Autonomic Drugs

LEARNING OBJECTIVES
1. Identify the major components and functional organization of the autonomic nervous system.
2. Discuss the pharmacologic effects, adverse reactions, contraindications, and dental considerations of cholinergic agents.
3. Discuss the pharmacologic effects, adverse reactions, contraindications, and dental considerations of anticholinergic agents.
4. Identify the major components of the sympathetic nervous system.
5. Discuss the pharmacologic effects, adverse reactions, contraindications, and dental considerations of adrenergic agents.
6. Explain the workings of adrenergic blocking agents and neuromuscular blocking agents.

The dentist and the dental hygienist should become familiar with the autonomic nervous system (ANS) drugs for three reasons. First, certain ANS drugs are used in dentistry. For example, both the vasoconstrictors added to some local anesthetic solutions and the drugs used to increase salivary flow are ANS drugs. Second, some ANS drugs produce oral adverse reactions. For example, the anticholinergics produce xerostomia. Third, members of other drug groups have effects similar to the ANS drugs. Antidepressants and antipsychotics are drug groups with autonomic side effects, specifically anticholinergic effects. An understanding of the effects of the autonomic drugs on the body will facilitate an understanding of the action of other drug groups that have autonomic effects. Before the ANS drugs can be understood, the normal functioning of the ANS must be reviewed. A review of the physiology of the ANS is helpful in understanding these drugs.

AUTONOMIC NERVOUS SYSTEM

The ANS functions largely as an automatic modulating system for many bodily functions, including the regulation of blood pressure and heart rate, gastrointestinal tract motility, salivary gland secretions, and bronchial smooth muscle. This system relies on specific neurotransmitters (chemicals that are released to send messages) and a variety of receptors to initiate functional responses in the target tissues. Before ANS pharmacology is discussed, the anatomy and physiology of this system are reviewed.

Anatomy

The ANS has two divisions, the sympathetic autonomic nervous system (SANS) and the parasympathetic autonomic nervous system (PANS). Each consists of afferent (sensory) fibers (What's happening?), central integrating areas (Let's coordinate all this info! Hey, what did you find out?), efferent (peripheral) motor preganglionic fibers, and postganglionic motor fibers (Begin sweating! Heart begin palpitating!).
The preganglionic neuron (Figure 4-1) originates in the central nervous system (CNS) and passes out to form the ganglia at the synapse with the postganglionic neuron. The space between the preganglionic and postganglionic fibers is termed the synapse or synaptic cleft. The postganglionic neuron originates in the ganglia and innervates the effector organ or tissue.

**Parasympathetic Autonomic Nervous System**

Cell bodies in the CNS give rise to the preganglionic fibers of the parasympathetic division. They originate in the nuclei of the third, seventh, ninth, and tenth cranial nerves (CN III, VII, IX, and X) and the second through the fourth sacral segments (S2 to S4) of the spinal cord. The preganglionic fibers of the PANS are relatively long and extend near to or into the innervated organ. The distribution is relatively simple for the third, seventh, and ninth cranial nerves, whereas the tenth or **vagus** nerve has a complex distribution. There usually is a low ratio of synaptic connections between preganglionic and postganglionic neurons, which leads to a discrete response when the PANS is stimulated. The postganglionic fibers, originating in the ganglia, are usually short and terminate on the innervated tissue.

**Sympathetic Autonomic Nervous System**

The cell bodies that give origin to the preganglionic fibers of the SANS span from the thoracic (T1) to the **lumbar** (L2) portion of the spinal cord (sometimes referred to as the “in between” distribution, that is, between the two locations of the innervation of the PANS). This produces a more diffuse effect in the SANS. The preganglionic fibers exit the cord to enter the sympathetic chain located along each side of the vertebral column. Once a part of the sympathetic chain (groups of nerves a few inches from the vertebral column), preganglionic fibers form multiple synaptic connections with postganglionic cell bodies located up and down the sympathetic chain. Thus a single SANS preganglionic fiber often synapses with numerous postganglionic neurons. This produces a more diffuse effect in the SANS. The postganglionic fibers then terminate at the effector organ or tissues.

The **adrenal medulla** is also innervated by the sympathetic preganglionic fibers. It functions much like a large sympathetic ganglion, with the glands in the medulla representing the postganglionic component. When the SANS is stimulated, the adrenal medulla releases primarily epinephrine and a small amount of norepinephrine (NE) into the systemic circulation. A diffuse response is produced when the SANS is stimulated because of the high ratio of synaptic connections between the preganglionic and postganglionic fibers and because epinephrine is released by the adrenal medulla, into the bloodstream, when stimulated.

**Functional Organization**

In general, the divisions of the ANS, the parasympathetic and the sympathetic, tend to act in opposite directions (Figure 4-2). The parasympathetic division of the ANS is concerned with the conservation of the body processes. Both digestion and intestinal tract motility are greatly influenced by the PANS. The sympathetic division is designed to cope with sudden emergencies such as the “fright or flight” or “fight or flight” situation. In most but not all instances, the actions produced by each system are opposite; one increases the heart rate and the other decreases it; one dilates the pupils of the eye and the other constricts them. The receptors being innervated for each function may be different. For example, both the PANS and the SANS stimulate muscles in the eye that change the size of the pupil. The SANS stimulates the radial smooth muscles (out from the pupil like sun rays), producing an increase in pupil size. When the pupils are dilated the effect is termed *mydriasis*. The PANS stimulates the circular smooth muscles (like a bull’s-eye), producing a decrease in pupil size. When pupils are constricted the effect is termed *miosis*.

Almost all body tissues are innervated by the ANS, with many but not all, organs receiving both parasympathetic and sympathetic innervation. The response of a specific tissue to stimuli at any one time will be equal to the sum of the excitatory and inhibitory influences of the two divisions of the ANS (if a tissue receives both innervations). Table 4-1 summarizes the effects of the ANS on major tissues and organ systems.

In addition to the dual innervation of tissues, there is another way in which the two divisions of the ANS can interact. Sensory fibers in one division can influence the motor fibers in the other. Thus, although in an isolated tissue preparation the stimulation of one of the divisions would produce a specific response, in the intact body a more complex and integrated response can be expected. The net effect would be a combination of the direct and indirect effects.
**Neurotransmitters**

Communication between nerves or between nerves and effector tissue takes place by the release of chemical neurotransmitters across the synaptic cleft.

Neurotransmitters are released in response to the nerve action potential (or pharmacologic agents in certain cases) to interact with a specific membrane component: the receptor. Receptors are usually found on the postsynaptic fiber and the effector organ but may be located on the presynaptic membrane as well (Table 4-2). The interaction between neurotransmitter and receptor is specific and is rapidly terminated by disposition of the neurotransmitter substance. There are several specific mechanisms by which the neurotransmitter produces an effect on the receptor.

Disposition occurs most often by either reuptake into the presynaptic nerve terminal or enzymatic breakdown of the neurotransmitter. Nerves in the ANS contain the necessary enzyme systems and other metabolic processes to synthesize, store, and release neurotransmitters. Thus drugs can modify ANS activity by altering any of the events associated with neurotransmitters: (1) synthesis, (2) storage, (3) release, (4) receptor interaction, and (5) disposition. The specificity of the neurotransmitters and receptors dictates the tissue response, which occurs as follows:

- Between the preganglionic and postganglionic nerves: Acetylcholine is the neurotransmitter in the synapse (ganglia) formed between the preganglionic and postganglionic nerves. Nerves that release acetylcholine are termed cholinergic. Because this synapse is also stimulated by nicotine, it is also termed nicotinic in response.
- Between postganglionic nerves and the effector tissues:
  - PANS: The neurotransmitter released from the postganglionic nerve terminal is acetylcholine; it is also termed cholinergic. Because the postsynaptic tissue responds to muscarine, it is identified as muscarinic. Thus the cholinergic synapses are distinguished from one another.
  - SANS: NE is the transmitter substance released by the postganglionic nerves and is designated as adrenergic.
  - Neuromuscular junction: Although not within the ANS, the neuromuscular junction (Figure 4-3) of skeletal muscle releases the neurotransmitter acetylcholine and is termed cholinergic. The neuromuscular junction is part of the somatic system and is also discussed in Chapter 11. Figures 4-4, 4-5, and 4-6 illustrate the PANS, SANS, and neuromuscular junction.

**Drug Groups**

The four drug groups in the ANS exert their effects primarily on the organs or tissues innervated by the ANS. (They are just doing the same thing that the body would normally do when it is working.) Each of the divisions of the nervous system, the PANS and the SANS, can be affected. The action of each of the divisions of the ANS can be increased or decreased.

These four functions divide the ANS drugs into four groups: P+, P−, S+, and S−. Stimulation of the PANS can be abbreviated P+, and blocking of the PANS can be abbreviated P−. Stimulation of the SANS can be abbreviated S+, and blocking of the SANS can be abbreviated S−. These abbreviations are not routinely used in the literature but are helpful with note taking, outlines, and discussions. The groups are named by several methods, but the basic concepts of naming include the following:

- A drug that acts at the location where acetylcholine is released as the neurotransmitter is termed cholinergic (from acetylcholine).
TABLE 4-1 EFFECTS OF THE AUTONOMIC NERVOUS SYSTEM (ANS) ON EFFECTOR ORGANS

<table>
<thead>
<tr>
<th>Organ</th>
<th>Aspect</th>
<th>PANS</th>
<th>Receptor</th>
<th>SANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Lens (ciliary muscle)</td>
<td>Contraction (near vision)</td>
<td>$\beta_2$</td>
<td>Relaxation (distant vision)</td>
</tr>
<tr>
<td></td>
<td>Iris</td>
<td>Contraction miosis</td>
<td>$\alpha_1$</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>Heart force (inotropic)</td>
<td>Decreases heart rate</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Increases force</td>
</tr>
<tr>
<td></td>
<td>Heart, SA node rate (chronotropic)</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Increases heart rate</td>
</tr>
<tr>
<td>Blood vessels, smooth muscles</td>
<td>Coronary</td>
<td>Dilation</td>
<td>$\alpha_1$, $\beta_1$, $\beta_2$</td>
<td>Constriction ((\alpha)), dilation ((\beta))</td>
</tr>
<tr>
<td></td>
<td>Skin/mucosa</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal viscera</td>
<td></td>
<td>$\alpha_1$, $\beta_1$, $\beta_2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salivary glands</td>
<td>Dilation</td>
<td>$\alpha_1$, $\beta_1$</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchial smooth muscle</td>
<td>Contraction</td>
<td>$\beta_2$</td>
<td>Relaxation increase/decrease</td>
</tr>
<tr>
<td></td>
<td>Secretions bronchial, nasopharyngeal</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract/</td>
<td>Motility/tone</td>
<td>Contracts, increases</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Relaxes</td>
</tr>
<tr>
<td>genitourinary tract</td>
<td></td>
<td></td>
<td>$\text{increase/decrease}$</td>
<td></td>
</tr>
<tr>
<td>Stomach, intestine, bladder</td>
<td>Sphincters</td>
<td>Relaxation</td>
<td>$\alpha_1$</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Secretions from gastrointestinal tract</td>
<td></td>
<td>$\alpha_2$</td>
<td>Inhibition</td>
</tr>
<tr>
<td></td>
<td>Secretion from salivary glands</td>
<td>Increase profuse and watery</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Viscous thick</td>
</tr>
<tr>
<td></td>
<td>Uterus</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Pancreas, acini</td>
<td>Secretion</td>
<td>$\alpha_1$</td>
<td>Decreases secretions</td>
</tr>
<tr>
<td></td>
<td>Pancreas, islet cells</td>
<td>Secretion epinephrine/norepinephrine</td>
<td>$\alpha_2$</td>
<td>Decreases secretions</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla</td>
<td></td>
<td>$\alpha_1$, $\beta_1$, $\beta_2$</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Sweat</td>
<td>Secretion, generalized</td>
<td>$\alpha_1$</td>
<td>Secretion, local</td>
</tr>
<tr>
<td></td>
<td>Pilomotor muscles</td>
<td></td>
<td>$\beta_2$</td>
<td>Contraction</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogen synthesis</td>
<td></td>
<td>$\alpha_1$</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\beta_2$</td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td>Other</td>
<td>Adipose tissue</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Lipolysis</td>
</tr>
<tr>
<td></td>
<td>Male sex organs</td>
<td>Erection</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Ejaculation</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td></td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$</td>
<td>Contraction</td>
</tr>
</tbody>
</table>

CVS, Cardiovascular system; PANS, parasympathetic autonomic nervous system; SA, sinoatrial; SANS, sympathetic autonomic nervous system.

TABLE 4-2 TYPES OF CHOLINERGIC RECEPTORS

<table>
<thead>
<tr>
<th>Receptor Site</th>
<th>Location</th>
<th>Neurotransmitter</th>
<th>Stimulating Agent</th>
<th>Blocking Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscarinic</td>
<td>B</td>
<td>Acetylcholine</td>
<td>Muscarine</td>
<td>Atropine</td>
</tr>
<tr>
<td>Nicotinic</td>
<td>C</td>
<td>Acetylcholine</td>
<td>Nicotine</td>
<td>Hexamethonium</td>
</tr>
<tr>
<td>Somatic-skeletal muscle</td>
<td>D</td>
<td>Acetylcholine</td>
<td>Nicotine</td>
<td>$d$-Tubocurarine (curare)</td>
</tr>
</tbody>
</table>

B, Muscarinic cholinergic; C, nicotinic cholinergic; D, cholinergic somatic.

- A drug that acts at the location where NE is the neurotransmitter released is termed *adrenergic* (taken from the early trade name of epinephrine, Adrenalin).
- A drug that acts at the location where the PANS acts has the prefix *parasympatho-*.  
- A drug that acts at the location where the SANS acts has the prefix *sympatho-*.  
- A drug that acts at the location where a division of the ANS acts and produces the same effect as the neurotransmitter has the suffix *-mimetic* (as in mime, acts like). It can also be referred to as an agonist (see Chapter 2).
- A drug that acts at the location where a division of the ANS acts and blocks the action of the neurotransmitter has the suffix *-lytic* or *-blocker*. It can also be referred to as an antagonist (see Chapter 2).

Using this nomenclature, the four groups of ANS drugs can be abbreviated as P+ (cholinergics, parasympathomimetics), P− (anticholinergics, parasympatholytics, or cholinergic-blockers),
Some of the postsynaptic tissues respond to acetylcholine because of an interaction between acetylcholine and these tissues. To be an effective mediator, acetylcholine must fit both physically and chemically at the receptor. It has been shown that atropine (A-troe-peen) can block the action of acetylcholine at the postganglionic endings in the PANS but not at the neuromuscular junction. In contrast, curare blocks the response of skeletal muscle to acetylcholine but does not block its effect on tissues such as the salivary gland. Hexamethonium blocks the action of acetylcholine at the ganglia. From these observations, one can infer that there are differences among receptors that have acetylcholine as a neurotransmitter—subtypes of acetylcholine-innervated receptors that are located in anatomically different synapses. Other factors, such as the amount of acetylcholine released, the size of the synaptic cleft, and the tissue penetration of a drug, may also account for differences in the response of the receptor to drugs at each acetylcholine-mediated junction.

**Cholinergic (Parasympathomimetic) Agents**

Depending on their mechanism of action (Table 4-3) the cholinergic (parasympathomimetic) agents are classified as direct acting (acts on receptor) or indirect acting (causes release of neurotransmitter). The direct-acting agents (Figure 4-8) include the choline derivatives and pilocarpine. The choline derivatives include both acetylcholine and other, more stable choline derivatives. These derivatives of acetylcholine possess activity similar to PANS stimulation but have a longer duration of action and are more selective.

The indirect-acting (see Figure 4-8) parasympathomimetic agents or cholinesterase inhibitors act by inhibiting the enzyme cholinesterase.

When the enzyme that normally destroys acetylcholine is inhibited, the concentration of acetylcholine builds up (it is not being destroyed), resulting in PANS stimulation.
PHARMACOLOGIC EFFECTS

Cardiovascular Effects. The cardiovascular effects associated with the cholinergic agents are the result of both direct and indirect actions. The direct effect on the heart produces a negative chronotropic and negative inotropic action. A decrease in cardiac output is associated with these agents.

The cholinergic agents’ effects on the smooth muscles around the blood vessels result in relaxation and vasodilation, producing a decrease in total peripheral resistance. The indirect effect of these agents is an increase in heart rate and cardiac output. Because the direct and indirect effects of these agents on the heart rate and cardiac output are opposite, the resulting effect will depend on the concentration of the drug present. Generally, there is bradycardia and a decrease in blood pressure and cardiac output.

Gastrointestinal Effects. The cholinergic agents excite the smooth muscle of the gastrointestinal tract, producing an increase in activity, motility, and secretion.
**Effects on the Eye.** The cholinergic agents produce miosis and cause cycloplegia. Cycloplegia is a paralysis of the ciliary muscles of the eye that results in the loss of visual accommodation. Because intraocular pressure is also decreased, these agents are useful in the treatment of glaucoma.

**ADVERSE REACTIONS**

The adverse reactions that are associated with the administration of the cholinergic agents are essentially extensions of their pharmacologic effects. When large doses of these agents are ingested, the resultant toxic effects are described by the acronym SLUD: salivation, lacrimation, urination, and defecation. With even larger doses, neuromuscular paralysis can occur as a result of the effect on the neuromuscular junction. CNS effects, such as confusion, can be seen if toxic doses are administered.

The treatment of an overdose of cholinesterase inhibitors, such as the insecticides or organophosphates (parathion), includes a combination of pralidoxime (pra-li-DOX-eem) (2-PAM, Protopam) and atropine. Pralidoxime regenerates the irreversibly bound acetylcholine receptor sites that are bound by the inhibitors (knocks them off like a prizefighter), and atropine blocks (competitively) the muscarinic effects of the excess acetylcholine present.

**CONTRAINDICATIONS**

The relative contraindications to or cautions with the use of the cholinergic agents stem from these agents’ pharmacologic effects and adverse reactions. They include the following:

- **Bronchial asthma:** Cholinergic agents may cause bronchospasms or precipitate an asthmatic attack.
- **Hyperthyroidism:** Hyperthyroidism may cause an increased risk of atrial fibrillation.
- **Gastrointestinal tract or urinary tract obstruction:** If either the gastrointestinal tract or the urinary tract is obstructed and a cholinergic agent is given, an increase in secretions and motility could cause pressure and the system could “back up.”
- **Severe cardiac disease:** The reflex tachycardia that can result from administering cholinergic agents may exacerbate a severe cardiac condition.
- **Myasthenia gravis treated with neostigmine:** Patients with myasthenia gravis should not be given irreversible cholinesterase inhibitors because neostigmine occupies the enzyme and the irreversible agent would not function.
- **Peptic ulcer:** Cholinergic agents stimulate gastric acid secretion and increase gastric motility. This action could exacerbate an ulcer.

**USES**

The direct-acting agents are used primarily in the treatment of glaucoma, a condition in which the intraocular pressure is elevated. Occasionally, they are used to treat myasthenia gravis, a disease resulting in muscle weakness from an autoimmune reaction that reduces the effect of acetylcholine on the voluntary muscles. The **urinary retention** that occurs after surgery is also treated with the choline esters (see Table 4-3).

Pilocarpine (pye-loe-KAR-peen) (Salagen), a naturally occurring cholinergic agent, is used in the treatment of xerostomia, but its success may be limited because of the myriad of potential side effects. Common side effects from pilocarpine include perspiration (sweating), nausea, rhinitis, chills, and **flushing**. Pilocarpine is available in 5-mg tablets. The usual dose of pilocarpine is 5 mg three times a day (tid). This can be obtained by giving one 5-mg tablet tid [three times a day]. Pilocarpine is also available as ophthalmic solution in strengths ranging from 0.5% to 10%. It is used topically in the eye to treat glaucoma. Several strengths (e.g., 2%) are available as generic preparations.

The indirect-acting cholinergic agents, the cholinesterase inhibitors, are divided into groups based on the degree of reversibility with which they are bound to the enzyme. Edrophonium is rapidly reversible, whereas physostigmine and neostigmine are slowly reversible. These agents are used to treat glaucoma and myasthenia gravis.

Physostigmine (fi-zoe-STIG-meen) (Antilirium) has been used to treat reactions caused by several different kinds of drugs. Acute toxicity from the anticholinergic agents (e.g., atropine) and other agents that have anticholinergic action (e.g., the phenothiazones, tricyclic antidepressants, and antihistamines) has been treated with physostigmine.

The cholinesterase inhibitors developed for use as insecticides and chemical warfare agents are essentially irreversible and are called the **irreversible cholinesterase inhibitors.** Members of this
group include parathion, malathion, and sarin (used on a subway in Japan to poison riders).

**Anticholinergic (Parasympatholytic) Agents**

The anticholinergic agents prevent the action of acetylcholine at the postganglionic parasympathetic endings. The release of acetylcholine is not prevented, but the receptor site is competitively blocked by the anticholinergics (Figure 4-9). Thus the anticholinergic drugs block the action of acetylcholine on smooth muscles (e.g., intestines), glandular tissue (e.g., salivary glands), and the heart. These agents are called antimuscarinic agents because they block the muscarinic receptors and not the nicotinic receptors.

♦ **PHARMACOLOGIC EFFECTS**

**Central Nervous System Effects.** Depending on the dose administered, the anticholinergics can produce CNS stimulation or depression. For example, usual therapeutic doses of scopolamine more often cause sedation, whereas atropine in high doses can cause stimulation. Atropine and scopolamine are tertiary agents, and propantheline (proe-PAN-the-leen) (Pro-Banthine) and glycopyrrolate (Robinul) are quaternary agents (Figure 4-10). Because of their water solubility, quaternary agents do not penetrate the CNS well. The tertiary agents are lipid soluble, and they can easily penetrate the brain. The quaternary agents have fewer CNS adverse reactions because they are less likely to enter the brain.

**Effects on Exocrine Glands.** The anticholinergics affect the exocrine glands by reducing the flow and the volume of their secretions. These glands are located in the respiratory, gastrointestinal, and genitourinary tracts. This effect is used therapeutically in dentistry to decrease salivation and create a dry field for certain dental procedures such as obtaining a difficult impression.

**Effects on Smooth Muscle.** Anticholinergics relax the smooth muscle in the respiratory and gastrointestinal tracts. Ipratropium is an anticholinergic inhaler used to treat asthma. The effect of anticholinergics on gastrointestinal motility has given rise to the name spasmolytic agents. If these drugs are used repeatedly, constipation can result. By delaying gastric emptying and by decreasing esophageal and gastric motility, the anticholinergics may exacerbate the condition. The smooth muscle in the respiratory tract is relaxed by the anticholinergic agents, causing bronchial dilation. This effect is used to treat asthma.

**Effects on the Eye.** The parasympatholytics have two effects on the eye, mydriasis and cycloplegia. Cycloplegia refers to paralysis of the ciliary muscles of the eye that results in the loss of visual accommodation. The effects of cycloplegia and mydriasis are useful to prepare the eye for ophthalmologic examinations. For eye examinations, mydriasis dilates the pupil so that the retina can be examined, and cycloplegia allows for proper measurements to make glasses. These effects occur when the drug is given topically or systemically.

**Cardiovascular Effects.** With large therapeutic doses, the anticholinergic agents can produce vagal blockade, resulting in tachycardia. This effect has been used therapeutically to prevent cardiac slowing during general anesthesia. With small doses, bradycardia predominates. This variable response in the heart rate occurs because heart rate is a function of both

![FIGURE 4-9](http://www.us.elsevierhealth.com/product.jsp?isbn=9780323065580)

**FIGURE 4-9**
Anticholinergic response. The anticholinergic drug occupies the receptor sites, blocking acetylcholine. _ACh_, Acetylcholine; _D_, anticholinergic drug. (From Kee JL, Hayes ER, McCuiston LE: Pharmacology: a nursing process approach, ed 6, St Louis, 2009, Saunders.)

![FIGURE 4-10](http://www.us.elsevierhealth.com/product.jsp?isbn=9780323065580)

**FIGURE 4-10**
Anticholinergics, brain penetration. Quaternary amines are charged and hydrophilic (water soluble), so they cannot easily penetrate the brain. Tertiary amines are uncharged and lipophilic (lipid soluble), so they easily penetrate the brain. CNS, Central nervous system.

http://www.us.elsevierhealth.com/product.jsp?isbn=9780323065580
direct (increased heart rate) and indirect (decreased heart rate) effects.

♦ ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivation</td>
<td>Atropine</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Scopolamine</td>
</tr>
<tr>
<td>Urination</td>
<td>Dicyclomine</td>
</tr>
<tr>
<td>Defecation</td>
<td>Propantheline</td>
</tr>
</tbody>
</table>

The adverse reactions associated with the anticholinergics are essentially extensions of their pharmacologic effects. These can include xerostomia (see Appendix E for a discussion of drugs that cause xerostomia and a discussion of artificial salivas), blurred vision, photophobia, tachycardia, fever, and urinary and gastrointestinal stasis. Hyperpyrexia (elevated temperature) and hot, dry, flushed skin caused by a lack of sweating are also seen. Hyperpyrexia is treated symptomatically.

Anticholinergic toxicity can cause signs of CNS excitation including delirium, hallucinations, convulsions, and respiratory depression.

♦ CONTRAINDICATIONS

Specific contraindications or cautions to the use of the anticholinergic agents include the following.

Glaucoma. Anticholinergics are the only ANS drug group that can cause an acute rise in intraocular pressure in patients with narrow-angle glaucoma (angle closure). Glaucoma is divided into narrow-angle (5% of glaucoma cases) and open-angle glaucoma (95% of glaucoma cases); cases of narrow-angle glaucoma are uncommon. Anticholinergic drugs can precipitate an acute attack in unrecognized cases of this rare condition. If narrow-angle glaucoma is diagnosed, emergency ophthalmic surgery must be performed to relieve the eye pressure. In contrast, the patient with open-angle glaucoma who is currently receiving treatment with eyedrops (many types) can be given a few doses of anticholinergic agents with impunity.

Prostatic Hypertrophy. Because the anticholinergic agents can exacerbate urinary retention, older men with prostatic hypertrophy (many men older than 50 years) who already have difficulty urinating should not be given these drugs. Acute urinary retention that may require catheterization can occur.

Intestinal or Urinary Obstruction or Retention. Constipation or acute urinary retention can be precipitated by the use of these agents in susceptible patients. Constipation can be exacerbated, especially in patients with chronic constipation. (One should not give them an opioid [narcotic] for pain control.)

Cardiovascular Disease. Because anticholinergic agents have the ability to block the vagus nerve, resulting in tachycardia, patients with cardiovascular disease should be given these agents cautiously.

♦ USES

Table 4-4 provides examples of anticholinergic (parasympatholytic) agents, as well as their usual oral doses and routes of administration.

Preoperative Medication. The anticholinergic agents are used preoperatively for two reasons. First, they inhibit the secretions of saliva and bronchial mucus that can be stimulated by general anesthesia. Second, they have the ability to block the vagal slowing of the heart that results from general anesthesia.

Treatment of Gastrointestinal Disorders. Many types of gastrointestinal disorders associated with increased motility or acid secretion have been treated with anticholinergic agents. For example, patients with gastric ulcers are sometimes treated with the anticholinergic agents, although there is little proof of their effectiveness. Both nonspecific diarrhea and hypermotility of the colon have also been treated with these agents. In the doses used, it is difficult to prove that the anticholinergic agents are effective for these purposes.

<table>
<thead>
<tr>
<th>Category</th>
<th>Agent</th>
<th>PO Dose (mg)</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary</td>
<td>Natural alkaloids</td>
<td>Atropine</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Scopolamine (hyoscine)</td>
<td>(Maldemar)</td>
<td>(Transderm-Scop)</td>
</tr>
<tr>
<td></td>
<td>Synthetic esters</td>
<td>Dicyclomine (Bentyl)</td>
<td>10, 20; 10 mg/5 ml (syrup)</td>
</tr>
<tr>
<td>Quaternary</td>
<td>Esters</td>
<td>Ipratropium (Atrovent)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Propantheline</td>
<td>(Pro-Banthine)</td>
<td>7.5, 15</td>
</tr>
</tbody>
</table>

ophth, Ophthalmic; P, parenteral (injection); PO, oral.

♦ DRUG INTERACTIONS

The most important drug interaction associated with the anticholinergic agents is an additive anticholinergic effect. Other agents that have anticholinergic effects, such as the phenothiazines, antihistamines, and tricyclic antidepressants, can be additive with the parasympatholytics. Mixing more than one drug
group possessing anticholinergic effects can lead to symptoms of anticholinergic toxicity, including urinary retention, blurred vision, acute glaucoma, and even paralytic ileus. Dental office personnel must pay careful attention to the medications the patient is taking to rule out excessive anticholinergic effects.

**Nicotinic Agonists and Antagonists**

Nicotine, which is present in cigarettes, is so toxic that one drop on the skin is rapidly fatal. In low doses, it produces stimulation because of depolarization. At high doses, it produces paralysis of the ganglia, resulting in respiratory paralysis. Peripherally, it increases blood pressure and heart rate and increases gastrointestinal motility and secretions. Nicotine constricts the blood vessels and reduces blood flow to the extremities. Nicotine is addicting, and withdrawal can occur. It is used as an insecticide.

**SYMPATHETIC AUTONOMIC NERVOUS SYSTEM**

The major neurotransmitters in the SANS include NE and epinephrine. They are synthesized in the neural tissues and stored in synaptic vesicles. NE is the major neurotransmitter released at the terminal nerve endings of the SANS. With stimulation, epinephrine is released from the adrenal medulla and distributed throughout the body via the blood. Dopamine receptors are important in the brain and splanchnic and renal vasculature. There are currently several dopamine receptor subtypes (D₁ to D₅). They are divided into two groups: one group is D₁ and D₂, and the other group is D₃, D₄, and D₅. Each of these receptor subtypes may be further divided into A and B, for example, D₁A and D₁B.

The term catecholamine is made up of two terms that relate to their structure. Catechol refers to 1,2-dihydroxybenzene. Amine refers to the chemical structure NH₂. NE, epinephrine, and dopamine are endogenous sympathetic neurotransmitters that are catecholamines. Isoproterenol (Isuprel) is an exogenous catecholamine. This term is used to refer to the epinephrine contained in a lidocaine with epinephrine solution.

The adrenergic drugs can be classified by their mechanism of action (Figure 4-11) as follows:

- **Direct acting**: Epinephrine, NE, and isoproterenol produce their effects directly on the receptor site by stimulating the receptor.
- **Indirect acting**: These agents, such as amphetamine, release endogenous NE, which then produces a response. Depletion of the endogenous NE with reserpine diminishes the response to these agents.
- **Mixed acting**: These agents, such as ephedrine, can either stimulate the receptor directly or release endogenous NE to cause a response.

NE’s action is terminated primarily by reuptake into the presynaptic nerve terminal by an amine-specific pump. The NE taken up in this manner is stored for reuse. In addition, two enzyme systems, monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), are involved in the metabolism of a portion of both epinephrine and NE.

**Sym pathetic Autonomic Nervous System Receptors**

As early as 1948, the existence of at least two types of adrenergic receptors, termed alpha (α) and beta (β), was recognized. The activation of α-receptors causes a different response than the activation of β-receptors. More subreceptor types are now known.

- **α-RECEPTORS**

  The stimulation of the α-receptors results in smooth-muscle excitation or contraction, which then causes vasoconstriction. Because α-receptors are located in the skin and skeletal muscle, vasoconstriction of the skin and skeletal muscle follows stimulation. Drugs that block the action of neurotransmitters on the α-receptors are referred to as α-adrenergic blocking agents.

- **β-RECEPTORS**

  There are at least two types of β-receptors, β₁ and β₂. β₁-Receptor excitation causes stimulation of the heart muscle, resulting in a positive chronotropic effect (increased rate) and a positive inotropic effect (increased strength). The β₁-receptor controls the heart (one can remember the receptor that controls the heart by remembering that humans have only one heart) (Figure 4-12). Other actions thought to be associated primarily with β₁-receptor stimulation include metabolic effects on glycogen formation.

  The stimulation of the β₂-receptors results in smooth muscle relaxation. Because the blood vessels of the skeletal muscle are innervated by β₂-receptors, stimulation causes vasodilation. Relaxation of the smooth muscles of the bronchioles, also containing β₂-receptors, results in bronchodilation. β₂-Receptor stimulation produces bronchodilation in the lungs (one can remember the receptor that controls the lungs by remembering that humans have two lungs) (see Figure 4-12). Drugs with this effect have been used in the treatment of asthma. The type of receptor found in a given tissue determines the effect adrenergic agents will produce on that tissue (see Table 4-1).

  Agents that block β-receptor effects are called β-adrenergic blocking agents. Some (e.g., propranolol) are nonspecific, blocking both β₁-receptors and β₂-receptors, whereas others are more selective, blocking primarily β₂-receptors.

**Adrenergic (Sympathomimetic) Agents**

Adrenergic agents play an important part in the treatment of anaphylaxis and asthma and are added to local anesthetic solutions (vasoconstrictors) to prolong their action. Table 4-5 lists some adrenergic agents.
**PHARMACOLOGIC EFFECTS**

When discussing the pharmacologic effects associated with the adrenergic drugs, it is important to note the proportion of α-receptor and β-receptor activity each possesses. For example, epinephrine has both α-receptor and β-receptor activity, NE and phenylephrine stimulate primarily α-receptors, and isoproterenol acts mainly on β-receptors. Although the effects of these agents depend on their ability to stimulate various receptors, the general actions of the adrenergic agents are discussed with specific reference to α-receptor or β-receptor effects as applicable.

**Central Nervous System Effects.** The sympathomimetic agents, such as amphetamine, produce CNS excitation, or alertness. With higher doses, anxiety, apprehension, restlessness, and even tremors can occur.

**Cardiovascular Effects**

*Heart.* The general effect of the sympathomimetics, such as epinephrine, on the heart is to increase its force and strength of contraction. The final effect on blood pressure is a combination of the direct and the indirect effects. NE, primarily an α-agonist, produces vasoconstriction that increases peripheral resistance, resulting in an increase in blood pressure. With an increase in blood pressure, the vagal reflex decreases the heart rate. Epinephrine, an α- and β-agonist, constricts the α-receptors and dilates the β-receptors. This produces a widening of the pulse pressure (systolic blood pressure–diastolic blood pressure) with an increase in systolic and a decrease in diastolic blood pressures. Isoproterenol, primarily a β-agonist, produces vasodilation (lowers peripheral resistance) that triggers an increase in heart rate (vagal reflex).

*Vessels.* The vascular responses observed with the sympathomimetics depend on the location of the vessels and whether they are innervated by α-receptors, β-receptors, or both. Agents with α-receptor effects will produce vasoconstriction primarily in the skin and mucosa (innervated with α-receptor fibers), whereas agents with β-receptor effects will produce vasodilatation of the skeletal muscle (innervated with β-receptor fibers). The resultant effect on the total peripheral resistance is an increase with an α-receptor agent and a reduction with a β-receptor agent.

**(Blood Pressure.** The sympathomimetic effect on the blood pressure is generally an increase. With epinephrine,
which has both α-receptor–stimulating and β-receptor–stimulating properties, there is a rise in systolic pressure and a decrease in diastolic pressure. With NE, there is a rise in both systolic and diastolic pressures. With isoproterenol, there is little change in systolic pressure, but a decrease in diastolic pressure occurs.

**Effects on the Eye.** The sympathomimetic agents have at least two effects on the eye: a decrease in intraocular pressure, which makes them useful in the treatment of glaucoma, and mydriasis.

**Effects on the Respiratory System.** These agents cause a relaxation of the bronchiole smooth muscle because of their β-adrenergic effect. This has made them useful in the treatment of asthma and anaphylaxis.

**Metabolic Effects.** The hyperglycemia resulting from β-receptor stimulation can be explained on the basis of increased glycogenolysis and decreased insulin release. Fatty acid mobilization, lipolysis, and gluconeogenesis are stimulated, and the basal metabolic rate is increased.

**Effects on the Salivary Glands.** The mucus-secreting cells of the submaxillary glands and sublingual glands are stimulated by the sympathomimetic agents to release a small amount of thick, viscous saliva. Because the parotid gland has no sympathetic innervation (only parasympathetic) and the sympathomimetics produce vasoconstriction, the flow of saliva is often reduced, resulting in xerostomia.

♦ **ADVERSE REACTIONS**

The adverse reactions associated with the adrenergic drugs are extensions of their pharmacologic effects. Anxiety and tremors may occur, and the patient may have palpitations. Serious arrhythmias can result. Agents with an α-adrenergic action can also cause a dramatic rise in blood pressure. The sympathomimetic agents should be used with caution in patients with angina, hypertension, or hyperthyroidism.

♦ **CONTRAINDICATIONS**

These drugs should not be used in persons with uncontrolled hypertension, angina, or hyperthyroidism. These drugs stimulate α- and β-receptors in the heart and as such would further increase blood pressure and heart rate in persons with already increased blood pressure and heart rates. This could lead to arrhythmias or a myocardial infarction.

♦ **USES**

**Vasoconstriction**

**Prolonged Action.** The sympathomimetic agents are used in dentistry primarily because of their vasoconstrictive action on the blood vessels. Agents with an α-effect (vasoconstriction) are often added to local anesthetic solutions. These vasoconstrictors prolong the action of the local anesthetics and reduce their potential for systemic toxicity.

**Hemostasis.** The adrenergic agents have been used in dentistry to produce hemostasis. Epinephrine can be applied topically or infiltrated locally around the bleeding area. Epinephrine-containing retraction cords, used to stop bleeding and to retract the gingiva before taking an impression, can produce problems such as systemic toxicity. Epinephrine is quickly absorbed after topical application if the tissue is injured. The total amount of epinephrine given by all routes must be noted to prevent an overdose.

**Decongestion.** Sympathomimetic agents are often incorporated into nose drops or sprays (see Table 4-5) to treat nasal congestion. These agents provide symptomatic relief by constricting the vessels and reducing the swelling of the mucous membranes of the nose. Within a short time, the congestion can return; this is a condition called rebound congestion. With repeated local use, systemic absorption can cause problems even greater than rebound congestion. Systemic decongestants or topical intranasal steroids are now preferred.

**Cardiac Effects**

**Treatment of Shock.** The value of the adrenergic agents in the treatment of shock is controversial. These drugs will elevate a lowered blood pressure, but correcting the cause of shock is more important. Some agents with both α-effects and β-effects (e.g., epinephrine) are used.

**Treatment of Cardiac Arrest.** The sympathomimetic agents, especially epinephrine, are used to treat cardiac arrest.

**Bronchodilation.** The use of the sympathomimetic agents in the treatment of respiratory disease stems from their action as bronchodilators. Patients with asthma or emphysema are often treated with adrenergic agents to provide bronchodilation. In the treatment of anaphylaxis, when bronchoconstriction is predominant, epinephrine is the drug of choice.

**Central Nervous System Stimulation.** Amphetamine-like agents have been used and abused as “diet pills.” They are indicated for the treatment of attention deficit disorder (ADD) and narcolepsy.

Adrenergic agonists with some specificity for CNS stimulation are used for both legitimate and illegitimate purposes.

Methylphenidate (meth-ill-FEN-i-date) (Ritalin) and dextroamphetamine (dex-tro-am-FET-a-meen) (Dexedrine) are adrenergic agents used to treat ADD in both children and adults. These agents, given to hyperactive children and adults, reduce impulsivity and increase attention span. Some children with ADD will exhibit excessive motor activity—turn around in the chair, stand up from the chair, grab dental instruments, squirt water, and ask about everything. Side effects exhibited with this use include insomnia and anorexia. ADD has also been known as attention deficit hyperactivity disorder (ADHD) and minimal brain dysfunction (MBD), and children with the disorder have been referred to as hyperkinetic children.

Dietethylpropion (dye-eth-il-PROE-pee-on) (Tenuate) is an adrenergic drug that is used as a “diet pill.” Uses for weight loss, to produce euphoria, and for “staying awake” are not legitimate medical uses for adrenergic agents. Truck drivers have used these agents to keep themselves awake for long hours. Hallucinations and psychosis make these truck drivers dangerous.

**Narcolepsy**, a disease in which spontaneous deep sleep can occur at any time, is treated with the sympathomimetic amines. Tolerance to the effect does not seem to occur.

♦ **SPECIFIC ADRENERGIC AGENTS**

**Epinephrine.** The drug of choice for acute asthmatic attacks and anaphylaxis, epinephrine (Epi) (ep-i-NEF-rin) (Adrenalin), may be administered by both the intravenous and subcutaneous routes. It is also used in patients with cardiac arrest. It is added to local anesthetic solutions to delay absorption and reduce systemic toxicity (see Chapter 9). Epinephrine should be stored in amber-colored containers and placed out of the reach of sunlight because light causes deterioration. As it deteriorates, epinephrine first turns pink, then brown, and finally
precipitates. Solutions of epinephrine with any discoloration or precipitate should be discarded immediately. (One should check the expiration date, too.)

**Phenylephrine.** Phenylephrine (fen-ill-EF-rin) (Neo-Synephrine) causes primarily $\alpha$-receptor stimulation, which produces vasoconstriction in the cutaneous vessels. This leads to an increase in total peripheral resistance and systolic and diastolic pressures. A reflex vagal bradycardia also results. Phenylephrine is used as a mydriatic and in nose sprays (Neo-Synephrine) or drops to relieve congestion.

**Levonordefrin.** Levonordefrin (lee-voe-nor-DEF-rin) (Neo-Cobefrin), a derivative of NE, is a vasoconstrictor often added to local anesthetic solutions. Although claims made for this drug include less CNS excitation and cardiac stimulation, the dose required to produce vasoconstriction equal to that caused by epinephrine is higher. Therefore it is difficult to distinguish levonordefrin’s effects from those of other vasoconstrictors. Its effects resemble those of $\alpha$-receptor stimulation.

**Ephedrine and Pseudoephedrine.** In contrast to the catecholamines, ephedrine and pseudoephedrine (soo-doe-e-FED-rin) (Sudafed) are effective when taken orally and have a longer duration of action. They have both $\alpha$- and $\beta$-receptor activity. Their mechanism of action is mixed, that is, they have both direct and indirect action. Ephedrine is often used in combination with other agents for patients with asthma as nonprescription remedies. Pseudoephedrine is also present in OTC products designed for the treatment of the common cold or allergies such as pseudoephedrine (Sudafed). The newest use of these agents is to “cook” them to produce methamphetamine, which is used illicitly. Because of this, their availability has been restricted. Ephedrine, in any form (herbal or chemical), is no longer available in dietary supplements. Its use, as such, is illegal in the United States. Pseudoephedrine is now kept “behind the counter” with a pharmacist. Those wishing to purchase pseudoephedrine must be older than 18 and need to go to the pharmacist to purchase it. In most states, the patient must sign a log. There is also a limit as to how much a person can purchase each month.

**Dopamine.** Dopamine (DOE-pa-meen) (Intropin) is a neurotransmitter in parts of the CNS. It is both an $\alpha$-agonist and a $\beta$-agonist and is used primarily in the treatment of shock. It is a precursor of NE and epinephrine synthesis, as shown in Figure 4-13. Dopamine first acts on the $\beta$-receptors of the heart, producing a positive chronotropic and inotropic effect. In higher doses, it stimulates the $\alpha$-receptors, producing vasoconstriction. However, it exerts an unusual vasodilating effect in certain vessels and produces an increase in blood flow to the renal, splanchic, cerebral, and coronary vessels. Ventricular arrhythmias and hypotension can occur.

**Dipivefrin.** Dipivefrin (dye-PIV-e-frin) (Propine) and epinephrine are sympathomimetic ophthalmics that are used to treat glaucoma. They decrease the production of aqueous humor ($\beta$-receptor effect), increase its outflow ($\beta$-effect), and produce mydriasis (primarily $\alpha$-effect). Dipivefrin, a prodrug, is metabolized in vivo to epinephrine. It may produce fewer side effects than epinephrine because it penetrates into the eye better and is used to treat chronic open-angle glaucoma.

**Adrenergic Blocking Agents**

Adrenergic blocking agents can block all the adrenergic receptors ($\alpha$- and $\beta$-blockers), just the $\alpha$-receptors ($\alpha$-blockers), just the $\beta$-receptors ($\beta$-blockers), or just $\alpha_1$-receptors ($\alpha_1$-blockers), $\alpha_2$-receptors ($\alpha_2$-blockers), $\beta_1$-receptors ($\beta_1$-blockers), or $\beta_2$-receptors ($\beta_2$-blockers) (Table 4-6).

![FIGURE 4-13](http://www.us.elsevierhealth.com/product.jsp?isbn=9780323065580)

Synthesis of epinephrine from tyrosine, including the intermediate steps involving dopamine. DOPA, 3, 4 dihydrophenylalanine; EPI, epinephrine; NE, norepinephrine.

<table>
<thead>
<tr>
<th>Table 4-6 Examples of Adrenergic Receptor Antagonists (Sympatholytics, Adrenergic Blockers)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor</strong></td>
</tr>
<tr>
<td>$\alpha$-Adrenergic Receptor Antagonists</td>
</tr>
<tr>
<td>$\alpha$</td>
</tr>
<tr>
<td>$\alpha_1 &gt; \alpha_2$</td>
</tr>
<tr>
<td>$\alpha_2 &gt;&gt; \alpha_2$</td>
</tr>
<tr>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>$\alpha_1$ Partial agonist and antagonist</td>
</tr>
<tr>
<td>$\beta$-Adrenergic Receptor Antagonists (L = low, I = intermediate, H = high ISA)</td>
</tr>
<tr>
<td>Nonselective (nonselective) $\beta$</td>
</tr>
<tr>
<td>Specific (selective) $\beta_1 &gt; \beta_2$</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
</tr>
<tr>
<td>$\alpha$- and $\beta$-Adrenergic Antagonists</td>
</tr>
<tr>
<td>$\beta$</td>
</tr>
</tbody>
</table>

ISA, Intrinsic sympathetic activity.

$\alpha$-adrenergic blocking agents competitively inhibit the vasoconstricting effects ($\alpha$-receptor effects) of the adrenergic agents. This reduces the sympathetic tone in the blood vessels, producing a decrease in the total peripheral resistance. The resulting decrease in blood pressure stimulates the vagus, thereby producing a reflex tachycardia. Patients who are pre-treated with $\alpha$-blocking agents and given epinephrine exhibit a predominance of $\beta$-effects (vasodilation), which lowers blood pressure. This effect is termed epinephrine reversal because the blood pressure goes down instead of going up. The $\alpha$-adrenergic blockers also block the mydriasis that these agents normally cause.
The agents phenoxybenzamine (fen-ox-ee-BEN-za-meen) (Dibenzyline) and phentolamine (fen-TOLE-a-meen) (Regitine) are α-blockers. They are used in the treatment of peripheral vascular disease in which vascular spasm is a common feature (e.g., Raynaud’s syndrome) and in the diagnosis and treatment of pheochromocytoma, a catecholamine-secreting tumor of the adrenal medulla.

Other examples of α1-adrenergic blocking agents are tolazoline (toe-LAZ-ah-zen) (Priscoline), prazosin (PRA-zoe-sin) (Minipress), terazosin (ter-AY-zoe-sin) (Hytrin), and doxazosin (dox-AY-zoe-sin) (Cardura), which are competitive blockers of the α-receptor. They are effective in the treatment of hypertension and are discussed in Chapter 15. These agents are also indicated in the management of Raynaud’s vasospasm and in the treatment of benign prostatic hypertrophy (to increase ease of urination).

♦ β-ADRENERGIC BLOCKING AGENTS

The β-blocking drugs competitively block the β-receptors in the adrenergic nervous system. Their generic names end in olol, so they can be easily recognized. Because β-receptor stimulation produces vasodilation, bronchodilation, and tachycardia, β-blockers would block these effects, producing bradycardia and in asthmatics, possible bronchoconstriction. Their exact effect is determined by the tone in the sympathetic nervous system. The β-blockers may be either nonselective (nonspecific), such as propranolol (proe-PRAN-oh-lol) (Inderal), or specific (selective) such as atenolol (a-TEN-oh-lol) (Tenormin). The specific β-blockers have more activity on the heart and blood vessels (β-receptors) than on the lungs (β-receptors). This specificity, or selectivity, produces fewer side effects. The selective β-blockers also have a lower chance of causing drug interactions.

Propranolol (Inderal) is a β-blocker that depresses the heart (negative chronotropic and inotropic effect), produces bronchoconstriction, and can cause hypoglycemia. It is used in the treatment of arrhythmias (for its quinidine-like effect), angina, hypertension, and migraine headache prophylaxis. Diseases in which tachycardia occurs, such as hyperthyroidism and pheochromocytoma, can be symptomatically treated with propranolol. The β-blockers are discussed in Chapter 15.

♦ α- AND β-BLOCKING AGENTS

Labetalol (la-BET-a-lol) (Normodyne, Trandate) has both α- and β-blocking action. Because the β-blockers are designated using the suffix -olol, this α- and β-blocker uses the suffix -olol. It is a selective α-blocker and nonselective β-blocker. It is indicated for the treatment of hypertension and produces a fall in blood pressure without reflex tachycardia.

Neuromuscular Blocking Drugs

The neuromuscular blocking drugs are agents that affect transmission between the motor nerve endings and the nicotinic receptors on the skeletal muscle. These blocking agents act either as antagonists (nondepolarizing) or as agonists (depolarizing).

♦ NONDEPOLARIZING (COMPETITIVE) BLOCKERS

Indigenous people living along the Amazon have used poison arrows when hunting animals. The poison is the neuromuscular blocking drug curare, or α-tubocurarine. This nondepolarizing blocker combines with the nicotinic receptor and blocks the action of acetylcholine. The depolarization of the membrane is inhibited and muscle contraction is blocked. These competitive blockers can be overcome by the administration of cholinesterase inhibitors such as neostigmine. Current examples include vecuronium and pancuronium.

Paralysis of the small facial muscles is followed by paralysis of the fingers, limbs, extremities, and trunk. The function of the muscles involved in respiration is lost, beginning with the intercostal muscles. The last function lost is the most primitive diaphragmatic breathing. Nature has planned that loss of function is in the order of least important to most important (the diaphragm). The duration of action of these drugs range between 20 minutes and 2 hours, depending on the dose.

♦ DEPOLARIZING AGENTS

Depolarizing agents, such as succinylcholine (suk-sin-ill-KOE-leen), attach to the nicotinic receptor and like acetylcholine, result in depolarization. The constant stimulation of the receptor causes the sodium channel to open, producing depolarization (phase I). Transient fasciculations of the muscles result. With time, the receptor cannot transmit any further impulses and repolarization occurs as the sodium channel closes (phase II). A flaccid paralysis is produced by resistance to depolarization.

Succinylcholine produces muscle fasciculations followed by paralysis. The paralysis lasts only a few minutes because succinylcholine is broken down by plasma cholinesterase.

Succinylcholine can produce cardiac arrhythmias, hyperkalemia, and increased intraocular pressure. When it is used in general anesthesia in conjunction with halothane, succinylcholine precipitates malignant hyperthermia in susceptible patients (heredity). The drug of choice for malignant hyperthermia is dantrolene (Dantrium). Sometimes a small dose of curare is administered before the administration of succinylcholine to block the fasciculations of the succinylcholine. This reduces postoperative muscle pain.

DENTAL HYGIENE CONSIDERATIONS

Cholinergic Drugs

• Dental hygienists need to encourage patients to use good oral hygiene to help with the effects of increased salivation from cholinergic drugs.

• The dental hygienist should raise a patient into the sitting position slowly and have the patient rise slowly from the dental chair to help minimize the hypotensive effects from cholinergic drugs.

Anticholinergic Drugs

Xerostomia

• Xerostomia can be minimized with meticulous oral hygiene, including brushing and flossing.

• Patients should also drink plenty of water and keep a glass of water by their bedside at night.

• Patients should avoid prescription and nonprescription mouth rinses that contain alcohol because alcohol can exacerbate dry mouth.

• Caffeinated beverages can also exacerbate dry mouth.

• Fruit juices and sodas contain sugar, which can put the patient at increased risk for caries.

• Have the patient chew tart, sugarless gum or suck on tart, sugarless candy to help minimize dry mouth.
**DENTAL HYGIENE CONSIDERATIONS—cont’d**

**Tachycardia**
- Always check the patient’s pulse and blood pressure, especially before a procedure that may require epinephrine.

**Sedation**
- Caution should be used if another sedating drug, such as an opioid analgesic, is necessary.
- The patient should have someone drive him or her to and from the appointment.
- The patient should avoid any activity that requires thought or concentration.

**Adrenergic Agonists**

**Tachycardia**
- The patient’s blood pressure and pulse rate should be checked at each visit, especially if epinephrine or levonordefrin is required.
- Patients with uncontrolled hypertension or uncontrolled hyperthyroidism should not receive these drugs.

**Central Nervous System Excitation and Tremors**
- These effects can be exacerbated in a patient with existing CNS health issues or with hyperthyroidism.
- Both can be avoided or minimized with detailed medication/health histories and lower doses of a vasoconstrictor.

**Drug Interactions**
- Many over-the-counter (OTC) cough and cold products contain adrenergic agonists, which can interact with vasoconstrictors that can lead to increased blood pressure.
- Check the patient’s blood pressure and pulse rate.
- This can be avoided by carefully questioning the patient about his or her OTC drug use.

**Oral β-Adrenergic Agonists**
- These drugs have the ability to increase blood pressure and heart rate, especially in combination with a vasoconstrictor.
- This can be avoided or minimized by measuring the patient’s blood pressure and pulse rate before administering a vasoconstrictor.
- Ask specific questions about the patient’s medications and health.

---

**CLINICAL SKILLS ASSESSMENT**

1. Explain the difference in mechanism of action between the direct-acting and indirect-acting cholinergic agents.
2. Describe the pharmacologic effects of the cholinergic agents on the heart, gastrointestinal tract, and eye.
3. State two major uses of the cholinergic agents.
4. Describe a unique dental use for pilocarpine.
5. Describe the pharmacologic effects of the anticholinergic agents on the exocrine glands, smooth muscle, and eye.
6. List the adverse reactions associated with the anticholinergic agents.
7. State the contraindications and cautions to the use of anticholinergic agents and explain their relationship to the pharmacologic effects of these agents.
8. State the major therapeutic uses of the anticholinergics.
9. State the pharmacologic effect of the adrenergic agents on the eye, bronchioles, and salivary glands.
10. State the therapeutic uses of the adrenergic agents, especially the uses these agents have in dentistry.
11. Explain the limits to the accepted medical uses of the amphetamine-like agents. Explain why ephedrine tablets are bought by the case by some individuals.
12. Name the pharmacologic class to which atenolol (Tenormin) belongs. Describe the effects that make β-blockers useful in the treatment of arrhythmias, angina, and hypertension.
13. Differentiate between “selective” and “nonselective” β-blockers. Name a difference important to the dental health team (drug interaction).

**Evolve**

Please visit http://evolve.elsevier.com/Haveles/pharmacology for review questions and additional practice and reference materials.