surgery. Drowsiness is a possible adverse effect (see p. 552).

C. Antidepressants

Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be seriously considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances. The SSRIs, TCAs, *venlafaxine, duloxetine* and MAOIs all have potential usefulness in treating anxiety. Please refer to Chapter 12 for a discussion of the antidepressant agents.

V. Barbiturates

The barbiturates were formerly the mainstay of treatment to sedate the patient or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance,

drug-metabolizing enzymes, physical dependence, and are associated with very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting *thiopental*, are still used to induce anesthesia (see p. 135).

A. Mechanism of action

The sedative-hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of *pentobarbital* also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 9.7). For example, *thiopental* [thye-oh-PEN-tal], which acts within seconds and has a duration of action of about 30 minutes, is used in the intravenous induction of anesthesia. By contrast, *phenobarbital* [fee-noe-BAR-bi-tal], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 178). *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe-BAR-bi-tal], and *amobarbital* [am-oh-BAR-bi-tal] are short-acting barbiturates, which are effective as sedative and hypnotic (but not antianxiety) agents.

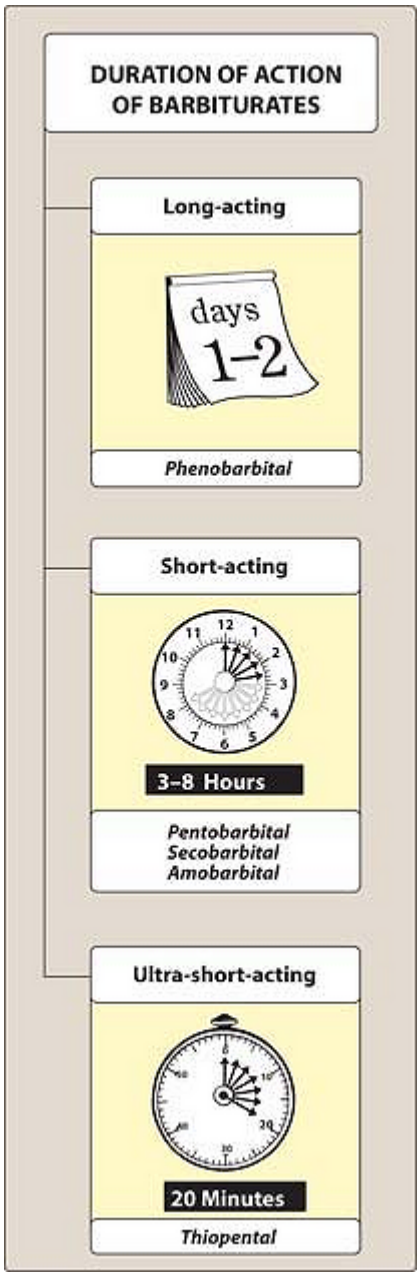


Figure 9.7 Barbiturates classified according to their durations of action.

1. **Depression of CNS:** At low doses, the barbiturates produce sedation (calming effect, reducing excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.
2. **Respiratory depression:** Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death.
3. **Enzyme induction:** Barbiturates induce P450 microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on P450 metabolism to reduce their

concentration.

C. Therapeutic uses

1. **Anesthesia:** Selection of a barbiturate is strongly influenced by the desired duration of action. The ultrashort-acting barbiturates, such as *thiopental*, are used intravenously to induce anesthesia.
2. **Anticonvulsant:** *Phenobarbital* is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. *Phenobarbital* has been regarded as the drug of choice for treatment of young children

with recurrent febrile seizures. However, *phenobarbital* can depress cognitive performance in children, and the drug should be used cautiously. *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

3. **Anxiety:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines.

D. Pharmacokinetics

Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute in the body from the brain to the splanchnic areas, to skeletal muscle, and finally, to adipose tissue. This movement is important in causing the short duration of action of *thiopental* and similar short-acting derivatives. They readily cross the placenta and can depress the fetus. Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.

Figure 9.8 Adverse effect of barbiturates.

E. Adverse effects

1. **CNS:** Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness (Figure 9.8). The CNS depressant effects of barbiturates synergize with those of *ethanol*.
2. **Drug hangover:** Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.
3. **Precautions:** As noted previously, barbiturates induce the P450 system and, therefore, may decrease the duration of action of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin

synthesis, and are contraindicated in patients with acute intermittent porphyria.

4. **Physical dependence:** Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

5. **Poisoning:** Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression, and results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. [Note: No specific barbiturate antagonist is available.] Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of *phenobarbital* .

VI. Other Hypnotic Agents

A. Zolpidem

The hypnotic *zolpidem* [ZOL-pi-dem] is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor family, BZ_1. *Zolpidem* has no anticonvulsant or muscle-relaxing properties. It

shows few withdrawal effects, and exhibits minimal rebound insomnia, and little or no tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed from the gastrointestinal tract, and it has a rapid onset of action and short elimination half-life (about 2 to 3 hours). [Note: An extended-release formulation is now available.] *Zolpidem* undergoes hepatic oxidation by the cytochrome P450 system to inactive products. Thus, drugs such as *rifampin*, which induce this enzyme system, shorten the half-life of *zolpidem,* and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life this drug. Adverse effects of *zolpidem* include nightmares, agitation, headache, gastrointestinal upset, dizziness, and daytime drowsiness.

B. Zaleplon

Zaleplon (ZAL-e-plon) is very similar to *zolpidem* in its hypnotic actions, but it causes fewer residual effects on psychomotor and cognitive functions compared to *zolpidem* or the benzodiazepines. This may be due to its rapid elimination, with a half-life that approximately 1 hour. The drug is metabolized by CYP3A4 (see p. 15).

C. Eszopiclone

Eszopiclone [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic (also utilizing the BZ_1 receptor similar to *zolpidem* and *zaleplon*) and is also used for treating insomnia. *Eszopiclone* been shown to be effective for up to 6 months compared to a placebo. *Eszopiclone* is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the cytochrome enzyme system and mainly excreted in the urine. Elimination half-life is approximately 6 hours. Adverse events reported with *eszopiclone* include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

D. Ramelteon

Ramelteon [ram-EL-tee-on] is a selective agonist at the MT_1 and MT_2 subtypes of melatonin receptors. Normally, light stimulating the retina transmits a signal to the suprachiasmatic nucleus (SCN) of the hypothalamus, that in turn relays a signal via a lengthy nerve pathway to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin. Stimulation of MT_1 and MT_2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep-wake cycle. *Ramelteon* is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The potential for abuse of *ramelteon* is believed to be minimal, and no evidence of dependence or withdrawal effects has been observed. Therefore, *ramelteon* can be administered long-term. Common adverse

effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels.

E. Chloral hydrate

Chloral hydrate [KLOR-al-HYE-drate] is a trichlorinated derivative of acetaldehyde that is converted to the active metabolite, trichloroethanol, in the body. The drug is an effective sedative and hypnotic that induces sleep in about 30 minutes and the duration of sleep is about 6 hours. *Chloral hydrate* is irritating to the gastrointestinal tract and causes epigastric

distress. It also produces an unusual, unpleasant taste sensation. It synergizes with *ethanol*.

F. Antihistamines

Nonprescription antihistamines with sedating properties, such as *diphenhydramine* and *doxylamine*, are effective in treating mild types of insomnia. However, these drugs are usually ineffective for all but the milder forms of situational insomnia. Furthermore, they have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines. These sedative antihistamines are marketed in numerous over-the-counter products.

G. Ethanol

Ethanol (*ethyl alcohol*) has anxiolytic and sedative effects, but its toxic potential outweighs its benefits. Alcoholism is a serious medical and social problem. *Ethanol* [ETH-an-ol] is a CNS depressant, producing sedation and, ultimately, hypnosis with increasing dosage. *Ethanol* has a shallow doseâ€“response curve; therefore, sedation occurs over a wide dosage range. It is readily absorbed orally and has a volume of distribution close to that of total body water. *Ethanol* is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase and then to acetate by aldehyde dehydrogenase (Figure 9.9). Elimination is mostly through the kidney, but a fraction is excreted through the lungs. *Ethanol* synergizes with many other sedative agents and can produce severe CNS depression with benzodiazepines, antihistamines, or barbiturates. Chronic consumption can lead to severe liver disease, gastritis, and nutritional deficiencies. Cardiomyopathy is also a consequence of heavy drinking. The treatment of choice for alcohol withdrawal are the benzodiazepines. *Carbamazepine* is effective in treating convulsive episodes during withdrawal.

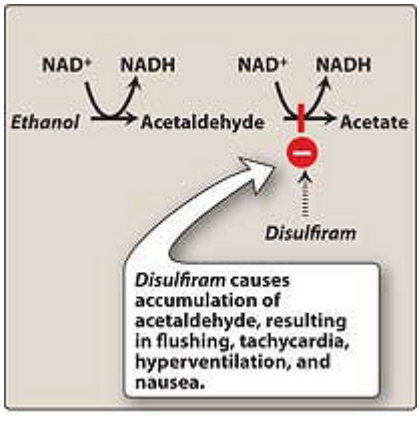


Figure 9.9 Metabolism of ethanol, and the effect of *disulfiram. NAD+ = oxidized form of nicotinamide-adenine dinucleotide; NADH = reduced form of nicotinamide-adenine dinucleotide*.

1. **Disulfiram:** *Disulfiram* [dye-SUL-fi-ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting

aldehyde dehydrogenase (see Figure 9.9). This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea. *Disulfiram* has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of *disulfiram*-induced acetaldehyde accumulation.

2. **Naltrexone:** *Naltrexone* [nal-TREX-own] is a long-acting opiate antagonist (available orally or as a long-acting injectable) that is U.S. Food and Drug Administrationâ€“approved for the treatment of alcohol dependence and should be utilized in conjunction with supportive psychotherapy. It is better tolerated than *disulfira*m and does not produce the aversive reaction that *disulfiram* does.
3. **Acamprosate:** An agent utilized in alcohol dependence treatment programs with an as yet poorly understood mechanism of action that should also be utilized in conjunction with supportive psychotherapy.

Figure 9.10 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

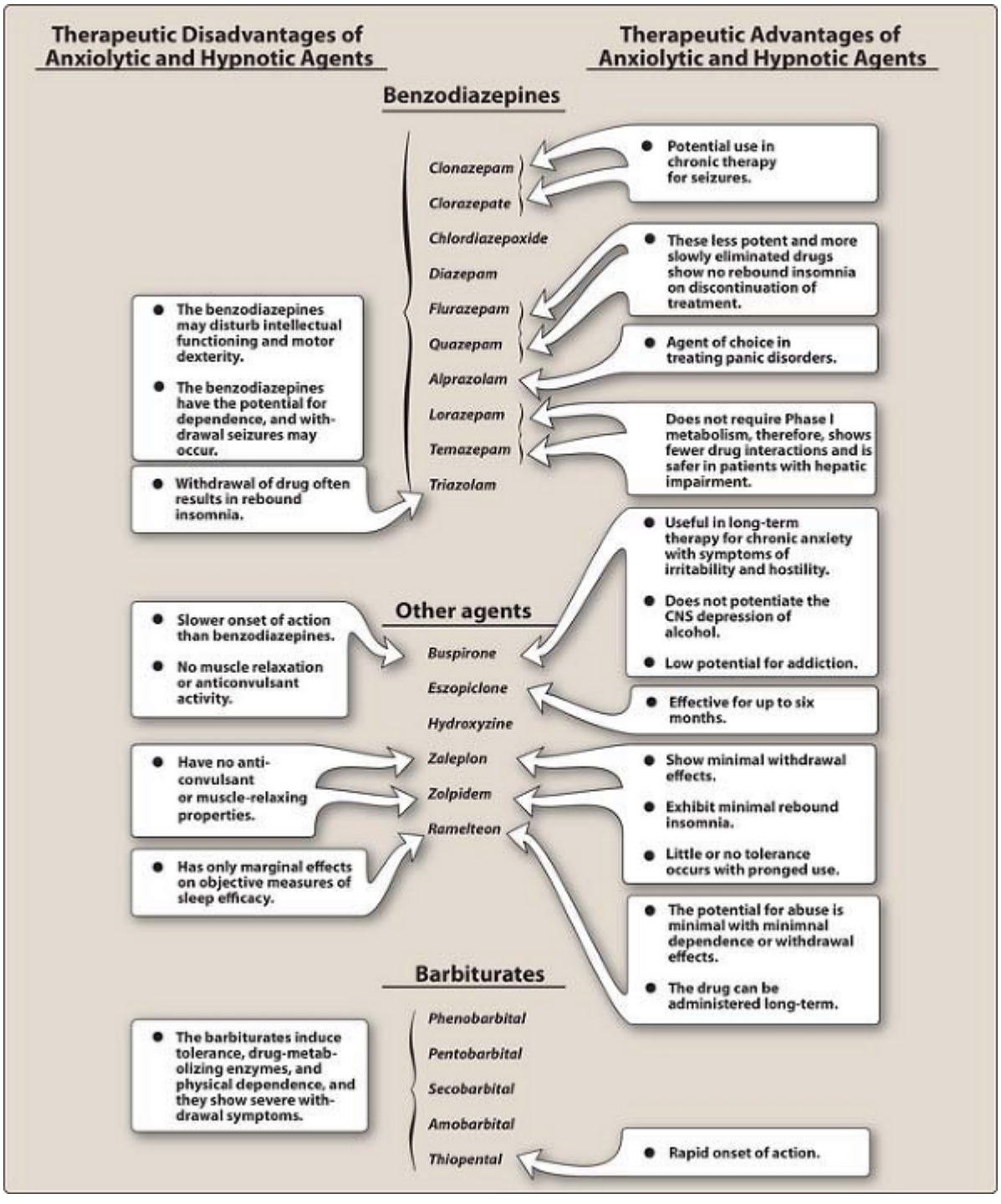


Figure 9.10 Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.

Study Questions

Choose the ONE best answer.

9.1 Which one of the following statements is correct?

A. Benzodiazepines directly open chloride channels.

B. Benzodiazepines show analgesic actions.

C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.

D. All benzodiazepines have some sedative effects.

E. Benzodiazepines, like other CNS depressants, readily produce general anesthesia.

View Answer

9.2 Which one of the following is a short-acting hypnotic?

A. Phenobarbital.

B. Diazepam.

C. Chlordiazepoxide.

D. Triazolam.

E. Flurazepam.

View Answer

9.3 Which one of the following statements is correct?

A. Phenobarbital shows analgesic properties.

B. Diazepam and phenobarbital induce the P450 enzyme system.

C. Phenobarbital is useful in the treatment of acute intermittent porphyria.

D. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol.

E. Buspirone has actions similar to those of the benzodiazepines.

View Answer

9.4 A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. None.

B. Lorazepam.

C. Pentobarbital.

D. Phenytoin.

E. Buspirone

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 10

CNS Stimulants

I. Overview

This chapter describes two groups of drugs that act primarily to stimulate the central nervous system (CNS). The first group, the psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group, the hallucinogens, or psychotomimetic drugs, produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. Figure 10.1 summarizes the CNS stimulants. As a group, the CNS stimulants have diverse clinical uses and are important as drugs of abuse, as are the CNS depressants described in Chapter 9 and the narcotics described in Chapter 14 (Figure 10.2).

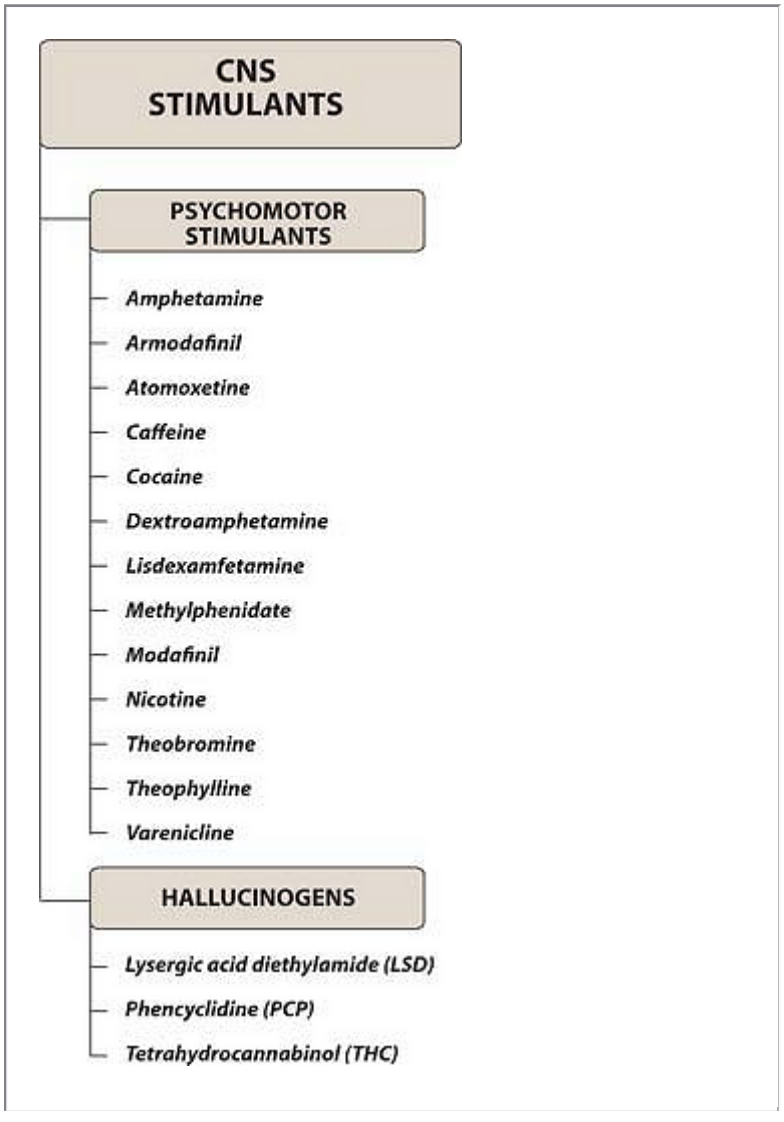


Figure 10.1 Summary of central nervous system (CNS) stimulants.

II. Psychomotor Stimulants

A. Methylxanthines

The methylxanthines include *theophylline* [thee-OFF-i-lin] which is found in tea; *theobromine* [thee-o-BRO-min], found in cocoa; and *caffeine* [kaf-EEN]. *Caffeine*, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also present in tea, cola drinks, chocolate candy, and cocoa.

1. **Mechanism of action:** Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of *caffeine*-containing beverages.
2. **Actions:**
    a. **CNS:** The *caffeine* contained in one to two cups of coffee (100â€“200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of *caffeine* (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2â€“5 g) of *caffeine*. Tolerance can rapidly develop to the stimulating properties of *caffeine*; withdrawal consists of feelings of fatigue and sedation.
    b. **Cardiovascular system:** A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note:

    Increased contractility can be harmful to patients with angina pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]
    c. **Diuretic action:** *Caffeine* has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.
    d. **Gastric mucosa:** Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid beverages containing methylxanthines.

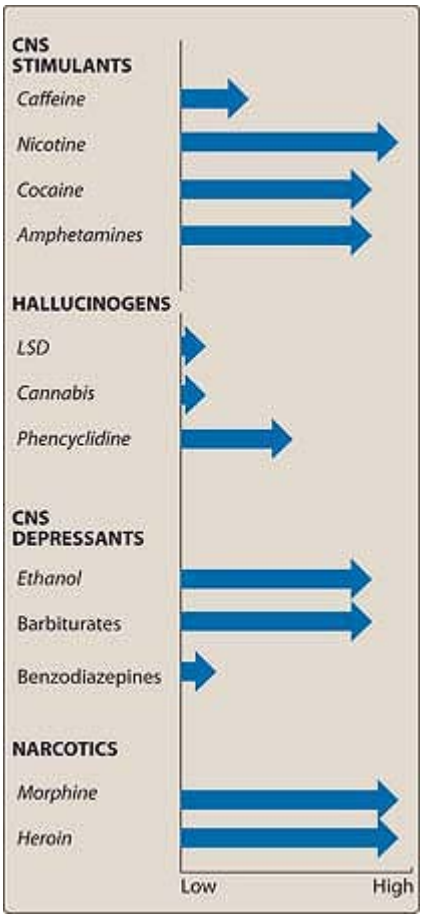


Figure 10.2 Relative potential for physical dependence on commonly abused substances.

3. **Therapeutic uses:** *Caffeine* and its derivatives relax the smooth muscles of the bronchioles. [Note: Previously the mainstay of asthma therapy, *theophylline* has been largely replaced by other agents, such as $\hat{I}^2_2$ agonists and corticosteroids.]

4. **Pharmacokinetics:** The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including the brain. The drugs cross the placenta to the fetus and is secreted into the mother's milk. All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

5. **Adverse effects:** Moderate doses of *caffeine* cause insomnia, anxiety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is about 10 g of *caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias; death from *caffeine* is thus highly unlikely. Lethargy, irritability, and headache occur in users who have routinely consumed more than 600 mg of *caffeine* per day (roughly six cups of coffee per day) and then suddenly stop.

B. Nicotine

Nicotine [NIC-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy, see p. 118), *nicotine* remains important, because it is second only to *caffeine* as the most widely used CNS stimulant and second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, *nicotine* represents a serious risk factor for lung and

cardiovascular disease, various cancers, as well as other illnesses. Dependency on the drug is not easily overcome.

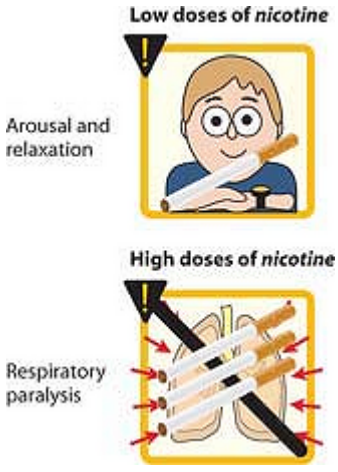


Figure 10.3 Actions of *nicotine* on the central nervous system.

1. **Mechanism of action:** In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade. *Nicotine* receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.
2. **Actions:**
   a. **CNS:** *Nicotine* is highly lipid soluble and readily crosses the blood-brain barrier. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria and arousal as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3). Nicotine is an appetite suppressant.

   b. **Peripheral effects:** The peripheral effects of *nicotine* are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, *nicotine*-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal tract and bladder musculature as a result of a *nicotine*-induced block of parasympathetic ganglia.

Figure 10.4 *Nicotine* has potential for addiction.

3. **Pharmacokinetics:** Because *nicotine* is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, gastrointestinal mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the milk of lactating women. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette (most cigarettes contain 6 to 8 mg of *nicotine*). The acute lethal dose is 60 mg. More than 90 percent of the *nicotine* inhaled in smoke is absorbed. Clearance of *nicotine* involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of *nicotine* develops rapidly, often within days after beginning usage.

4. **Adverse effects:** The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs.

5. **Withdrawal syndrome:** As with the other drugs in this class, *nicotine* is an addictive substance, and physical dependence on *nicotine* develops rapidly and can be severe (Figure 10.4). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and gastrointestinal pain often occurs. [Note: Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking.] The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine* withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from nicotine chewing gum is typically about one-half the peak level observed with smoking (Figure 10.5). *Bupropion*, an antidepressant (see p. 145), can reduce the craving for cigarettes.

C. Varenicline

Varenicline [ver-EN-e-kleen] is a partial agonist at a_4b_2 neuronal nicotinic acetylcholine receptors in the CNS. Because it is only a partial agonist at these receptors, it produces less euphoric effects than those produced by *nicotine* itself (nicotine is a full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with *nicotine* withdrawal symptoms. Additionally, *varenicline* tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco. Patients should be monitored for suicidal thoughts, vivid nightmares and mood changes.

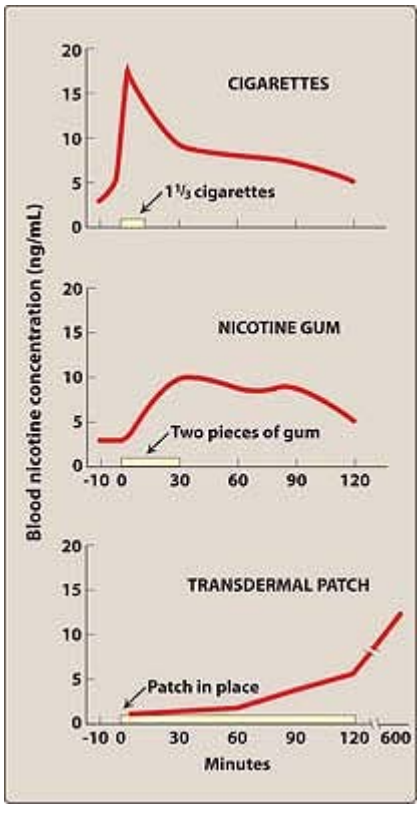


Figure 10.5 Blood concentrations of *nicotine* in individuals who smoked cigarettes, chewed nicotine gum, or received nicotine by transdermal patch.

D. Cocaine

Cocaine [KOE-kane] is a widely available and highly addictive drug that is currently abused daily by more than 3 million people in the United States. Because of its abuse potential, *cocaine* is classified as a Schedule II drug by the U.S. Drug Enforcement Agency (see p. 541).

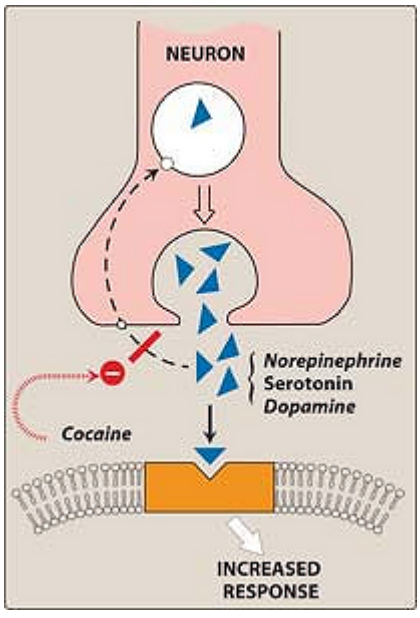


Figure 10.6 Mechanism of action of *cocaine*.

1. **Mechanism of action:** The primary mechanism of action underlying the central and peripheral effects of *cocaine* is blockade of reuptake of the monoamines (*norepinephrine*, serotonin, and *dopamine*) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by *cocaine* binding to the monoaminergic reuptake transporters and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes *dopamine*. This depletion triggers the vicious cycle of craving for *cocaine* that temporarily relieves severe depression (Figure 10.7).

2. **Actions:**

    a. **CNS:** The behavioral effects of *cocaine* result from powerful stimulation of the cortex and brainstem. *Cocaine* acutely increases mental awareness and produces a feeling of well-being and euphoria similar to that caused by *amphetamine*. Like *amphetamine, cocaine* can produce hallucinations and delusions of paranoia or grandiosity. *Cocaine* increases motor activity, and at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression.

Figure 10.7 *Cocaine* and *amphetamine* have potential for addiction.

b. **Sympathetic nervous system:** Peripherally, *cocaine* potentiates the action of *norepinephrine*, and it produces the â€œfight or flightâ€ syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction. Recent evidence suggests that the ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired.

c. **Hyperthermia:** *Cocaine* is unique among illicit drugs in that death can result not only as a function of dose but also from the drug's propensity to cause hyperthermia. [Note: Mortality rates for *cocaine* overdose rise in hot weather.] Even a small dose of intranasal *cocaine* impairs sweating and cutaneous vasodilatation. Perception of thermal discomfort is also decreased.

3. **Therapeutic uses:** *Cocaine* has a local anesthetic action that represents the only current rationale for the therapeutic use of *cocaine*. For example, *cocaine* is applied topically as a local anesthetic during eye, ear, nose, and throat surgery. Whereas the local anesthetic action of *cocaine* is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to the ability of *cocaine* to cause cardiac arrhythmias. [Note: *Cocaine* is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of *cocaine* powder.]

4. **Pharmacokinetics:** *Cocaine* is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. The peak effect occurs at 15 to 20 minutes after intranasal intake of *cocaine* powder, and the â€œhighâ€ disappears in 1 to 1.5 hours. Rapid but short-lived effects are achieved following IV injection of *cocaine* or by smoking the freebase form of the drug (â€œcrackâ€). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking. *Cocaine* is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifies a user.

5. **Adverse effects:**

a. **Anxiety:** The toxic response to acute *cocaine* ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. Because of the irritability, many users take *cocaine* with alcohol. A product of *cocaine* metabolites and *ethanol* is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.

b. **Depression:** Like all stimulant drugs, *cocaine* stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from *cocaine* exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with benzodiazepines or phenothiazines.

c. **Toxic effects:** *Cocaine* can induce seizures as well as fatal cardiac arrhythmias (Figure 10.8). Use of IV *diazepam* and *propranolol* may be required to control *cocaine*-induced seizures and cardiac arrhythmias, respectively. The incidence of myocardial infarction in *cocaine* users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking *cocaine*.

E. Amphetamine

Amphetamine [am-FE-ta-meen] is a noncatecholaminergic sympathetic amine that shows neurologic and clinical effects quite similar to those of *cocaine*. *Dextroamphetamine* [dex-troe-am-FE-ta-meen] is the major member of this class of compounds. *Methamphetamine* [meth-am-FET-ah-mine] (also known as â€œspeedâ€) is a derivative

of *amphetamine* that can be smoked, and it is preferred by many abusers.

1. **Mechanism of action:** As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect; that is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 10.9). Because *amphetamine* also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral effects of *amphetamine* and its derivatives are similar to those of *cocaine*.

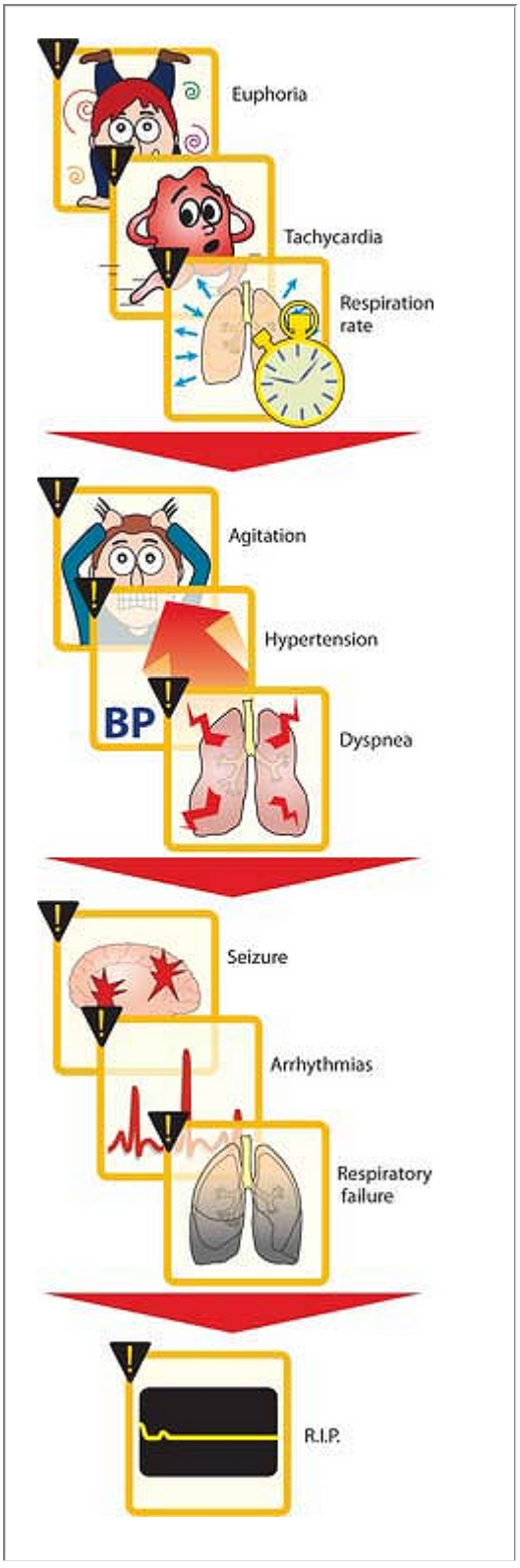


Figure 10.8 Major effects of *cocaine* use.

2. **Actions:**

   a. **CNS:** The major behavioral effects of *amphetamine* result from a combination of its *dopamine* and *norepinephrine* release-enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of *amphetamine* and its derivatives have led to their use in therapy for hyperactivity in children, narcolepsy, and for appetite control. At high doses, psychosis and convulsions can ensue.

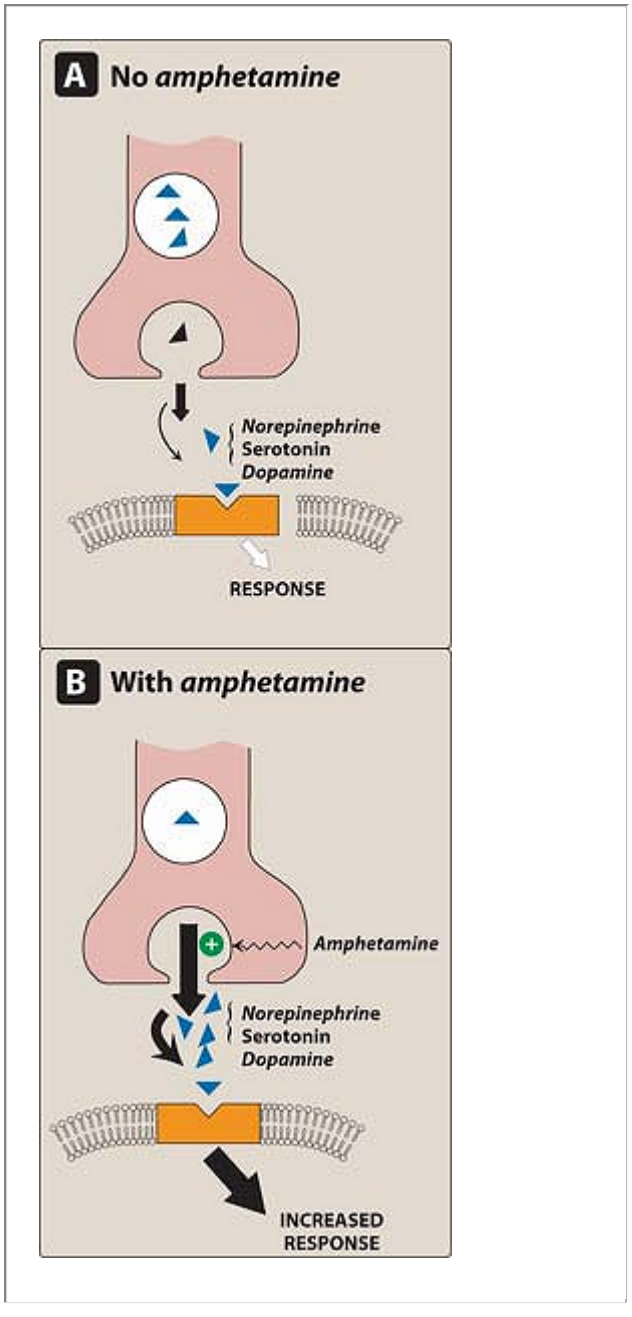


Figure 10.9 Mechanism of action of *amphetamine*.

b. **Sympathetic nervous system:** In addition to its marked action on the CNS, *amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through *norepinephrine* release.

3. **Therapeutic uses:** Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiological dependence similar to those with *cocaine* and the development of tolerance to the euphoric and anorectic effects with chronic use. [Note: Less tolerance to the toxic CNS effects (for example, convulsions) develops.]

   a. **Attention deficit hyperactivity disorder (ADHD):** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. *Dextroamphetamine* and the *amphetamine* derivative *methylphenidate* [meth-ill-FEN-i-date] are able to improve attention and to alleviate many of the behavioral problems associated with this syndrome, and to reduce the hyperkinesia that such children demonstrate. *Lisdexamfetamine* [lis-dex-am-FE-ta-meen] is a prodrug that is converted to the active component *dextroamphetamine* after gastrointestinal absorption and metabolism. The drug prolongs the patient's span of attention allowing better function in a school atmosphere. *Atomoxetine* [AT-oh-mox-e-teen] is a nonstimulant drug approved for ADHD in children and adults. [Note: It should not be taken by individuals on MAO inhibitors, and it is not recommended for patients with narrow-angle glaucoma.] Unlike *methylphenidate* which blocks *dopamine* reuptake, *atomoxetine* is a *norepinephrine* reuptake inhibitor. It is not habit forming and is not a controlled substance.

   b. **Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, or even paralysis brought on by strong emotions, such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs such as *amphetamine* or *methylphenidate*. Recently, a newer drug, *modafinil* (moe-DA-fi-nil), and its R-enantiomer derivative, *armodafinil*, have become available to treat narcolepsy. *Modafinil* produces fewer psychoactive and euphoric effects as well as, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action remains unclear but may involve the adrenergic and dopaminergic systems, although it has been shown to differ from that of *amphetamine*. *Modafinil* is effective orally. It is well

distributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in the urine. Headaches, nausea, and rhinitis are the primary adverse effects. There is some evidence to indicate the potential for abuse and physical dependence with *modafinil*.

4. **Pharmacokinetics:** *Amphetamine* is completely absorbed from the gastrointestinal tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the non-ionized species of the drug and decrease its excretion.] *Amphetamine* abusers often administer the drugs by IV injection and by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or four- to eight-fold longer than the effects of *cocaine*.

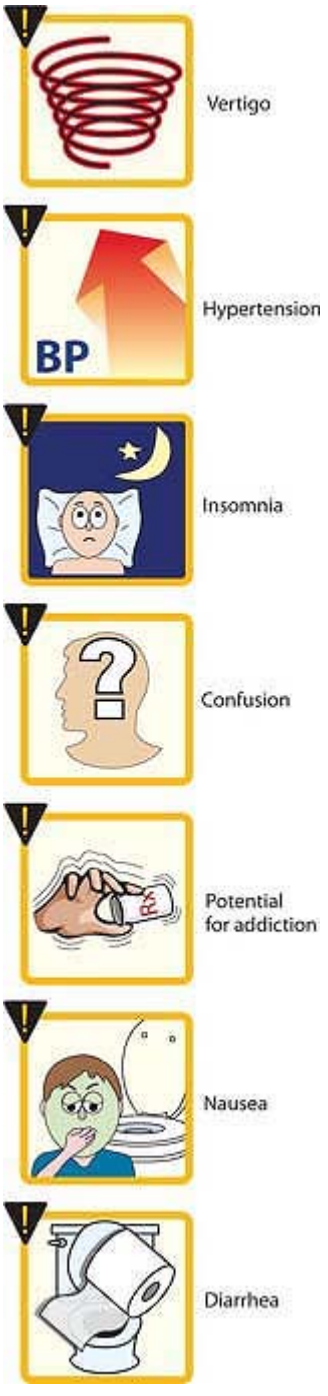


Figure 10.10 Adverse effects of amphetamines.

5. **Adverse effects:** The *amphetamines* may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects.

   a. **Central effects:** Undesirable side effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 10.10). *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic *amphetamine* use produces a state of â€œ*amphetamine* psychosisâ€ that resembles the psychotic episodes associated with

schizophrenia. Whereas long-term *amphetamine* use is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks. Overdoses of *amphetamine* are treated with *chlorpromazine* or *haloperidol*, which relieve the CNS symptoms as well as the hypertension because of their Î±-blocking effects. The anorectic effect of *amphetamine* is due to its action in the lateral hypothalamic feeding center. 3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy) is a synthetic derivative of *methamphetamine* with both stimulant and hallucinogenic properties (see p. 537).

b. **Cardiovascular effects:** In addition to its CNS effects, *amphetamine* causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. Because of its cardiovascular effects, *amphetamine* should not be given to patients with cardiovascular disease or those receiving MAO inhibitors.

c. **Gastrointestinal system effects:** *Amphetamine* acts on the gastrointestinal system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of *sodium bicarbonate* will increase the reabsorption of *dextroamphetamine* from the renal tubules into the bloodstream.

d. **Contraindications:** Patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma should not be treated with this drug, nor should patients with a history of drug abuse.

F. Methylphenidate

Methylphenidate has CNS stimulant properties similar to those of *amphetamine* and may also lead to abuse, although its addictive potential

is controversial. It is a Schedule II drug (see p. 541). It is presently one of the most prescribed medications in children. It is estimated that *methylphenidate* is taken daily by 4 to 6 million children in the United States for ADHD. The pharmacologically active isomer, *dexmethylphenidate*, has been approved in the United States for the treatment of ADHD.

1. **Mechanism of action:** Children with ADHD may produce weak *dopamine* signals, which suggests that usually interesting activities provide fewer rewards to these children. At present, the basis for the stimulant effect of *methylphenidate* is not understood. However, a recent study using positron-emission tomography has opened up some interesting possibilities. It showed that *methylphenidate* is a more potent *dopamine* transport inhibitor than *cocaine*, thus making more *dopamine* available. [Note: *Methylphenidate* may have less potential for abuse than *cocaine*, because it enters the brain much more slowly than *cocaine* and, thus, does not increase *dopamine* levels as rapidly.]

2. **Therapeutic uses:** *Methylphenidate* has been used for several decades in the treatment of ADHD in children aged 6 to 16. It is also effective in the treatment of narcolepsy. Unlike *methylphenidate, dexmethylphenidate* is not indicated in the treatment of narcolepsy.

3. **Pharmacokinetics:** Both *methylphenidate* and *dexmethylphenidate* are readily absorbed on oral administration. Concentrations in the brain exceed those in the plasma. The de-esterified product, ritalinic acid, is excreted in the urine.

4. **Adverse reactions:** Gastrointestinal effects are the most common. These include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In seizure patients, *methylphenidate* seems to increase the seizure frequency, especially if the patient is taking antidepressants. *Methylphenidate* is contraindicated in patients with glaucoma.

5. **Drug interactions:** Studies have shown that *methylphenidate* can interfere in the metabolism of *warfarin, diphenylhydantoin, phenobarbital, primidone*, and the tricyclic antidepressants.

III. Hallucinogens

A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams.

Many of these altered states are accompanied by bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision making, because the drug interferes with rational thought. These compounds are known as hallucinogens or psychotomimetic drugs.

A. Lysergic acid diethylamide

Multiple sites in the CNS are affected by *lysergic acid diethylamide* (*LSD*). The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT_1 receptors in the midbrain, and also stimulates 5-HT_2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of *LSD* can induce hallucinations with brilliant colors. Mood alteration also occurs. Tolerance

and physical dependence have occurred, but true dependence is rare. Adverse effects include hyperreflexia, nausea, and muscular weakness. High doses may produce long-lasting psychotic changes in susceptible individuals. *Haloperidol* and other neuroleptics can block the hallucinatory action of *LSD* and quickly abort the syndrome.

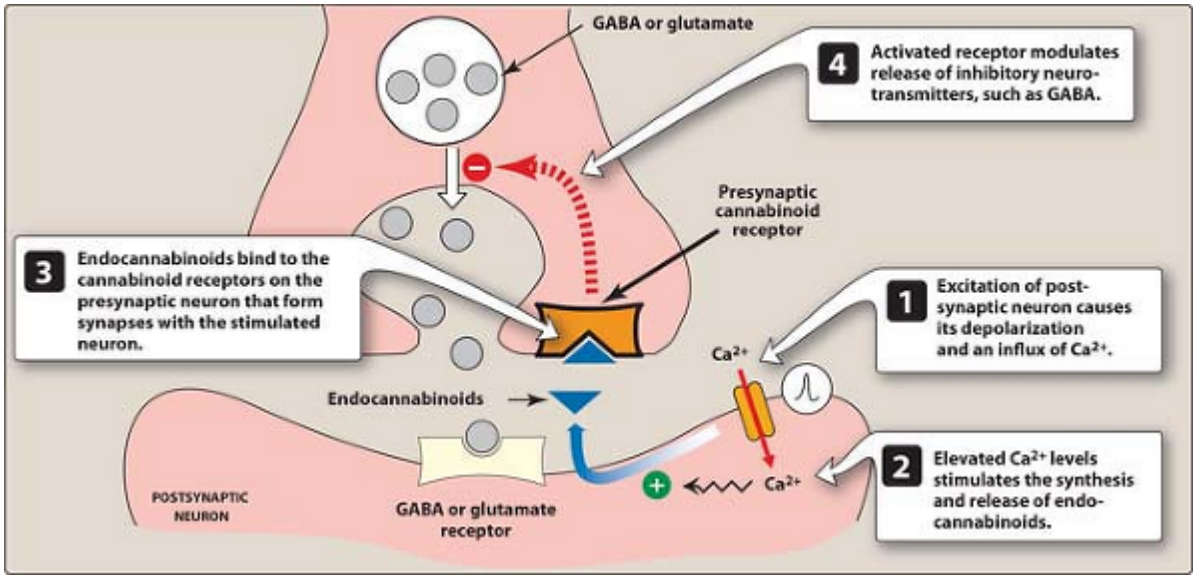


Figure 10.11 Cannabinoid receptor. GABA = Î»-aminobutyric aid.

B. Tetrahydrocannabinol

The main psychoactive alkaloid contained in marijuana is Î”^{9}-*tetrahydrocannabinol* [tet-ra-hi-dro-can-NAB-i-nol] (*THC*), which is available as *dronabinol* [droe-NAB-i-nol]. Depending on the social situation, *THC* can produce euphoria, followed by drowsiness and relaxation. In addition to affecting short-term memory and mental activity, *THC* decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car. Its wide range of effects include appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. *THC* receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals that interact synaptically with pyramidal neurons. CB1 is coupled to a G protein. Interestingly, like the endogenous ligands of the opioid system, endocannabinoids have been identified in the CNS. These compounds, which bind to the CB1 receptors, are membrane-derived and are synthesized on demand, and they may act as local neuromodulators (Figure 10.11). The action of *THC* is believed to be mediated through the CB1 receptors but is still under investigation. The effects of THC appear immediately after the drug is smoked, but maximum effects take

about 20 minutes. By 3 hours, the effects largely disappear. *Dronabinol* is administered orally and has a peak effect in 2 to 4 hours. Its psychoactive effects can last up to 6 hours, but its appetite-stimulant effects may persist for 24 hours. It is highly lipid soluble and has a large volume of distribution. *THC* itself is extensively metabolized by the mixed-function oxidases. Elimination

is largely through the biliary route. Adverse effects include increased heart rate, decreased blood pressure, and reddening of the conjunctiva. At high doses, a toxic psychosis develops (Figure 10.12). Tolerance and mild physical dependence occur with continued, frequent use of the drug. *Dronabinol* is indicated as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight. It is also sometimes given for the severe emesis caused by some cancer chemotherapeutic agents (see p. 337). The CB1-receptor antagonist, *rimonabant* [ri-MOH-nah-bant], is effective in the treatment of obesity and has been found to decrease appetite and body weight in humans. *Rimonabant* has also been found to induce psychiatric disturbances, such as anxiety and depression, during clinical trials.

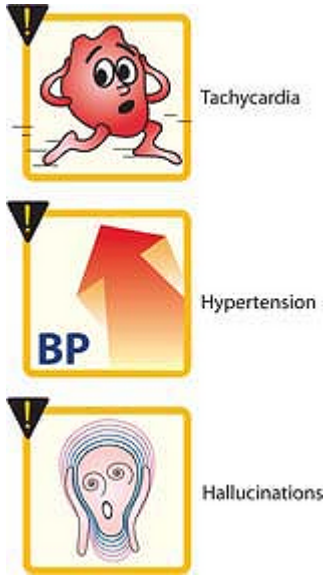


Figure 10.12 Adverse effects of *tetrahydrocannabinol*.

C. Phencyclidine

Phencyclidine [fen-SYE-kli-deen] (also known as PCP, or â€œangel dustâ€) inhibits the reuptake of *dopamine*, 5-HT, and *norepinephrine*. The major action of *phencyclidine* is to block the ion channel regulated by the NMDA subtype of glutamate receptor. This action prevents the passage of critical ions (particularly Ca^{2+}) through the channel. *Phencyclidine* also has anticholinergic activity but, surprisingly, produces hypersalivation. *Phencyclidine*, an analog of ketamine, causes dissociative anesthesia (insensitivity to pain, without loss of consciousness) and analgesia. In this state, it produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity. Sometimes, hostile and bizarre behavior occurs. At increased dosages, anesthesia, stupor, or coma result, but strangely, the eyes may remain open. Increased sensitivity to external stimuli exists, and the CNS actions may persist for a week. Tolerance often develops with continued use.

Study Questions

Choose the ONE best answer.

10.1 A very agitated young male was brought to the emergency room by the police. Psychiatric examination

revealed that he had snorted cocaine several times in the past few days, the last time being 10 hours previously. He was given a drug that sedated him, and he fell asleep. The drug that was used to counter this patient's apparent cocaine wihdrawal was very likely:

A. Phenobarbital.

B. Lorazepam.

C. Cocaine.

D. Hydroxyzine.

E. Fluoxetine.

View Answer