IV. DIRECT-ACTING ADRENERGIC AGONISTS

A. Epinephrine

B. Norepinephrine

Because norepinephrine [nor-ep-ih-NF-rin] is the neurotransmitter of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the α-adrenergic receptor is most affected.

1. Cardiovascular actions:

   a. Vasoconstriction: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α₁ effect). Both systolic and diastolic blood pressures increase (Figure 6.11). [Note: Norepinephrine causes greater vasoconstriction than epinephrine, because it does not induce compensatory vasodilation via β₂ receptors on blood vessels supplying skeletal muscles. The weak β₂ activity of norepinephrine also explains why it is not useful in the treatment of asthma or anaphylaxis.]

   b. Baroreceptor reflex: Norepinephrine increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which 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 (Figure 6.11). When atropine, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia.

2. Therapeutic uses: Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

3. Pharmacokinetics: Norepinephrine is given IV for rapid onset of action. The duration of action is 1 to 2 minutes, following the end of the infusion. It is rapidly metabolized by MAO and COMT, and inactive metabolites are excreted in the urine.

4. Adverse effects: These are similar to epinephrine. In addition, norepinephrine is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from norepinephrine may be treated with the α receptor antagonist phentolamine.
**B. Isoproterenol**

*Isoproterenol* [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that stimulates both $\beta_1$- and $\beta_2$-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on $\alpha$ receptors is insignificant. *Isoproterenol* produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output (Figure 6.12). It is as active as *epinephrine* in this action. *Isoproterenol* also dilates the arterioles of skeletal muscle ($\beta_2$ 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 pressures (Figure 6.12). *Isoproterenol* is a potent bronchodilator ($\beta_2$ effect). The use of *isoproterenol* has largely been replaced with other drugs, but it may be useful in atrioventricular (AV) block. The adverse effects of *isoproterenol* are similar to those of *epinephrine*.

**C. 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 $\alpha$- and $\beta$-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating $\alpha$ receptors, whereas at lower doses, it stimulates $\beta$ cardiac receptors. In addition, $D_1$ and $D_2$ dopaminergic receptors, distinct from the $\alpha$- and $\beta$-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 $\beta_1$ receptors of the heart, having both positive inotropic and chronotropic effects (Figure 6.13). At very high doses, *dopamine* activates $\alpha$ receptors on the vasculature, resulting in vasoconstriction.

   b. **Renal and visceral:** *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (Figure 6.13). These receptors are not affected by $\alpha$- or $\beta$-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

2. **Therapeutic uses:** *Dopamine* is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the $\beta_1$ receptors on the heart to increase cardiac output and $\alpha_1$ receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above.
Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. In this regard, dopamine is far superior to norepinephrine, which diminishes blood supply to the kidney and may cause renal shutdown. It is also used to treat hypotension and severe heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients who have oliguria.

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

D. Fenoldopam

Fenoldopam [fen-OL-de-pam] is an agonist of peripheral dopamine D₁ receptors. It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. Fenoldopam is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent.

E. Dobutamine

Dobutamine [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is a β₁ receptor agonist. It increases cardiac rate and output with few vascular effects. Dobutamine is used to increase cardiac output in acute heart failure (see Chapter 19), as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs. Dobutamine should be used with caution in atrial fibrillation, because it increases AV conduction. Other adverse effects are similar to epinephrine. Tolerance may develop with prolonged use.

F. Oxymetazoline

Oxymetazoline [OX-ee-mee-TAZ-ih-leen] is a direct-acting synthetic adrenergic agonist that stimulates both α₁- and α₂-adrenergic receptors. Oxymetazoline is found in many over-the-counter short-term nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. Oxymetazoline directly stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. It is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. Local irritation and sneezing may occur with intranasal administration. Rebound congestion and dependence are observed with long-term use.

Figure 6.13
Clinically important actions of isoproterenol and dopamine.
G. Phenylephrine

Phenylephrine [fen-il-EF-reen] is a direct-acting, synthetic adrenergic drug that binds primarily to \( \alpha_1 \) receptors. 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. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate). Large doses can cause hypertensive headache and cardiac irregularities. Phenylephrine acts as a nasal decongestant when applied topically or taken orally. Phenylephrine has replaced pseudoephedrine in many oral decongestants, since pseudoephedrine has been misused to make methamphetamine. Phenylephrine is also used in ophthalmic solutions for mydriasis.

H. Clonidine

Clonidine [KLOE-ni-deen] is an \( \alpha_2 \) agonist that is used for the treatment of hypertension. It can also be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines. Clonidine acts centrally on presynaptic \( \alpha_2 \) receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of clonidine are lethargy, sedation, constipation, and xerostomia. Abrupt discontinuance must be avoided to prevent rebound hypertension. Clonidine and another \( \alpha_2 \) agonist methyldopa are discussed along with antihypertensives in Chapter 17.

I. Albuterol and terbutaline

Albuterol [al-BYOO-ter-ole] and terbutaline [ter-BYOO-te-leen] are short-acting \( \beta_2 \) agonists used primarily as bronchodilators and administered by a metered-dose inhaler (Figure 6.14). Albuterol is the short-acting \( \beta_2 \) agonist of choice for the management of acute asthma symptoms. Inhaled terbutaline is no longer available in the United States, but is still used in other countries. Terbutaline is also used off-label as a uterine relaxant to suppress premature labor. One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to \( \beta_1 \) receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

J. Salmeterol and formoterol

Salmeterol [sa-lME-ter-ole] and formoterol [for-MOH-ter-ole] are long-acting \( \beta \) agonists (LABAs) that are \( \beta_2 \) selective. 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 (Figure 6.14). These agents are not recommended as monotherapy, but are highly efficacious
when combined with a corticosteroid. Salmeterol and formoterol are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications. LABAs have been shown to increase the risk of asthma-related deaths.

K. Mirabegron

Mirabegron [mir-a-BEG-ron] is a β3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder. Mirabegron may increase blood pressure and should not be used in patients with uncontrolled hypertension. It increases levels of digoxin and also inhibits the CYP2D6 isozyme, which may enhance the effects of other medications metabolized by this pathway (for example, metoprolol).

V. INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine (Figure 6.8). They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of amphetamine [am-FET-a-meen] is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α, agonist action on the vasculature, as well as β1-stimulatory effects on the heart. Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. Thus, amphetamine is an indirect-acting adrenergic drug. The actions and therapeutic uses of amphetamine and its derivatives are discussed under stimulants of the CNS (see Chapter 16).

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 aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, 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 sodium-chloride (Na+/Cl−)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced 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 cocaine. In addition, the duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by $\alpha$, agonist actions and $\beta$ stimulatory effects. [Note: Cocaine as a drug of abuse is discussed in Chapter 15.]

VI. MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine [eh-FED-rin] and pseudoephedrine [soo-doe-eh-FED-rin] are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings (Figure 6.8) but also directly stimulate both $\alpha$ and $\beta$ 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. Therefore, these drugs have a long duration of action. Ephedrine and pseudoephedrine have excellent absorption orally and penetrate into the CNS, but pseudoephedrine has fewer CNS effects. Ephedrine is eliminated largely unchanged in urine, and pseudoephedrine undergoes incomplete hepatic metabolism before elimination in urine. Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension. Ephedrine produces bronchodilation, but it is less potent and slower acting than epinephrine or isoproterenol. It was previously used to prevent asthma attacks but has been replaced by more effective medications. Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of ephedrine is declining because of the availability of better, more potent agents that cause fewer adverse effects. Ephedrine-containing herbal supplements (mainly ephedra-containing products) have been banned by the U.S. Food and Drug Administration because of life-threatening cardiovascular reactions.] Pseudoephedrine is primarily used orally to treat nasal and sinus congestion. Pseudoephedrine has been illegally used to produce methamphetamine. Therefore, products containing pseudoephedrine have certain restrictions and must be kept behind the sales counter in the United States. Important characteristics of the adrenergic agonists are summarized in Figures 6.15–6.17.
### VI. Mixed-Action Adrenergic Agonists

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>RECEPTOR TYPE</th>
<th>ACTION</th>
<th>OPPOSING ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sinus and AV</td>
<td>$\beta_1$</td>
<td>↑ Automaticity</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>• Conduction pathway</td>
<td>$\beta_1$</td>
<td>↑ Conduction velocity, automaticity</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>• Myofibrils</td>
<td>$\beta_1$</td>
<td>↑ Contractility, automaticity</td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>$\beta_2$</td>
<td>Vasodilation</td>
<td>$\alpha$-Adrenergic receptors</td>
</tr>
<tr>
<td>Bronchial smooth muscle</td>
<td>$\beta_2$</td>
<td>Bronchodilation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Kidneys</td>
<td>$\beta_1$</td>
<td>↑ Renin release</td>
<td>$\alpha$-Adrenergic receptors</td>
</tr>
<tr>
<td>Liver</td>
<td>$\beta_2\alpha_1$</td>
<td>↑ Glycogenolysis and gluconeogenesis</td>
<td>—</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>$\beta_3$</td>
<td>↑ Lipolysis</td>
<td>$\alpha_2$-Adrenergic receptors</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\beta_2$</td>
<td>↑ Increased contractility</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potassium uptake; glycogenolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilates arteries to skeletal muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremor</td>
<td></td>
</tr>
<tr>
<td>Eye-ciliary muscle</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td>Cholinergic receptors</td>
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<td>GI tract</td>
<td>$\beta_2$</td>
<td>↓ Motility</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Urinary bladder detrusor muscle</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Uterus</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td>Oxytocin</td>
</tr>
</tbody>
</table>

**Figure 6.16**

Summary of $\beta$-adrenergic receptors. AV = atrioventricular; GI = gastrointestinal.
### Adrenergic Agonists

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECEPTOR SPECIFICITY</th>
<th>THERAPEUTIC USES</th>
</tr>
</thead>
</table>
| Epinephrine   | $\alpha_1$, $\beta_2$ $\alpha_1$, $\beta_1$, $\beta_2$ | Acute asthma  
Anaphylactic shock  
In local anesthetics to increase duration of action |
| Norepinephrine| $\alpha_1$, $\alpha_2$, $\beta_1$ | Treatment of shock                                    |
| Isoproterenol | $\beta_1$, $\beta_2$ | As a cardiac stimulant                                |
| Dopamine      | Dopaminergic $\alpha_1$, $\beta_1$ | Treatment of shock  
Treatment of congestive heart failure  
Raise blood pressure |
| Dobutamine    | $\beta_1$            | Treatment of acute heart failure                      |
| Oxymetazoline | $\alpha_1$           | As a nasal decongestant                               |
| Phenylephrine | $\alpha_1$           | As a nasal decongestant  
Raise blood pressure  
Treatment of paroxysmal supraventricular tachycardia |
| Clonidine     | $\alpha_2$           | Treatment of hypertension                            |
| Albuterol     | $\beta_2$            | Treatment of bronchospasm (short acting)              |
| Terbutaline   | $\beta_2$            | Treatment of bronchospasm (long acting)               |
| Salmeterol    | $\beta_2$            | Treatment of bronchospasm (long acting)               |
| Formoterol    | $\alpha$, $\beta$, CNS | As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control |
| Amphetamine   | $\alpha$, $\beta$, CNS | As a nasal decongestant  
Raise blood pressure |
| Ephedrine     | $\alpha$, $\beta$, CNS | As a nasal decongestant  
Raise blood pressure |
| Pseudoephedrine| $\alpha$, $\beta$, CNS | As a nasal decongestant  
Raise blood pressure |

**CATECHOLAMINES**
- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

**NONCATECHOLAMINES**
Compared to catecholamines:
- Longer duration of action
- All can be administered orally or via inhalation

---

**Figure 6.17**
Summary of the therapeutic uses of adrenergic agonists. CNS = central nervous system.
Study Questions

Choose the ONE best answer.

Which of the following is correct regarding adrenergic neurotransmission?

A. Epinephrine is the major neurotransmitter released from sympathetic nerve terminals.
B. Norepinephrine is mainly released from the adrenal glands.
C. Tricyclic antidepressants and cocaine prevent reuptake of norepinephrine into the nerve terminals.
D. Monoamine oxidase (MAO) converts dopamine to norepinephrine in the nerve terminal.

All of the following are correct regarding adrenergic receptors, except:

A. α1 Receptors are primarily located on the postsynaptic membrane in the effector organs.
B. α2 Receptors are primarily located on the presynaptic sympathetic nerve terminals.
C. β1 Receptors are found mainly in the heart.
D. β2 Receptors are found mainly in adipose tissue.

A hypertensive patient was accidentally given an α1 agonist instead of an α1 blocker. Which of the following is correct in this situation?

A. α1 Agonists can increase the release of norepinephrine from sympathetic nerve terminals.
B. α1 Agonists can reduce blood pressure in this patient.
C. α1 Agonists can increase blood pressure in this patient.
D. α1 Agonists will not affect blood pressure in this patient.

Which of the following is correct regarding responses mediated by adrenergic receptors?

A. Stimulation of α1 receptors increases blood pressure.
B. Stimulation of α1 receptors reduces blood pressure.
C. Stimulation of sympathetic presynaptic α2 receptors increases norepinephrine release.
D. Stimulation of β2 receptors increases heart rate (tachycardia).
E. Stimulation of β2 receptors causes bronchoconstriction.

An asthma patient was given a nonselective β agonist to relieve bronchoconstriction. Which of the following adverse effects would you expect to see in this patient?

A. Bradycardia.
B. Tachycardia.
C. Hypotension (reduction in blood pressure).
D. Worsening bronchoconstriction.
6. Adrenergic Agonists

Which of the following adrenergic agonists is most likely to cause CNS side effects when administered systemically?
A. Epinephrine.
B. Norepinephrine.
C. Isoproterenol.
D. Dopamine.
E. Ephedrine.

A 12-year-old boy who is allergic to peanuts was brought to the emergency room after accidentally consuming peanuts contained in fast food. He is in anaphylactic shock. Which of the following drugs would be most appropriate to treat this patient?
A. Norepinephrine.
B. Phenylephrine.
C. Dobutamine.
D. Ephedrine.

A 70-year-old patient was brought to the emergency room with a blood pressure of 76/60 mm Hg, tachycardia, and low cardiac output. He was diagnosed with acute heart failure. Which of the following drugs would be the most appropriate to improve his cardiac function?
A. Epinephrine.
B. Fenoldopam.
C. Dobutamine.
D. Isoproterenol.

Which of the following adrenergic agonists is commonly present in nasal sprays available over-the-counter (OTC) to treat nasal congestion?
A. Clonidine.
B. Albuterol.
C. Oxymetazoline.
D. Dobutamine.
E. Norepinephrine.

One of your patients who is hypertensive and gets mild asthma attacks occasionally bought an herbal remedy online to help with his asthma. He is not on any asthma medications currently but is receiving a β₁-selective blocker for his hypertension. The herbal remedy seems to relieve his asthma attacks, but his blood pressure seems to increase despite the β-blocker therapy. Which of the following drugs is most likely present in the herbal remedy he is taking?
A. Phenylephrine.
B. Norepinephrine.
C. Dobutamine.
D. Ephedrine.
E. Salmeterol.

Correct answer = E. Ephedrine is more lipophilic compared to the other drugs listed and therefore is more likely to cross the blood–brain barrier when administered systemically. Therefore, ephedrine is more likely to cause CNS side effects compared to other listed drugs.

Correct answer = D. Norepinephrine has more α agonistic effects and activates mainly α₁, α₂, and β receptors. Epinephrine has more β agonistic effects and activates mainly α₁, α₂, β₁, and β₂ receptors. Phenylephrine has predominantly α effects and activates mainly α₁ receptors. Dobutamine mainly activates β₁ receptors and has no significant effects on β₂ receptors. Thus, epinephrine is the drug of choice in anaphylactic shock that can both stimulate the heart (β₁ activation) and dilate bronchioles (β₂ activation).

Correct answer = C. Among the choices, the ideal drug to increase contractility of the heart in acute heart failure is dobutamine, since it is a selective β₁-adrenergic agonist. Fenoldopam is a dopamine agonist used to treat severe hypertension. Other drugs are nonselective adrenergic agonists that could cause unwanted side effects.

Correct answer = C. Drugs with selective α₁ agonistic activity are commonly used as nasal decongestants because of their ability to cause vasoconstriction in the nasal vessels. Oxymetazoline is an α₁ agonist and therefore the preferred drug among the choices as a nasal decongestant. Clonidine is an α₂ agonist, albuterol is a β₂ agonist, dobutamine is a β₁ agonist, and norepinephrine is a nonselective adrenergic agonist.

Correct answer = D. Two drugs among the choices that could relieve asthma are ephedrine and salmeterol, as they activate β₂ receptors in the bronchioles and cause bronchodilation. However, salmeterol is a selective β₂ agonist and should not cause an increase in blood pressure. Ephedrine on the other hand stimulates the release of norepinephrine and acts as a direct agonist at α₁- and β-adrenergic receptors, thus causing an increase in blood pressure. Phenylephrine (a nonselective α agonist) does not cause bronchodilation. Norepinephrine is a nonselective adrenergic agonist that does not have any stimulatory effects on β₂ receptors. Also, norepinephrine is not active when given orally.
Adrenergic Antagonists
Rajan Radhakrishnan

I. OVERVIEW

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are, therefore, considered in that section.] The adrenergic antagonists discussed in this chapter are summarized in Figure 7.1.

II. α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-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. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. [Note: β receptors, including β, adrenoceptors on the heart, are not affected by α blockade.] The α-adrenergic blocking agents, phenoxybenzamine and phentolamine, have limited clinical applications.

A. Phenoxybenzamine

*Phenoxybenzamine* [fen-ox-een-BEN-za-meen] is nonselective, linking covalently to both α₁ and α₂ receptors (Figure 7.2). The block is irreversible and noncompetitive, and the only way the body can overcome the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of phenoxybenzamine last about 24 hours. After the drug is injected, a delay of a few hours occurs before a blockade develops.
1. Actions:

a. Cardiovascular effects: By blocking \(\alpha\) 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 \(\alpha_2\) receptors in the heart can contribute to an increased cardiac output. [Note: Blocking these receptors results in more norepinephrine release, which stimulates \(\beta_1\) receptors on the heart, increasing cardiac output.] Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

b. Epinephrine reversal: All \(\alpha\)-adrenergic blockers reverse the \(\alpha\) agonist actions of epinephrine. For example, the vasoconstrictive action of epinephrine is interrupted, but vasodilation of other vascular beds caused by stimulation of \(\beta_1\) receptors is not blocked. Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine (Figure 7.3). [Note: The actions of norepinephrine are not reversed but are diminished because norepinephrine lacks significant \(\beta\) agonist action on the vasculature.] Phenoxybenzamine has no effect on the actions of isoproterenol, which is a pure \(\beta\) agonist (Figure 7.3).

2. Therapeutic uses: Phenoxybenzamine is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. It may be used prior to surgical removal of the tumor to prevent a hypertensive crisis, and it is also useful in the chronic management of inoperable tumors. Phenoxybenzamine is sometimes effective in treating Raynaud disease and frostbite.

3. Adverse effects: Phenoxybenzamine can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. Phenoxybenzamine should be used with caution in patients with cerebrovascular or cardiovascular disease.

B. Phentolamine

In contrast to phenoxybenzamine, phentolamine [fen-TOLE-a-meen] produces a competitive block of \(\alpha_1\) and \(\alpha_2\) receptors that lasts for approximately 4 hours after a single injection. 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 \(\alpha_2\) receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain, and phentolamine is contraindicated in patients with coronary artery disease. Phentolamine is used for the short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis following extravasation of norepinephrine. Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors.

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

Prazosin [PRAY-zoe-sin], terazosin [ter-AY-zoe-sin], and doxazosin [dox-AY-zoe-sin] are selective competitive blockers of the \(\alpha_1\) receptor.
In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension. *Tamsulosin* [tam-SUE-loh-sin] and *alfuzosin* [al-FYOO-zoe-sin] are examples of other selective $\alpha_1$ antagonists indicated for the treatment of benign prostatic hyperplasia (BPH). Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1. **Mechanism of action:** All of these agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. *Tamsulosin* has the least effect on blood pressure because it is less selective for $\alpha_{1a}$ receptors found in the blood vessels and more selective for $\alpha_{1a}$ receptors in the prostate and bladder. Blockade of the $\alpha_{1a}$ receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

2. **Therapeutic uses:** Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response (Figure 7.4) that can result in syncope (fainting). This action, termed a “first-dose” 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. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives, $\alpha_1$ antagonists are not used as monotherapy for the treatment of hypertension (see Chapter 17). The $\alpha_1$ receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH (see Chapter 32).

3. **Adverse effects:** $\alpha_1$-Blockers such as *prazosin* and *doxazosin* 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 $\alpha_1$ antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, *sildenafil*), thereby necessitating cautious dose titration and use at the lowest possible doses. By blocking $\alpha$ receptors in the ejaculatory ducts and impairing smooth muscle contraction, $\alpha_1$ antagonists may cause inhibition of ejaculation and retrograde ejaculation. These agents may cause “floppy iris syndrome,” a condition in which the iris billows in response to intraoperative eye surgery. Figure 7.5 summarizes some adverse effects observed with $\alpha$-blockers.

**D. Yohimbine**

*Yohimbine* [yo-HIM-bean] is a selective competitive $\alpha_2$-blocker. It is found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended, due to lack of demonstrated efficacy. *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery. It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction because it may worsen these conditions.
III. β-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β₁ and β₂ receptors, whereas cardioselective β antagonists primarily block β₁ receptors. [Note: There are no clinically useful β₂ antagonists.] These drugs also differ in intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics (Figure 7.6). Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β-Blockers are effective in treating hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol" except for labetalol and carvedilol.]

A. Propranolol: A nonselective β antagonist

Propranolol [proe-PRAN-oh-lole] is the prototype β-adrenergic antagonist and blocks both β₁ and β₂ receptors with equal affinity. 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 7.7). It directly depresses sinoatrial and atrioventricular nodal activity. The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β₁ receptors, and these effects are useful in the treatment of angina (see Chapter 21). The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

   b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β₂-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 7.7). The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of propranolol. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

   c. Bronchoconstriction: Blocking β₂ receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 7.7). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

   d. Disturbances in glucose metabolism: β blockade leads to decreased glycogenolysis and decreased glucagon secretion.
Therefore, if propranolol is given to a diabetic patient receiving insulin, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection. β-blockers also attenuate the normal physiologic response to hypoglycemia.

e. Blocked action of isoproterenol: Nonselective β-blockers, including propranolol, have the ability to block the actions of isoproterenol (β₁, β₂ agonist) on the cardiovascular system. Thus, in the presence of a β-blocker, isoproterenol does not produce cardiac stimulation (β₁ mediated) or reductions in mean arterial pressure and diastolic pressure (β₂ mediated; Figure 7.3). [Note: In the presence of a nonselective β-blocker, epinephrine no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α receptors) remains unimpaired. The actions of norepinephrine on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

2. Therapeutic uses:

a. Hypertension: Propranolol does not reduce blood pressure in people with normal blood pressure. 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, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects (see Chapter 17).

b. Angina pectoris: Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. Propranolol is, thus, useful in the chronic management of stable angina.

c. Myocardial infarction: Propranolol and other β-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 β-blockers. In addition, administration of a β-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.

d. Migraine: Propranolol is effective in reducing migraine episodes when used prophylactically (see Chapter 36). It is one of the more useful β-blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as sumatriptan are used, as well as other drugs.]

e. Hyperthyroidism: Propranolol and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm),
3. Pharmacokinetics: After oral administration, propranolol is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation. The volume of distribution of propranolol is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity. Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

4. Adverse effects:

a. Bronchoconstriction: Propranolol has the potential to cause significant bronchoconstriction due to blockade of β₂ receptors (Figure 7.8). Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, propranolol is contraindicated in patients with COPD or asthma.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

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

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers. A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by β₂ and β₃ receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers have increased low-density lipoprotein (“bad” cholesterol), increased triglycerides, and reduced high-density lipoprotein (“good” cholesterol). These effects on the serum lipid profile may be less pronounced with the use of β₁-selective antagonists such as metoprolol.

e. CNS effects: Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with more
hydrophilic β-blockers (for example, atenolol), since they do not cross the blood–brain barrier as readily.

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

B. Nadolol and timolol: Nonselective β antagonists

Nadolol [NAH-doh-lole] and timolol [TIM-o-lole] also block β₁- and β₂-adrenoceptors and are more potent than propranolol. Nadolol has a very long duration of action (Figure 7.6). 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.

1. Treatment of glaucoma: β-blockers, such as topically applied timolol, betaxolol, or carteolol, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours. The β-blockers are only used for chronic management of glaucoma. In an acute attack of glaucoma, pilocarpine is still the drug of choice for emergency lowering of intraocular pressure. Other agents used in the treatment of glaucoma are summarized in Figure 7.9.

<table>
<thead>
<tr>
<th>CLASS OF DRUG</th>
<th>DRUG NAMES</th>
<th>MECHANISM OF ACTION</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenergic antagonists (topical)</td>
<td>Betaxolol, carteolol, levobunolol, metipranolol, timolol</td>
<td>Decrease of aqueous humor production</td>
<td>Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.</td>
</tr>
<tr>
<td>α-Adrenergic agonists (topical)</td>
<td>Apraclonidine, brimonidine</td>
<td>Decrease of aqueous humor production and increase of aqueous outflow</td>
<td>Red eye and ocular irritation, allergic reactions, malaise, and headache.</td>
</tr>
<tr>
<td>Cholinergic agonists (topical)</td>
<td>Pilocarpine, carbachol</td>
<td>Increase of aqueous outflow</td>
<td>Eye or brow pain, increased myopia, and decreased vision.</td>
</tr>
<tr>
<td>Prostaglandin-like analogues (topical)</td>
<td>Latanoprost, travoprost, bimatoprost</td>
<td>Increase of aqueous humor outflow</td>
<td>Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors (topical and systemic)</td>
<td>Dorzolamide and brinzolamide (topical), acetazolamide, and methazolamide (oral)</td>
<td>Decrease of aqueous humor production</td>
<td>Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).</td>
</tr>
</tbody>
</table>

Figure 7.9
Classes of drugs used to treat glaucoma.
C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective $\beta_1$ antagonists

Drugs that preferentially block the $\beta_1$ receptors minimize the unwanted bronchoconstriction ($\beta_2$ effect) seen with propranolol use in asthma patients. Cardioselective $\beta$-blockers, such as acebutolol [ace-BYOO-toe-lole], atenolol [a-TEH-noe-lole], and metoprolol [me-TOE-proe-lole], antagonize $\beta_1$ receptors at doses 50- to 100-fold less than those required to block $\beta_2$ receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Since $\beta_1$ selectivity of these agents is lost at high doses, they may antagonize $\beta_2$ receptors.]

1. **Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (Figure 7.7). Esmolol [ES-moe-lole] has a very short half-life (Figure 7.6) due to metabolism of an ester linkage. It is only available intravenously and is used to control blood pressure or heart rhythm during surgery or diagnostic procedures. In contrast to propranolol, the cardioselective $\beta$-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. In addition to its cardioselective $\beta$ blockade, nebivolol releases nitric oxide from endothelial cells and causes vasodilation.

2. **Therapeutic uses:** The cardioselective $\beta$-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina. Bisoprolol and the extended-release formulation of metoprolol are indicated for the management of chronic heart failure. Because these drugs have less effect on peripheral vascular $\beta_1$ receptors, coldness of extremities (Raynaud phenomenon), a common side effect of $\beta$-blockers, is less frequent.

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. **Actions:**

   a. **Cardiovascular:** Acebutolol ($\beta_1$-selective antagonist) and pindolol (nonselective $\beta$-blocker) are not pure antagonists. These drugs also have the ability to weakly stimulate both $\beta_1$ and $\beta_2$ receptors (Figure 7.10) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the $\beta$ 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 diminished effect on cardiac rate and cardiac output compared to that of $\beta$-blockers without ISA.

   b. **Decreased metabolic effects:** $\beta$-blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other $\beta$-blockers. For example, these agents do not decrease plasma HDL levels.
2. Therapeutic use in hypertension: β-blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.] Figure 7.11 summarizes some of the indications for β-blockers.

E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

1. Actions: Labetalol [lah-BET-a-bole] and carvedilol [CAR-ve-dil-ol] are nonselective β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2. Therapeutic use in hypertension and heart failure: Labetalol is 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 Chapter 17). β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, carvedilol as well as metoprolol and bisoprolol are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time (see Chapter19).

3. Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade. Figure 7.12 summarizes the receptor specificities and uses of the β-adrenergic antagonists.

### IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. Reserpine [re-SER-pee-n] is one of the remaining agents in this category.

Reserpine, a plant alkaloid, blocks the Mg2+/adenosine triphosphate–dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. Reserpine has a slow onset, a long duration of action, and effects that persist for many days after discontinuation. It has been used for the management of hypertension but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions.

Figure 7.11
Some clinical applications of β-blockers.
AV = atrioventricular.
### Study Questions

Choose the ONE best answer.

A 60-year-old female patient started on a new antihypertensive medication recently. Her blood pressure seems to be under control, but she complains of fatigue, drowsiness, and fainting when she gets up from the bed (orthostatic hypotension). Which of the following drugs is she most likely taking?

A. Metoprolol.
B. Propranolol.
C. Prazosin.
D. Clonidine.

Correct answer = C. α-Blockers (prazosin) are more likely to cause orthostatic hypotension compared to β-blockers (metoprolol, propranolol) and α₂ agonists (clonidine).

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<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECEPTOR SPECIFICITY</th>
<th>THERAPEUTIC USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>β₁, β₂</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Migraine</td>
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<td>Hyperthyroidism</td>
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<td>Angina pectoris</td>
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<td></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Nadolol</td>
<td>β₁, β₂</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Pindolol¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>β₁, β₂</td>
<td>Glaucoma, hypertension</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Bisoprolol²</td>
<td></td>
<td>Angina</td>
</tr>
<tr>
<td>Esmolol</td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Metoprolol²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol²</td>
<td>β₁</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Askovolol</td>
<td>β₁, NO↑</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Carvedilol²</td>
<td>α₁, β₁, β₂</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Labetalol</td>
<td></td>
<td></td>
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**Figure 7.12**
Summary of β-adrenergic antagonists. NO = nitric oxide. ¹Acebutolol and pindolol are partial agonists, as well. ²Bisoprolol, metoprolol, and carvedilol are also used for the treatment of heart failure.
A 30-year-old male patient was brought to the ER with amphetamine overdose. He presented with high blood pressure and arrhythmia. Which of the following is correct regarding this patient?

A. Amphetamine can activate all types of adrenergic receptors.
B. β-Blockers are the ideal antidotes for amphetamine poisoning.
C. α-Blockers can normalize the blood pressure in this patient.
D. Miosis could be a possible symptom of amphetamine poisoning.

Correct answer = A. Amphetamine is an indirect adrenergic agonist that mainly enhances the release of norepinephrine from peripheral sympathetic neurons. Therefore, it activates all types of adrenergic receptors (that is, α and β receptors) and causes an increase in blood pressure. Since both α and β receptors are activated by amphetamine, α-blockers or β-blockers alone cannot relieve the symptoms of amphetamine poisoning. Since amphetamine causes sympathetic activation, it causes mydriasis, not miosis.

A new antihypertensive drug was tested in an animal model of hypertension. The drug when given alone reduces blood pressure in the animal. Norepinephrine when given in the presence of this drug did not cause any significant change in blood pressure or heart rate in the animal. The new drug is similar to which of the following drugs in terms of its pharmacological mechanism of action?

A. Prazosin.
B. Clonidine.
C. Propranolol.
D. Metoprolol.
E. Carvedilol.

Correct answer = E. Norepinephrine activates both α1 and β1 receptors and causes an increase in heart rate and blood pressure. A drug that prevents the increase in blood pressure caused by norepinephrine should be similar to carvedilol that antagonizes both α1 and β1 receptors. Prazosin is an α1 antagonist, clonidine is an α2 agonist, and propranolol and metoprolol are β blockers, and these drugs cannot completely prevent the cardiovascular effects of norepinephrine.

A β-blocker was prescribed for hypertension in a female asthma patient. After about a week of treatment, the asthma attacks got worse, and the patient was asked to stop taking the β-blocker. Which of the following β-blockers would you suggest as an alternative in this patient that is less likely to worsen her asthma?

A. Propranolol.
B. Metoprolol.
C. Labetalol.
D. Carvedilol.

Correct answer = B. The patient was most likely given a nonselective β-blocker (antagonizes both β1 and β2 receptors) that made her asthma worse due to β2 antagonism. An alternative is to prescribe a cardioselective (antagonizes only β1) β-blocker that does not antagonize β2 receptors in the bronchioles. Metoprolol is a cardioselective β-blocker. Propranolol, labetalol, and carvedilol are nonselective β-blockers and could worsen the asthma.

A 70-year-old male needs to be treated with an α-blocker for overflow incontinence due to his enlarged prostate. Which of the following drugs would you suggest in this patient that will not affect his blood pressure significantly?

A. Prazosin.
B. Doxazosin.
C. Phentolamine.
D. Tamsulosin.
E. Terazosin.

Correct answer = D. Tamsulosin is an α1 antagonist that is more selective to the α1 receptor subtype (α1A) present in the prostate and less selective to the α1 receptor subtype (α1D) present in the blood vessels. Therefore, tamsulosin does not affect blood pressure significantly. Prazosin, doxazosin, terazosin, and phentolamine antagonize both these subtypes and cause significant hypotension as a side effect.
A 50-year-old male was brought to the emergency room after being stung by a hornet. The patient was found to be in anaphylactic shock, and the medical team tried to reverse the bronchoconstriction and hypotension using epinephrine. However, the patient did not fully respond to the epinephrine treatment. The patient’s wife mentioned that he is taking a prescription medication for his blood pressure, the name of which she does not remember. Which of the following medications is he most likely taking that could have prevented the effects of epinephrine?

A. Doxazosin.
B. Propranolol.
C. Metoprolol.
D. Acebutolol.

Correct answer = B. Propranolol is used in the treatment of asthma as it does not antagonize β receptors. β-Adrenergic blockers antagonize only β receptors and do not worsen asthma as they do not antagonize β2 receptors.

Correct answer = B. Propranolol is a cardioselective β-blocker with a-blocking activity. Since it also blocks β2 receptors in the lungs, carvedilol could exacerbate asthma. Carvedilol is not used in patients with acute exacerbation of heart failure but is used in the treatment of stable, chronic heart failure.