CHAPTER 5

Autonomic Nervous System Drugs

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KEY TERMS

Acetylcholine
Acetylcholinesterase
Adrenal medulla
Adrenergic agonists
Adrenergic antagonists
Adrenergic nerves
Adrenergic receptors
Autonomic nervous system (ANS)
Cardioselective
Catecholamine
Cholinergic agonists

Cholinergic antagonists
Cholinergic nerves
Competitive inhibition
Craniosacral system
Direct-acting
Dopamine
Dual innervation
Effector organs
Endogenous
Enteric nervous system
Epinephrine

Ganglia
Indirect-acting
Muscarinic acetylcholine receptors
Nicotinic acetylcholine receptors
Noncompetitive inhibition
Norepinephrine
Parasympathetic nervous system
Pheochromocytoma

Postganglionic neuron
Preganglionic neuron
Selectivity
Sympathetic nervous system
Sympathomimetic
Synapse
Thoracolumbar system
Vasopressor

CHAPTER OBJECTIVES

At the end of the chapter, the student will be able to:

1. Understand which functions the autonomic nervous system (ANS) controls.
2. Understand the mechanism of action for ANS drugs.
3. Compare and contrast the various classes of ANS drugs.
4. Understand common indications and contraindications of ANS drugs.
5. Detect adverse effects of ANS drugs.

Introduction

The **autonomic nervous system (ANS)** controls a variety of involuntary regulatory responses that affect heart and respiration rates. It is responsible both for the "fight or flight" responses that represent the body's physiological response to crisis or stress and for the less crisis-driven functions of resting, repairing, digesting, and reproductive activities. Many of the drugs used to treat common conditions of the heart, circulation, and especially blood pressure do so by intentionally altering the functioning of the ANS.

THE THREE SYSTEMS OF THE ANS

An early view of the ANS described it as being separate from the central nervous system (CNS), which integrates sensory information in the brain and spinal cord. It is more accurate to say that the ANS carries out tasks that originate in the CNS (Blessing & Gibbins, 2008), but in some instances it acts more or less autonomously in doing so. It is important to recognize, though, that the ANS and the CNS are *not* separate systems; they simply have different key functional responsibilities. Whereas the CNS supervises all motor and cognitive functions, voluntary or otherwise, the ANS is primarily tasked with the involuntary functions of the body such as heartbeat, respiration, digestion, and so forth.

There are three key components to the ANS (**FIGURE 5-1**), two of which are of primary concern in this discussion: the **sympathetic nervous system** (SNS) and the **parasympathetic nervous system** (PNS). The third component, the **enteric nervous system** (ENS), is intrinsic to the digestive system—yet it is still very important. The ENS carries out key functions in support of systemic neurologic and immunologic well-being, and is highly responsive to both physical and emotional stimuli. For purposes of this discussion, however, the focus will mainly be on the SNS and PNS.
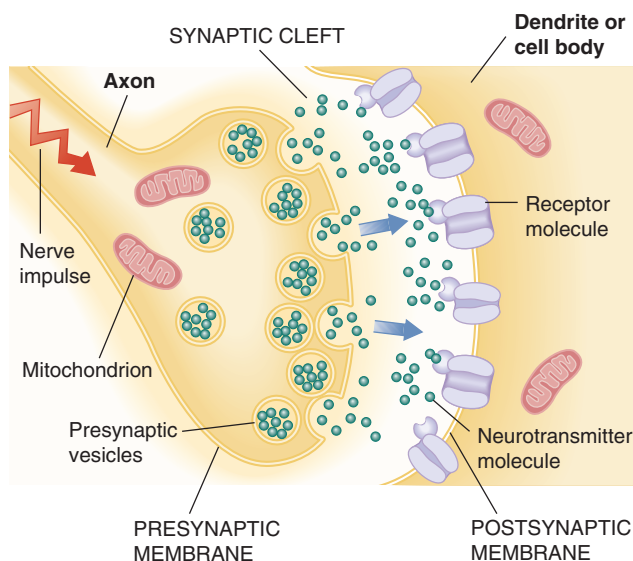
FIGURE 5-1 Comparison of the two divisions of the autonomic nervous system.

AAOS. (2004). Paramedic: Anatomy & Physiology. Sudbury, MA: Jones and Bartlett

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

The ANS is, in essence, an extension of the CNS that manages the involuntary functions of the body; thus all signals that pass through ANS pathways originate in either the spinal cord (both SNS and PNS) or the medulla of the brain (PNS). These impulses pass through a **preganglionic neuron** to bundles of **synapses** called **ganglia**, most of which then synapse to **postganglionic neurons** that process the signal to the appropriate **effector organs**, muscles, and other structures that they innervate. In both the SNS and the PNS, **acetylcholine** is the key neurotransmitter facilitating the preganglionic synapse. In the SNS, **norepinephrine**—a stress hormone—acts on the postganglionic neuron, while the PNS postganglionic neuron is excited once again by acetylcholine.

The SNS and PNS often innervate the same organs (**dual innervation**), although their effects on that organ may be different. For example, the heart is innervated by both sympathetic and parasympathetic nerves. Increased parasympathetic stimulation of the heart will result in parasympathetic predominance and decreased heart rate, while decreased parasympathetic impulses may result in unopposed sympathetic stimulation and increased heart rate. Conversely, increased sympathetic stimulation of the heart produces increases in heart rate and decreased sympathetic stimulation produces decreases in heart rate.

Integration of ANS Systems

The ANS can be thought of as being equivalent to a car racing team. One part is tasked with driving the car, keeping the vehicle going lap after lap and dealing with the stresses and quick responses needed as circumstances change. The other part (the pit crew) is tasked with keeping fuel and repairs in place so that both the driver and the car can continue doing their jobs. In this metaphor, the SNS is the driver; it increases metabolism and stimulates the cardiovascular and pulmonary systems as the situation requires, whether that means maintaining a steady metabolic speed for normal activities or "revving the engine" in crisis situations. Meanwhile, the PNS functions are similar to the activities of the pit crew; the PNS produces more targeted responses that facilitate digestion, repair, and resting functions, enabling the body to maintain energy stores and recover from incidental damage. Finally, the ENS is more like the car itself; it responds to input from both the SNS and the PNS; while its functions are fairly specific and somewhat limited in scope, it is nevertheless central to the operation of the whole team.

An important component of this metaphor is that the functions of the pit crew (PNS) and the driver (SNS) are rarely engaged at the same time. One operates under certain circumstances, while the other operates under different circumstances—yet together they can handle nearly all situations, whether it be routine maintenance, fueling, and upkeep or the critical stress of race time. The ENS, by comparison, is on the receiving end of signals from the PNS and SNS at any given moment; at the same time, it is always engaged and "running," even when at rest (just as the brain is).

Anyone who has seen cars race understands that the crew, the car, and the driver all need to work well and work *together* for the race to go well. Similarly, the ANS is a highly integrated system in

which the major parts are mutually interdependent. Consequently, medications that alter how the ANS functions may be intended to act on one system, yet affect the others in unexpected ways. Understanding how the SNS and PNS interact will help the clinician to identify both how medical interventions may affect the ANS overall, and how those treatments may have more specific effects on the functions of certain components of the ANS.

Sympathetic Nervous System

SNS impulses are responses to a fairly specific set of stimuli requiring activation of the "fight or flight" response. When someone crosses a street and sees a car moving quickly toward him or her, or suddenly coming around a corner and heading straight for the person—the rush of energy he or she experiences while jumping out of the way is exactly this type of impulse. It is, as may have been experienced by the reader, highly suited toward propelling the body into motion, as it originates from the spine rather than the brain: the ganglia and nerves of the SNS connect the spinal cord to a specific set of organs. The sympathetic ganglia extend from the upper neck down to the coccyx and are found in paired chains close to and along each side of the thoracic and lumbar spine. Nerves carrying sympathetic fibers exit the spinal cord from T1 to L2. For this reason, the SNS is sometimes also referred to as the **thoracolumbar system**.

The nerves in the ANS release specific neurotransmitters that target a number of different receptors, listed in **TABLE 5-1**. Preganglionic sympathetic nerves release acetylcholine into synapses. Acetylcholine stimulates postganglionic **nicotinic acetylcholine receptors**, and impulses are propagated along postganglionic sympathetic nerves, which release adrenergic neurotransmitters—primarily norepinephrine—to produce systemic effects. Because these preganglionic sympathetic nerves release acetylcholine, they are classified as **cholinergic nerves**. Postganglionic sympathetic nerves release adrenergic neurotransmitters and, therefore, are classified as **adrenergic nerves**. Receptors responsive to adrenergic neurotransmitters—**adrenergic receptors**—include alpha (α), beta (β), and dopamine (D) receptors.

Parasympathetic Nervous System

The PNS, similar to the SNS, is composed of preganglionic and postganglionic nerves. However, preganglionic parasympathetic nerve fibers originate in cranial nerves—II, VII, XI, and X—and sacral spinal nerves (S2 through S4). For this reason, the PNS is sometimes referred to as the **craniosacral system** (see Figure 5-1).

TABLE 5-1 Types of Autonomic Receptors

Neurotransmitter	Receptor	Primary Locations	Responses
Acetylcholine (cholinergic)	Nicotinic	Postganglionic neurons	Stimulation of smooth muscle and gland secretions
	Muscarinic	Parasympathetic target: organs other than the heart	Stimulation of smooth muscle and gland secretions
		Heart	Decreased heart rate and force of contraction
Norepinephrine (adrenergic)	Alpha$_1$	All sympathetic target organs except the heart	Constriction of blood vessels, dilation of pupils
	Alpha$_2$	Presynaptic adrenergic nerve terminals	Inhibition of release of norepinephrine
		Heart and kidneys	Increased heart rate and force of contraction; release of renin
	Beta$_1$	All sympathetic target organs except the heart	
	Beta$_2$		

Story, L. (2014). Pathophysiology: A practical approach, Second Edition. Burlington, MA: Jones & Bartlett Learning.

The PNS is the "rest and repair" part of the ANS. Its essential job is to transition the body to those functions that support the body's ability to renew itself. Thus it stimulates digestive secretions and gastrointestinal (GI) tract activity to promote processing of nutrients, and it slows the heart and constricts the pupils to promote resting. The principal route of PNS signaling is along the vagus nerve; in consequence, impulses tend to move more slowly through the PNS. This part of the nervous system is often conceived of as being "in opposition to" the SNS, but this is not entirely the case, although it is true that certain opposing functions are assigned to each system. Increases (SNS) and decreases (PNS) in heart rate, for example, are two such "opposing" functions.

NEUROTRANSMITTERS IN THE AUTONOMIC NERVOUS SYSTEM

Both the PNS and the SNS rely on two general types of neurotransmitters to pass nerve signals along. Preganglionic parasympathetic nerves in both systems are classified as cholinergic nerves and release acetylcholine. Acetylcholine attaches to nicotinic acetylcholine receptors on the postganglionic membrane, and impulses are propagated toward effector organs. Postganglionic parasympathetic nerves are also cholinergic nerves, and the acetylcholine they release attaches to **muscarinic acetylcholine receptors** at effector organs. Acetylcholine is rapidly metabolized to acetate and choline by the enzyme known as **acetylcholinesterase**, which is located on the postsynaptic membrane. Acetate diffuses away from the synapse and is metabolized in the liver, whereas choline is taken back up into the presynaptic membrane for synthesis of new neurotransmitters (**FIGURE 5-2**).

The postganglionic neurons of the SNS, unlike those in the PNS, primarily produce norepinephrine, a **direct-acting** neurotransmitter classified as a **catecholamine**. There are two specific places where postganglionic SNS neurons behave differently: sweat glands, in which postganglionic neurons produce acetylcholine (as in the PNS), and the **adrenal medulla**, where norepinephrine (also called *noradrenaline*) is converted to a different
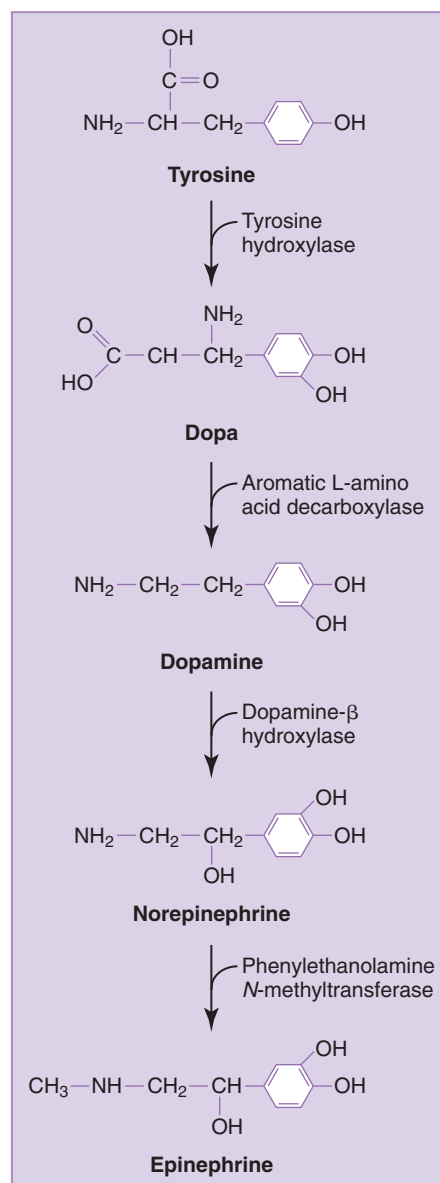

FIGURE 5-2 Catecholamine synthesis.
From Miller's Anesthesia, Elsevier.

catecholamine, **epinephrine** (also called *adrenaline*), by phenylethanolamine N-methyl transferase. Another **endogenous** catecholamine derivative is **dopamine**.

Both norepinephrine and epinephrine are metabolized by catechol-*o*-methyl transferase (COMT) and monoamine oxidase (MAO). Vanillylmandelic acid is the common metabolite for norepinephrine and epinephrine from both the COMT and MAO pathways (**FIGURE 5-3**).
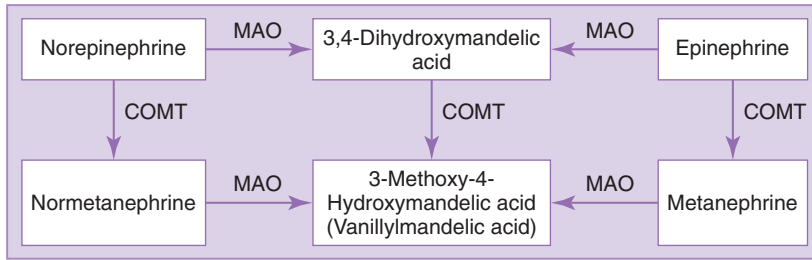
FIGURE 5-3 Catecholamine metabolism.
Copyright William Mark Enlow.

ADRENERGIC RECEPTORS

Catecholamines bind to specific receptors known as adrenergic receptors. There are two basic types of receptors: α-adrenergic receptors and β-adrenergic receptors. Each of these two types has various subtypes; there are two α-adrenergic receptor subtypes (α_1 and α_2) and three β-adrenergic receptor subtypes (β_1, β_2, and β_3). The action of neurotransmitters or **sympathomimetic** drugs upon these receptors is an important means of altering ANS function for therapy of different disease states—although this is not without its potential drawbacks, as will be discussed later in this chapter. **TABLE 5-2** identifies the various ways that stimulation acts upon particular receptors in particular organs. Note that β_3 receptors are found primarily in adipose tissue and are thought to play a role in thermoregulation and lipolysis; if stimulation of these receptors has an immediate effect on body functions, it is as yet unidentified. Thus β_3 responses are not listed in Table 5-2.

Drugs That Affect the ANS

Medications that affect the ANS are classified into several categories. Adrenergic drugs are those that either mimic or interfere with the activity of neurotransmitters secreted by the adrenal medulla—for example, norepinephrine and epinephrine. Specifically, **adrenergic agonists** are drugs that stimulate the SNS, either by direct activation of receptors or by promoting the release of receptor-activating catecholamines, whereas **adrenergic antagonists** block the activity of acetylcholine, norepinephrine, or other neurotransmitters.

ADRENERGIC AGONIST DRUGS

Adrenergic agonists can produce profound effects on the body's vital systems, typically requiring special care in their administration and monitoring of patient responses. Therapeutic activation of SNS receptors is useful for a range of clinical purposes, including cardiac stimulation, bronchodilation, and constriction of blood vessels. The clinical effects of adrenergic agonists, however, depend on the **selectivity** of the drug for the variety of receptor subtypes. For example, some agents may be used to treat hypotension, due to their preference for stimulation of α_1-adrenergic receptors (e.g., phenylephrine), whereas others may be used to treat hypertension, due to their selectivity for α_2-adrenergic receptors (e.g., clonidine).

Nonselective Agents

Nonselective adrenergic agonists act on particular adrenergic receptors anywhere in the body, producing a variety of systemic effects. Given their widespread action, they must be used with a fair amount of consideration for the possibility (or even probability) of unwanted or counterproductive effects, as well as careful review for the possibility of contraindications. **TABLE 5-3** describes a selection of potential effects of adrenergic drugs, along with therapeutic goals associated with their use.

EPINEPHRINE Epinephrine is a direct-acting adrenergic agonist that stimulates all α- and β-adrenergic receptors (α_1, α_2, β_1, β_2, and β_3). As a pharmacologic agent, epinephrine is a potent cardiac stimulant

TABLE 5-2   Actions of Neurotransmitter Stimuli on Receptors in Various Organs

Receptor	Effector Organ	Response to Stimulation
β_1	Heart	Increased heart rate
		Increased contractility
		Increased conduction velocity
	Fat cells	Lipolysis
β_2	Blood vessels (especially skeletal and coronary arteries)	Dilation
	Bronchioles	Dilation
	Uterus	Relaxation
	Kidneys	Renin secretion
	Liver	Glycogenesis
		Gluconeogenesis
	Pancreas	Insulin secretion
α_1	Blood vessels	Constriction
	Pancreas	Inhibition of insulin secretion
	Intestine and bladder	Relaxation
		Constriction of sphincters
α_2	Postganglionic (presynaptic sympathetic nerve ending)	Inhibition of norepinephrine release
	Central nervous system (postsynaptic)	Increase in potassium conductance (?)
	Platelets	Aggregation
D_1	Blood vessels	Dilation
D_2	Postganglionic (presynaptic) sympathetic nerve ending	Inhibition of norepinephrine release
Muscarinic	Heart	Decreased heart rate
		Decreased contractility
		Decreased conduction velocity
	Bronchioles	Constriction
	Salivary glands	Stimulation of secretions
	Intestine	Contraction
		Relaxation of sphincters
		Stimulation of secretions
	Bladder	Contraction
		Relaxation of sphincter
Nicotinic	Neuromuscular junction	Skeletal muscle contraction
	Autonomic ganglia	Sympathetic nervous system stimulation

that increases contractility and heart rate by β_1 receptor stimulation and characteristically leads to a dose-related increase in systolic blood pressure. Epinephrine also causes contraction of vascular smooth muscle and results in vasoconstriction due to activation of α_1 receptors. Conversely, stimulation of β_2 receptors by epinephrine leads to relaxation of respiratory and uterine smooth muscle, as well as skeletal smooth muscle vasculature. Because of these effects, epinephrine is used for treatment of bronchospasm in asthma and chronic obstructive pulmonary disease (COPD), for circulatory support and treatment of airway swelling in severe acute anaphylactic reactions and shock, and for promotion

TABLE 5-3 Nursing Diagnoses Related to Use of Adrenergic Drugs and Associated Therapeutic Goals

Nursing Diagnoses	Goals
Impaired gas exchange related to bronchoconstriction	Patient will experience relief of symptoms
Altered tissue perfusion related to hypotension or vasoconstriction due to adrenergic drug therapy	Patient will attain adequate profusion to the brain, heart, kidney, and peripheral tissue
Altered nutrition, less than body requirements, related to a loss of appetite	Patient will maintain his or her weight
Sleep pattern disturbance: insomnia, anxiety, restlessness, nervousness	Patient will reestablish his or her normal sleeping pattern
Potential for injury related to cardiac stimulation: hypertension, dysrhythmias	Patient will not experience any adverse effects

of return of circulation in cardiac arrest during cardiopulmonary resuscitation. Epinephrine is also commonly added to local anesthetic solutions to diminish the rate of systemic absorption of the anesthetic by means of localized vasoconstriction, thereby prolonging the desired anesthetic effect while reducing the risk of systemic toxicity. Epinephrine may be administered by a range of routes—intravenous, intramuscular, subcutaneous, intraosseous, oral inhalation, endotracheal, and topical—depending on the indication and clinical situation; it is also given in a wide variety of doses.

Adverse effects include anxiety, headache, tremors, pallor, sweating, nausea, vomiting, hypertension, tachycardia, cardiac arrhythmias, cardiac ischemia, and intracranial hemorrhage. Administration of epinephrine can provoke chest pain in patients with underlying ischemic heart disease due to β-mediated effects and can cause urinary retention in males with enlarged prostates due to α stimulation. Uterine relaxation caused by $β_2$ receptor activity can delay the second stage of labor after administration of epinephrine.

NOREPINEPHRINE Norepinephrine bitartrate is a potent **vasopressor** and cardiac stimulant that acts directly on α- and β-adrenergic receptors ($α_1$, $α_2$, and $β_1$). Like epinephrine, norepinephrine is a naturally occurring hormone in the body that mediates the stress response. It is also an important neurotransmitter within the SNS. Unlike epinephrine, however, norepinephrine has little impact on $β_2$ receptors. As a result, norepinephrine has a profound effect on peripheral vascular resistance, increasing both systolic and diastolic blood pressures, and is utilized clinically most often as a vasopressor to restore blood pressure in acute hypotensive states. This medication is administered intravenously by means of an infusion pump, with careful titration and frequent systemic blood pressure measurements. Indications include hypotension and shock that are refractory to fluid volume replacement in septicemia, myocardial infarction, trauma, and burns.

Adverse effects of norepinephrine are similar to those of epinephrine. Given nonepinephrine's potent vasoconstrictive properties, however, the risks of plasma volume depletion and organ damage to the bowel, kidneys, and liver are enhanced with this medication, especially in the context of hypovolemia or prolonged administration. Impaired circulation, tissue necrosis, and sloughing may occur at the infusion site even without demonstrable extravasation. Lower initial doses of norepinephrine are recommended for elderly patients because of their higher likelihood of concomitant organ dysfunction or coexisting disease.

EPHEDRINE Ephedrine is a natural substance found in plants of the genus *Ephedra* that has been widely used in traditional and modern medicine to treat symptoms of asthma and upper respiratory congestion. Ephedrine acts directly on α- and β-adrenergic receptors ($α_1$, $α_2$, $β_1$, and $β_2$), causing cardiac stimulation, bronchodilation, and vasoconstriction. Ephedrine also provokes an indirect effect by stimulating the release of norepinephrine from nerve terminals within the SNS. Ephedrine can cross the blood–brain barrier and enter the CNS, where mild stimulation can result. As a consequence, this medication has been used to treat narcolepsy and depression. CNS effects have also resulted in the misuse and abuse of ephedrine as an athletic performance enhancer

and as a dietary suppressant. A form of ephedrine used in nasal decongestants (pseudoephedrine) has been used in the illicit manufacture of methamphetamine, resulting in stricter controls of its over-the-counter sales. This agent is also used as a vasopressor in the treatment of hypotension during anesthesia.

Adverse effects of ephedrine include excessive CNS stimulation, which can manifest as anxiety, restlessness, headache, blurred vision, insomnia, and seizures. Ephedrine can cause palpitations, arrhythmias, pallor, tachycardia, chest pain, and severe hypertension. Nausea, vomiting, and anorexia can also occur with its use. Acute urinary retention can result from prolonged usage, especially in men with prostatism. Ephedrine can restrict renal blood flow with initial parenteral use and decrease urine formation. Caution must be exercised when prescribing this drug to patients with underlying hypertension, hyperthyroidism, ischemic heart disease, diabetes mellitus, and prostatic hypertrophy, because ephedrine can exacerbate these conditions. Severe hypertension from ephedrine can occur in patients who are taking MAO inhibitors. A reduced vasopressor response from ephedrine may be seen in patients taking reserpine and methyldopa, as well as those taking α- and β-adrenergic blocking agents.

Dopamine Dopamine is a potent vasoactive agent that acts on a variety of adrenergic receptors in a dose-dependent manner. At low and moderate doses, dopamine causes dopaminergic and β_1-adrenergic effects, resulting in increased renal and splanchnic blood flow and increased cardiac contractility, respectively. At higher doses, this agent promotes vasoconstriction by directly stimulating α-adrenergic receptors and by causing the release of norepinephrine from sympathetic nerve terminals. Dopamine is an endogenous catecholamine and the immediate precursor of norepinephrine. Its therapeutic indications include the treatment of shock states, low cardiac output syndromes, and hypotension, and as an adjunct to increase cardiac output and blood pressure during cardiopulmonary resuscitation. The ability of dopamine at low doses (less than 5 mcg/kg/min) to support renal perfusion through its dopaminergic receptor effects has led

to its use as a treatment or prophylactic agent for acute renal failure, although such use remains controversial (Bellamo, Chapman, Finfer, Hickling, & Myburgh, 2000; Ichai, Passeron, Carles, Bouregba, & Grimaud, 2000).

Adverse cardiac effects associated with dopamine include hypotension, hypertension, ectopic beats, tachycardia, palpitations, vasoconstriction, angina, dyspnea, and cardiac conduction abnormalities and widened QRS intervals. Dopamine can cause headaches, anxiety, nausea, and vomiting. Exaggerated effects can be seen in patients taking MAO inhibitors, tricyclic antidepressants, and methyldopa. Administration of intravenous phenytoin to patients receiving dopamine may precipitate hypotension, bradycardia, and seizures. Dopamine extravasation can cause tissue sloughing and necrosis. If this occurs, the tissue should be infiltrated immediately with 10–15 mL of normal saline with 5–10 mg of phentolamine.

Dopamine administration requires close monitoring of patient hemodynamics and careful titration of drug dosing using an infusion pump, based on the patient heart rate, blood pressure, peripheral perfusion, urinary output, and electrocardiogram (ECG) findings. Dopamine is contraindicated in hypovolemic states, pheochromocytoma, tachyarrhythmias, and ventricular fibrillation. It should be used with caution in patients with a history of occlusive vascular disease (atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, or Buerger's disease).

Selective Agents

Selective adrenergic agents act on adrenergic receptors in particular locations. As a consequence, they act in a targeted fashion, and therapies including these agents are therefore less likely than some other drugs to produce undesired responses elsewhere in the body.

Dobutamine Dobutamine is a synthetic β_1-selective agonist that is used in the short-term management of patients with depressed cardiac contractility from organic heart disease, cardiac surgical interventions, and acute myocardial infarction. It is also used to treat low cardiac output states following cardiac

arrest. Dobutamine acts on the β_1-adrenergic receptors in the heart, increasing the force of myocardial contraction. It causes a reduction in peripheral resistance and has a limited impact on heart rate. This agent is contraindicated in patients with hypovolemia, as well as those patients with idiopathic hypertrophic subaortic stenosis. Its use in the context of acute myocardial infarction is limited, but concerns about infarct extension have been articulated. Dobutamine increases atrioventricular conduction and may cause rapid ventricular responses in patients with atrial fibrillation, unless they have received digitalis prior to initiating dobutamine therapy.

Adverse effects of dobutamine include hypertension, increased heart rate, ectopic beats, and angina, as well as nausea, vomiting, headache, fever, and leg cramps. Increased effects may be seen with concomitant use of tricyclic antidepressants, furazolidone, and methyldopa. Patients require continuous monitoring of hemodynamics during dobutamine administration and careful titration of the medication based on their responses.

PHENYLEPHRINE Phenylephrine (Neosynephrine) is a potent synthetic vasopressor that acts predominately on α_1 receptors to produce vasoconstriction and dose-related elevations of both systolic and diastolic blood pressure. Phenylephrine is administered intravenously as an adjunct therapy to treat low vascular resistance states, hypotension, and shock, particularly the distributive shock seen in sepsis and spinal cord injury, after adequate fluid volume placement has been achieved. It is also commonly used to treat hypotension during spinal anesthesia, caused by a loss of vascular tone from the associated sympathectomy, and hypotension during general anesthesia, produced by the vasodilatory effects of anesthetic agents. Topical application of phenylephrine to the mucous membranes of the nasal passages is used to treat nasal congestion from allergic conditions or the common cold. Oral administration of this agent, either alone or in multidrug combinations with antipyretics and antihistamines, is used in the treatment of upper respiratory symptoms. Phenylephrine is also an ingredient in many over-the-counter products

for the treatment of hemorrhoids, as it is able to reduce the swelling of anorectal tissue through vasoconstriction.

Adverse effects of phenylephrine include anxiety, restlessness, tremor, pallor, headache, hypertension, and precordial pain. As a treatment for hypotension and shock states, phenylephrine may cause severe peripheral and visceral vasoconstriction, and like norepinephrine, its use may result in plasma volume depletion and end-organ damage. Phenylephrine may cause severe bradycardia and reduced cardiac output, and should be used with caution in elderly persons and in patients with diminished cardiac reserve or history of myocardial infarction.

Self-medication with products containing phenylephrine should be avoided in patients with high blood pressure, thyroid disorders, cardiac disease, and urinary difficulties due to enlarged prostate. According to the U.S. Food and Drug Administration (FDA, 2008), children younger than age four years should not be given nonprescription oral cough and cold preparations due to the risk of overdose and death. Patients taking MAO inhibitors may experience life-threatening, exaggerated sympathetic responses to phenylephrine and other adrenergic agonists, resulting in severe headache, hypertension, hyperpyrexia, and precipitation of a hypertensive crisis.

CLONIDINE Clonidine (Catapres, Duraclon) is a selective α_1-adrenergic agonist that is used as an antihypertensive and central analgesic. Clonidine stimulates α_1-adrenergic receptors in the CNS, mainly in the medulla oblongata, causing inhibition of the sympathetic vasomotor centers. This stimulation results in a reduction in peripheral SNS activity, peripheral vascular resistance, and systemic blood pressure. Clonidine produces a reduction in heart rate by inhibition of cardioaccelerator activity in the brain.

It also produces analgesia by activation of central pain suppression pathways in the brain and by inhibiting the transmission of pain signals to the brain through the spinal cord. Therapeutic indications for this medication include the treatment of hypertension and hypertensive urgencies, as well as in the multimodal management of chronic pain. Clonidine has also been used as a treatment for

vascular headaches, dysmenorrhea, and vasomotor symptoms associated with menopause; in smoking cessation therapy; as treatment for opiate and alcohol dependency; and in attention-deficit/hyperactivity disorder (ADHD.)

Adverse effects of clonidine include dizziness, drowsiness, sedation, dry mouth, fatigue, anxiety, nightmares, and depression. Cardiovascular effects can be pronounced, including palpations, tachycardia, bradycardia, orthostatic hypotension, and cardiac rhythm disturbances. Clonidine should not be discontinued abruptly because rebound phenomena can precipitate hypertension, tachycardia, and cardiac arrhythmias. Instead, therapy should be discontinued by gradual reduction of dosage tapered over several days. Clonidine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, and chronic renal failure. Children are more likely to experience signs of CNS depression with clonidine than are adults.

DEXMEDETOMIDINE Dexmedetomidine (Precedex) is a selective α_1-adrenergic agonist that has sedative, anxiolytic, and analgesic effects. Dexmedetomidine activates α_1 receptors in the locus ceruleus of the brain stem, suppressing firing of the noradrenergic neurons as well as activity in the ascending noradrenergic pathway. The inhibition by dexmedetomidine causes a decrease in the release of histamine, which then results in a hypnotic response, similar to that seen in normal sleep. Indications for the use of dexmedetomidine include sedation of mechanically ventilated patients in the intensive care unit (ICU), pediatric procedural sedation, and sedation for awake neurosurgical procedures. Dexmedetomidine has also been used as an anesthetic-sparing agent in a number of specialties, including bariatric and cardiac surgery, allowing for a reduction in the amount of agents that cause postoperative respiratory depression while significantly attenuating postoperative pain.

Adverse effects of dexmedetomidine administration are primarily hypotension and bradycardia. Bradycardia can be profound when increased vagal stimuli are present, and in young individuals with high vagal tone, requiring modulation of vagal tone

with intravenous anticholinergic agents (atropine, glycopyrrolate). Other adverse effects include hypertension, supraventricular and ventricular tachycardia, atrial fibrillation, anemia, pain, leukocytosis, and pulmonary edema. Caution should be exercised in patients who are volume depleted or who have high-degree heart block. The safety of this medication in lactating mothers has not been established.

Nursing Considerations for Adrenergic Drugs

ASSESSMENT For patients with respiratory disease, the nurse should assess respiratory status, including respiratory rate, heart rate, blood pressure, color, use of accessory muscles, oxygen saturation, and breath sounds, when adrenergic drugs are prescribed. For patients who have diabetes mellitus, the baseline serum glucose level should be checked. For all patients, cardiovascular status should be assessed:

- Assess for potential contraindications to using adrenergic medications: angina, hypertension, and tachydysrhythmias.
- Before, during, and after treatment monitor blood pressure, heart rate, respiratory rate, color, and temperature of skin.

There are also important life span considerations in using such drugs. Most adrenergic drugs are classified into risk category C with regard to use during pregnancy, so healthcare providers should determine whether females of childbearing age are pregnant before giving such medications. Use adrenergic drugs with caution in infants and the elderly as well, as these patients are at higher risk for adverse effects.

NURSING INTERVENTIONS

- For impaired gas exchange: Monitor oxygen saturation and/or arterial blood gases; check respiratory rate and breath sounds prior to administering adrenergic drugs and during treatment.
- For altered tissue perfusion: Monitor the level of consciousness, heart rate, blood pressure, ECG, chest pain, urine output, color and temperature of skin, and capillary refill.

- For altered appetite/nutrition concerns: Provide small frequent meals, feed when the medication effect is minimal, and serve foods the patient likes.
- For sleep pattern disturbances: Dim the lights, keep the area quiet, and offer a back rub.
- For the potential for injury: Monitor the ECG, blood pressure, heart rate, and any chest pain.

PATIENT TEACHING Patients should be taught to use adrenergic drugs as directed by their prescriber. Anxiety and insomnia are common feelings caused by the adrenergic drugs and should be reported to the prescribing clinician. Because of the potential for side effects or drug interactions, patients should be advised to check with their healthcare provider or pharmacist prior to taking any other medications, and to seek medical attention immediately if they experience chest pain. If the patient takes the medication as directed and has no relief of symptoms, he or she should let the prescriber know.

Patients who are prescribed epinephrine kits for emergency self-administration due to risk of anaphylaxis (EpiPen) should be advised to read the instructions and practice using the pen on an orange or a stuffed animal prior to using it on themselves. (EpiPen kits are packaged with a practice syringe containing no needle or drug.) If the patient is a child younger than age 13, this instruction should be given to parents; if the patient is an adolescent or teen, and with the parent's consent, it may be helpful for the nurse to show the patient what to do and then monitor (and correct) as the patient mimics the procedure under the nurse's guidance. Patients should be advised to seek medical attention immediately after use of the EpiPen, as epinephrine is short-acting and the source of the allergic response may still be present after the drug is metabolized.

ADRENERGIC ANTAGONISTS

Adrenergic antagonists are sometimes referred to as adrenergic blocking agents or adrenergic blockers, and for good reason: When they interact with their respective receptors, the normal receptor response does not occur. They merely attach to receptors and block binding sites for their respective agonists by **competitive** or **noncompetitive inhibition**. Responses to adrenergic antagonists depend on the receptor classes and subclasses with which the antagonists interact. A review of adrenergic receptors and their *activation* or *stimulation* (see Table 5-2) is useful to facilitate understanding of the effects of blocking receptor activation using adrenergic antagonists.

α-Adrenergic Antagonists

Drugs that attach to α-adrenergic receptors and block the effects of norepinephrine and epinephrine are categorized as α-adrenergic antagonists. Specific drug effects differ due to the degree of selectivity for α_1 or α_2 receptor subtypes. Moreover, patients' responses to these drugs may vary if they have had prior exposure to α-agonists or α-antagonists, or may reflect the concentration of endogenous catecholamines, receptor concentration on cell membranes (up- or down-regulation of receptors), or even simply a genetic variation in receptors. The following is an example: A typical response to endogenous catecholamines that stimulate α_1 receptors (e.g., norepinephrine) is vasoconstriction. If an α_1-receptor antagonist is administered, vascular smooth muscle contraction and other α_1-receptor–mediated effects caused by norepinephrine are blocked, and blood pressure decreases.

Generally, α-adrenergic receptor antagonists are useful in the management of hypertension, benign prostatic hypertrophy, and heart failure. It has been observed, however, that repeated exposure to the same drugs causes adaptive changes such that patients either no longer respond to the medication dose originally prescribed (tolerance) or become sensitized to it, so that they over-respond or develop allergic reactions (sensitization). Studies of this phenomenon (Kojima et al., 2011) show that use of such drugs up-regulates receptors over time, leading to changes in the patient's response.

Selectivity

Alpha-adrenergic receptor antagonists may be nonselective or selective for α_1 receptors. With nonselective α-adrenergic antagonists, both α_1- and

α_2-adrenegic receptor subtypes are blocked, resulting in reduced blood pressure as the major cardiovascular effect. While the inhibitory actions caused by α_2-receptor activation, such as decreased release of norepinephrine, are blocked by nonselective α antagonists, blockade of α_1 receptors produces profound hypotensive effects that mask the actions at α_2 receptors. The α_1-selective antagonists spare α_2 receptors of blockade and the predominant effect is, similarly, decreased blood pressure. Other favorable actions of α_1-specific antagonists include decreased urinary outflow obstruction caused by benign prostatic hypertrophy and beneficial effects on glucose and lipid metabolism.

Yohimbine, used primarily in the treatment of erectile dysfunction, is the only α_2-selective receptor antagonist available for clinical use. However, newer, more reliable medications that inhibit phosphodiesterase (e.g., sildenafil) have made this drug virtually obsolete.

PHENOXYBENZAMINE Phenoxybenzamine is a noncompetitive, nonselective α-adrenergic antagonist agent that serves as the prototype for α-antagonists. When the α-receptor–mediated effects of norepinephrine and epinephrine are blocked by phenoxybenzamine, peripheral vascular resistance decreases and blood pressure falls. Heart rate often increases due to a compensatory baroreceptor reflex–mediated effect and perhaps to some extent due to increased circulating norepinephrine caused by α_2-receptor blockade. Additionally, phenoxybenzamine *irreversibly* binds to receptors and new receptors must be synthesized for termination of effects of the drug.

Phenoxybenzamine is primarily used in the preoperative management of episodic, dangerous hypertension in patients with **pheochromocytoma** prior to surgical excision. Beta-receptor antagonists are also useful in this setting but should be added *after* effective α blockade has been achieved to prevent unopposed alpha stimulation and possible pulmonary edema. Other indications include hypoplastic left heart syndrome and complex regional pain syndrome type 1.

Adverse effects of phenoxybenzamine include decreased blood pressure, which is an expected effect of the drug that can be detrimental if drug concentrations occur above the therapeutic range. Initiating phenoxybenzamine therapy at a low dose and increasing the dosage slowly over a period of several days may attenuate profound hypotension. As the peripheral vascular resistance decreases and the intravascular volume expands over several days, oral ingestion of fluids fills the expanded intravascular volume. Orthostatic hypotension may persist with associated increases in heart rate after slow initiation of therapy and appropriate volume repletion. Forced ejaculate is limited by α-receptor blockade, but orgasm and semen secretion are not impaired (Gerstenberg, Levin, & Wagner, 1990). Parasympathetic effects may become evident due to decreased α-adrenergic activity (e.g., nasal stuffiness, increased gastrointestinal motility, and increased glycogen synthesis).

Administration of exogenous catecholamines may be ineffective in treating hypotension due to phenoxybenzamine, as these drugs cannot compete with the irreversible phenoxybenzamine–receptor complex. Phenylephrine and norepinephrine may be completely ineffective. Because epinephrine is effective only at β-adrenergic receptors in individuals treated with nonselective α-receptor blockade, its administration will produce *hypotensive* responses due to unopposed vasodilation caused by β_2-receptor stimulation. This phenomenon, called "epinephrine reversal," may also be observed with other α_1-receptor *antagonists* due to stimulation of both β-adrenergic receptors and α_2-adrenergic receptors (Swan & Reynolds, 1971). Generous intravenous fluids administered to increase intravascular volume prior to and during phenoxybenzamine administration may prevent profound hypotension and reduce orthostatic hypotension and tachycardia. Vasopressin may correct hypotension due to phenoxybenzamine infusion proven to be refractory to norepinephrine administration (O'Blenes, Roy, Konstantinov, Bohn, & Van Arsdell, 2002).

PHENTOLAMINE Phentolamine is a competitive, nonselective α-receptor antagonist. It differs from phenoxybenzamine in that its interaction with receptors is reversible and drug effects can be overcome by increasing the concentrations

of an α-receptor agonist (e.g., phenylephrine, norepinephrine). Phentolamine also has affinity for 5-HT receptors, blocks potassium channels, stimulates gastrointestinal motility, increases secretion of gastric acid, and causes mast cell degranulation. It is used systemically to treat hypertension and injected locally after extravasation of vasoconstrictor drugs (e.g., dopamine) to prevent soft-tissue necrosis (Bey, El-Chaar, Bierman, & Valderrama, 1998). Phentolamine should be used with caution in patients with exaggerated histamine release or sensitivity to histamine effects (e.g., bronchoconstriction due to histamine, particularly in patients with asthma).

PRAZOSIN Prazosin is a competitive, selective α_1-receptor antagonist (1000:1::α_1:α_2). It also inhibits the phosphodiesterase enzyme, thereby decreasing smooth muscle contraction. This drug is used primarily in the treatment of hypertension. Antagonist effects at the α_1 receptor produce decreased peripheral vascular resistance and increased venous capacity, in turn leading to decreased preload and systemic blood pressure with little change in heart rate. Interestingly, prazosin increases the concentration of high-density lipoproteins and decreases the concentration of low-density lipoproteins via mechanisms that may be unrelated to α-receptor interactions. For this reason, it is sometimes prescribed for patients with both hypertension and hypercholesterolemia.

A number of prazosin analogs are also in use, including terazosin, doxazosin, and tamulosin. Terazosin is a less potent, longer-acting analog of prazosin that is similarly selective for α_1 receptors. It is primarily used in the management of benign prostatic hyperplasia (BPH) and may be taken once daily. Doxazosin is a selective α_1-receptor antagonist analog of prazosin that is used in the management of hypertension and BPH. Likewise, tamulosin is a selective α_1-receptor antagonist analog of prazosin, but its effects are weaker in the vasculature and more selective for α-receptors in the prostate. This agent is used in the management of BPH.

Adverse effects for prazosin and its analogs include orthostatic hypotension and syncope, which

may occur 30 to 90 minutes after the initial dose of any of these drugs, with the possible exception of tamulosin (as noted earlier, tamulosin's effects are weaker, so it is less likely to produce profound orthostatic hypotension than the other agents in this class). For this reason, the first dose is optimally taken just prior to bedtime. Postural hypotension may continue during long-term therapy with these drugs, so patients should be advised to rise from lying or sitting positions slowly to avoid dizziness and syncope. Headache and asthenia are common side effects.

Nursing Considerations for α-Receptor Antagonists

Because postural hypotension often persists with chronic therapy, it may be beneficial to assess and document the patient's standing, sitting, and recumbent blood pressures. Patients should be advised to take the first dose just prior to bedtime. Additionally, they should rise slowly from lying and sitting positions to avoid dizziness, syncope, and possible injury. Patients may be alarmed by some of the side effects (e.g., nasal stuffiness, increased gastrointestinal motility, abnormal ejaculate) and can be reassured with the understanding that these are common.

Beta-Adrenergic Antagonists

Beta-receptor antagonists are drugs that attach to β-adrenergic receptors and block the effects of agonists (e.g., epinephrine and norepinephrine) at those β-receptor sites. When β receptors are stimulated, sympathetic responses occur. For example, β_1-receptor stimulation elicits increases in heart rate, while β_2-receptor stimulation elicits bronchodilation. Blockade of these receptors prevents cardiac and pulmonary excitation, respectively. The effectiveness of β-adrenergic antagonists, like the effectiveness of other adrenergic agents, may vary widely among individuals due to membrane receptor concentration (up- and down-regulation of receptors), catecholamine concentration, interactions with other agents, and receptor genetics.

Selectivity

Beta antagonists are often classified as either nonselective or **cardioselective**. Nonselective β

antagonists block both β_1 and β_2 receptors. Cardioselective β antagonists preferentially block β_1 receptors. The predominant cardiovascular effects for these antagonists at the β_1 receptor include decreased heart rate and myocardial contractility (see Table 5-1). The effects of β_2-receptor antagonists include *inhibition* of vascular dilation and inhibition of pulmonary bronchiole dilation, which may be problematic in patients with obstructive lung disease.

Beta-adrenergic antagonists are useful in the management of a number of illnesses, including hypertension, ischemic heart disease, arrhythmia, hypertrophic obstructive cardiomyopathy, chronic open-angle glaucoma, migraine, thyrotoxicosis, variceal bleeding due to portal hypertension, and "stage fright." More recently, β antagonists have become important adjuncts in the management of chronic—*but not acute*—heart failure (Hunt et al., 2001).

Beta-antagonist drugs can produce a number of adverse effects. Common side effects include bradycardia, bronchospasm, fatigue, sleep disturbance, impotence in men, and attenuated responses to hypoglycemia. These drugs, particularly nonselective agents, are generally avoided in patients with asthma. More concerning effects include progressive heart block, bronchoconstriction, and heart failure. Additionally, abrupt discontinuation of long-term β-antagonist therapy may result in "rebound" increases in heart rate and blood pressure. These rebound effects can produce myocardial ischemia, infarction, or sudden death in susceptible individuals. Therefore, gradual tapering of the dose is recommended if β-adrenergic antagonist therapy must be terminated.

Symptomatic adverse effects of β-antagonist overdose may require intervention. Treatments for symptomatic bradycardia, hypotension, or heart block may include cessation of β-blocker therapy; administration of atropine, glucagon, or isoproterenol; or temporary cardiac pacing.

Administration of vasopressors such as norepinephrine and epinephrine in the context of β-antagonist pharmacotherapy or overdose may be harmful, as these agents' effects will be limited to α-receptor stimulation because β receptors are blocked. The combination of α-receptor–mediated hypertension from vasopressor administration and decreased contractility from β blockade may produce iatrogenic heart failure and pulmonary congestion. When β-adrenergic–antagonist therapy is used during cocaine intoxication, it may result in unopposed α-receptor stimulation, leading to hypertension and pulmonary edema (Houston, 1991). Nonsteroidal anti-inflammatory agents (ibuprofen, diclofenac sodium) are not recommended in patients taking β-adrenergic antagonists for hypertension because they attenuate the antihypertensive effects of these agents.

Beta-adrenergic antagonist therapy is indicated in the presurgical management of pheochromocytoma only *after* α-adrenergic antagonist therapy has been initiated. These drugs are *not* indicated in the management of *acute* heart failure. Patients with diabetes may not experience the typical responses to hypoglycemia, putting them at higher risk for hypoglycemic crisis.

PROPRANOLOL Propranolol is the prototype β-antagonist drug and has effects on both β_1 and β_2 receptors—it is a competitive, nonselective β-adrenergic antagonist. Propranolol has fallen out of favor since newer cardioselective β-antagonist agents have been developed. However, it remains useful in the management of intention tremor, thyroid storm, and pheochromocytoma.

Propranolol may interact with alcohol, α-antagonists, calcium-channel blockers, antiarrhythmic medications, α_2-agonists, digoxin, haloperidol, MAO inhibitors, nonsteroidal anti-inflammatory agents, thyroid medications, tricyclic antidepressants, and warfarin.

OTHER COMMONLY USED BETA-ADRENERGIC ANTAGONISTS Metoprolol is a competitive, cardioselective β_1-receptor antagonist. It is effective in limiting heart rate increases during exercise in patients with ischemic heart disease. It is also useful in hypertension, angina, acute myocardial infarction, supraventricular tachycardia, chronic (but not acute) heart failure, hyperthyroidism, long QT syndrome, performance anxiety, vasovagal syndrome, and migraine headaches.

Esmolol is a competitive, cardioselective β_1-receptor antagonist with a unique structure that

permits hydrolysis by erythrocyte esterases. This feature results in a drug with a short half-life, necessitating administration of this medication by intravenous infusion to achieve sustained effects.

Atenolol is a competitive, cardioselective β_1-receptor antagonist. It is eliminated unchanged in the urine and may accumulate in patients with impaired renal function, leading to overdose and toxicity.

Nadolol is a competitive, nonselective β-receptor antagonist with a long half-life, allowing for once-daily dosing. It is used in the management of angina, hypertension, migraine headaches, Parkinsonian tremors, and variceal bleeding.

Pindolol is a nonselective β-receptor antagonist. However, it is also thought to have some weak β-receptor agonist effects, which limit the degree to which heart rate and blood pressure are reduced. This agent is sometimes used in patients who are sensitive to the bradycardic effects of other β-receptor antagonists.

Labetalol is unique among the β-adrenergic antagonists. It actually consists of several isomers that have α_1-antagonist and nonselective β-adrenergic–antagonist effects. Labetalol produces significant decreases in blood pressure without compensatory increases in heart rate and is most commonly used in the treatment of hypertension.

Carvedilol is a unique drug that acts as an antagonist at α_1-, β_1-, and β_2-adrenergic receptors. It also demonstrates antioxidant and antiproliferative properties. This agent is useful in the management of chronic heart failure and postmyocardial infarction. Carvedilol improves ventricular function and reduces morbidity and mortality in these populations.

Nursing Considerations for Beta Adrenergic Antagonists

ASSESSMENT A number of factors are contraindications to use of β-adrenergic antagonists. Women of childbearing age should be assessed for pregnancy or likelihood of pregnancy, as most β-adrenergic antagonists are classified as pregnancy risk category C. Elderly patients may be at higher risk for injury when such agents are prescribed, due to bradycardia,

postural hypotension, and falls. The presence of conditions that might be worsened with these drugs—such as hypotension, bradycardia, unstable congestive heart failure, heart block, asthma, and COPD—should also be evaluated. Prior to, during, and after administration of β-adrenergic–antagonist medications, the nurse should monitor the patient's blood pressure and cardiovascular status.

In chronic treatment, the nurse should assess the patient for common effects such as fatigue, hypotension (especially orthostatic or postural), bradycardia, sleep disturbance, and depression. **TABLE 5-4** lists nursing diagnoses associated with use of β-adrenergic antagonists and the goals associated with them.

Nursing interventions for β-adrenergic antagonists include the following:

- Monitor the blood pressure while the patient is supine, sitting, and standing for the possibility of postural hypotension.
- Teach the patient to minimize postural hypotension:
  - Dangle legs for a few minutes before standing.
  - Rise slowly and stand for a moment.

TABLE 5-4　Nursing Diagnoses Related to β-Adrenergic Antagonist Use

Nursing Diagnoses	Goals
Activity intolerance related to fatigue, lethargy, or depression due to β-adrenergic antagonist administration	Patient will maintain his or her activity level
Altered tissue perfusion related to hypotension or bradycardia related to β-adrenergic antagonist drug	Patient will maintain adequate tissue perfusion
Risk for sleep pattern disturbance related to fatigue, lethargy, and depression	Patient will maintain his or her normal sleep and waking patterns
Alteration in comfort: nausea related to β-adrenergic antagonist drug	Patient will maintain his or her weight
Potential for injury related to potential postural hypotension	Patient will remain injury free and learn to change positions slowly

- Move slowly and do not change positions readily.
- Check with your healthcare provider or pharmacist prior to taking any other prescription or over-the-counter medications.
- Do *not* stop taking the medication abruptly, as this medication needs to be weaned.
- Administer by mouth with milk or food to decrease gastric irritation.

Cholinergic Drugs

Cholinergic drugs are divided into two distinct classes: **cholinergic antagonists** and **cholinergic agonists**. Understanding the normal physiology of cholinergic nerves, acetylcholine, acetylcholinesterase, and cholinergic receptors is necessary to understand the actions of cholinergic drugs.

While drugs affecting the somatic (voluntary) nervous system are beyond the scope of this chapter, acetylcholine is also released at the neuromuscular junction and affects nicotinic acetylcholine receptors at or near postjunctional muscle membranes. When stimulated, nicotinic acetylcholine receptors cause skeletal muscle membrane depolarization and trigger a complex series of subsequent events resulting in muscle contraction. Drugs with cholinergic activity in the ANS may have significant effects on neuromuscular transmission (cholinesterase inhibitors,

e.g., neostigmine), and vice versa (neuromuscular blocking agents, e.g., pancuronium).

There are a number of conditions in which using cholinergic antagonists is not advised (TABLE 5-5). These contraindications arise because such medications may actually exacerbate a disease process in which stimulation of the receptors is already weak, or because the side effects of their use may exacerbate a condition related to the disease process.

CHOLINERGIC AGONISTS

Cholinergic agonists can be separated into two subclasses of drugs: direct-acting acetylcholine receptor agonists (bethanechol) and **indirect-acting** acetylcholinesterase enzyme inhibitors (neostigmine). The actions and adverse drug effects of this class of medications are listed in TABLE 5-6.

Directly-Acting Acetylcholine Receptor Agonist

Bethanechol (Urecholine) is the only commonly used cholinergic agonist. It stimulates muscarinic receptors on the bladder, causing contraction and urination. It also stimulates peristalsis of the urethra and relaxes the external sphincter. Spinal cord injury does not limit the use of bethanechol, as the drug is a direct-acting agonist. This agent is the drug of choice to treat postpartum and postoperative

TABLE 5-5 Contraindications to the Use of Cholinergic Antagonists

Contraindication	Rationale
Myasthenia gravis	Cholinergic antagonists will decrease the effects of the anticholinesterase medications, putting the patient at risk for a myasthenic crisis.
Tachydysrhythmias	Cholinergic antagonists block parasympathetic vagal stimulation, increasing the heart rate and increasing the myocardial oxygen demand.
Myocardial infarction	Cholinergic antagonists increase heart rate, increase myocardial oxygen demand, potentiate arrhythmias, and exacerbate a myocardial infarction.
Glaucoma	With narrow-angle glaucoma, cholinergic antagonists can increase the intraocular pressure and precipitate an occurrence of acute glaucoma.
Prostatic hypertrophy	Cholinergic antagonists affect the muscarinic receptors in the smooth muscle of the bladder and can cause urinary retention.
Hyperthyroidism	Cholinergic antagonists can aggravate the cardiac effects of tachycardia.
Pregnancy and lactation	Most cholinergic antagonists are classified in category C.

TABLE 5-6   Cholinergic Agonist Actions and Adverse Effects

	Cholinergic Agonist Action	Cholinergic Agonist Adverse Drug Effects (ADE)
Cardiovascular	↓ Heart rate, vasodilation	Serious ADE: bradycardia, hypotension
Pulmonary	Bronchoconstriction, ↑ respiratory secretions ↑ Salivation	Serious ADE: bronchoconstriction, ↑ secretions → shortness of breath
Pupils	Constriction (miosis), ↓ intraocular pressure	
Gastrointestinal	↑ Motility, ↑ secretions	Common ADE: ↑ gastric emptying, nausea, abdominal cramping, vomiting, diarrhea
Blood sugar	~	~
Sweating	↑	Diaphoresis, loss of fluids
Urinary	Voiding	Frequency of urination
CNS	~	~
Uses	Limited, but varied: Urinary retention or atony Paralytic ileus Diagnosis and therapy of myasthenia gravis Alzheimer's disease Glaucoma	
	"Wet"	
Drugs	Bethanechol (Urecholine) Neostigmine (Prostigmine) Mestinon Tensilon Aricept	

unobstructed urinary retention. In the gastrointestinal tract, bethanechol stimulates the muscarinic receptors to increase peristalsis and motility, causing defecation.

Acetylcholinesterase Inhibitors

Acetylcholinesterase enzyme inhibitors (or anticholinesterases) block the metabolic effects of the enzyme acetylcholinesterase on the neurotransmitter acetylcholine in both the ANS and the neuromuscular junctions of voluntary skeletal muscle. This inhibition allows acetylcholine to accumulate in synapses

and subsequently increases acetylcholine receptor stimulation. It is important to note that acetylcholinesterase is not selective for the synapses where it acts. Therefore, cholinergic stimulation occurs in all autonomic ganglia, in parasympathetic end-organs (muscarinic effects), and in neuromuscular junctions. Parasympathetic effects predominate due to increased acetylcholine activity at muscarinic sites.

Anticholinesterase agents are used in the management of Alzheimer's disease, for the treatment of delirium, and in the diagnosis and treatment of myasthenia gravis. They are also useful in the indirect reversal of certain paralytic agents by specially trained professionals.

NEOSTIGMINE Neostigmine (Prostigmine) is the prototype of the anticholinesterase drugs. It is also used for the long-term treatment of myasthenia gravis. When used for this purpose, resistance may develop, necessitating administration of larger doses to achieve the same effect. Myasthenia gravis is an autoimmune disease in which antibodies destroy postsynaptic nicotinic acetylcholine receptors in the neuromuscular junction. The levels of acetylcholine are normal, but due to a lack of receptors, the acetylcholine cannot attach to enough receptors to stimulate muscle contraction. This leads to muscle weakness, particularly of the voluntary muscles and often those muscles innervated by the cranial nerves. Symptoms usually include ptosis, diplopia, ataxia, dysarthria, difficulty swallowing, shortness of breath due to chest wall muscle weakness, and weakness in the arms, hands, and legs.

Neostigmine is also indicated to treat urinary retention and paralytic ileus. It is used as an antidote for nondepolarizing skeletal muscle relaxants (paralytic agents) used during surgery.

PHYSOSTIGMINE Physostigmine is useful in the treatment of myasthenia gravis, glaucoma, and impaired gastric motility. Perhaps most importantly, it is useful in the treatment of central toxic effects of atropine and scopolamine because it is the only anticholinesterase drug that crosses the blood–brain barrier in an intact form. It also has been used in the management of delirium associated with anesthesia.

EDROPHONIUM Edrophonium (Tensilon) is a short-acting cholinergic, making it ideal for the diagnosis of myasthenia gravis and to differentiate between myasthenic crisis and cholinergic crisis. When it is given in these situations, life support equipment such as atropine (the antidote), endotracheal tubes, oxygen, and ventilators must be available.

PYRIDOSTIGMINE Pyridostigmine (Mestinon) is similar in actions, uses, and adverse drug effects to neostigmine. Pyridostigmine is the maintenance drug of choice for patients with myasthenia gravis, as it has a long duration of action. It is also available in a slow-release form that is taken at bedtime. Because this agent is effective for 8 to 12 hours, the patient with myasthenia gravis does not have to take other medication at night and wakes strong enough to swallow a morning dose.

DONEPEZIL Donepezil (Aricept) is used to treat mild to moderate Alzheimer's disease. Alzheimer's disease is characterized by a loss of neurons that secrete acetylcholine in the brain. When acetylcholinesterase is blocked, the acetylcholine is not metabolized as quickly, allowing it to have a more prolonged effect at the cholinergic receptor sites. This can help improve memory, attention, reason, language, and the ability to perform simple tasks. Donepezil is given orally and can be taken without regard to meals.

Nursing Considerations for Cholinergic Agonists

ASSESSMENT Assess the patient for possible contraindications such as uncontrolled asthma, active peptic ulcer disease, and cardiovascular disease. Female patients of childbearing age should be assessed for possible pregnancy or breastfeeding, as these drugs should be used only if no other alternatives are available in pregnant or lactating women. Elderly patients may be at greater risk for visual disturbances, so nurses should have a baseline knowledge of their visual capacity for comparison to the patients' experiences during treatment.

In patients with urinary retention, note the last time and amount of the previous urinary output. Note fluid intake and assess for bladder distention. In patients with paralytic ileus, assess for the presence or absence of bowel sounds, abdominal distention, pain, and regular bowel patterns. In patients with myasthenia gravis, assess for muscle weakness such as drooping of the eyelids (ptosis) and double vision (diplopia). In more severe stages of the illness, the patient should be assessed for any difficulty in chewing, swallowing, speaking, or breathing. Assess for respiratory rate, rhythm, and muscle use, as these patients can develop respiratory failure due to muscle weakness. In patients with Alzheimer's disease, memory and cognitive functioning, as well as self-care abilities, should be assessed.

Nursing diagnoses and goals for patients taking cholinergic agonists and acetylcholinesterase inhibitors are found in **TABLE 5-7**.

Nursing Interventions

For patients with urinary retention:

- Ensure there is no obstruction of the urinary tract.
- Consider nonpharmacologic treatments such as providing privacy, bathing the perineum with warm water, and, if possible, allowing the patient to sit up to urinate or ambulate to the bathroom.

For patients with paralytic ileus:

- Ensure there is no obstruction in the gastrointestinal tract.
- Implement preventive measures including early ambulation, adequate fluid intake, providing privacy, and, if possible, allowing the patient to sit up or ambulate to the bathroom.

For patients with myasthenia gravis:

- Schedule activities to allow for periods of rest.
- Encourage the patient to wear a medical alert bracelet.
- With the permission of the patient, involve family members in patient care.
- Suggest a family member be trained in cardiopulmonary resuscitation.

For patients with Alzheimer's disease:

- Encourage self-care activities.
- Maintain a consistent routine.

CHOLINERGIC ANTAGONISTS

Cholinergic antagonists are often referred to as anticholinergic drugs or antimuscarinic drugs. Their actions are limited to muscarinic acetylcholine receptors, where they limit and block the actions of acetylcholine. Muscarinic receptors are found in most internal organs such as those of the cardiovascular, pulmonary, gastrointestinal, and genitourinary systems. Stimulation of the muscarinic receptors causes an increase in secretions. By blocking the action of acetylcholine, anticholinergic drugs decrease the action of acetylcholine on these organs.

Muscarinic receptors are also found on smooth muscle. By blocking the action of acetylcholine at these receptors in the gastrointestinal and urinary tracts, anticholinergic drugs can relax the spasms of smooth muscles.

Clinical Indications for Use

Anticholinergic drugs have multiple actions, so their indications vary. For example, they are used to treat spastic and hyperactive conditions of the gastrointestinal and urinary tracts, as anticholinergic drugs inhibit smooth muscle contraction and decrease gastrointestinal secretions.

Anticholinergic agents are used preoperatively to decrease respiratory and gastrointestinal secretions and to prevent a drop in the heart rate caused by vagal stimulation during intubation. Such drugs are used in ophthalmology because they cause mydriasis (pupil dilation), which facilitates examination and ocular surgical procedures. Other uses of anticholinergic drugs include the treatment of Parkinson's

TABLE 5-7 Cholinergic Agonists and Anticholinesterases: Nursing Diagnoses and Goals

Nursing Diagnoses	Nursing Goals
Ineffective airway clearance related to increased respiratory secretions and bronchoconstriction	Patient will maintain effective oxygenation of tissues
Self-care deficits related to cognitive impairment, diplopia, or muscle weakness	Patient will be encouraged to do what he or she is capable of
Ineffective elimination patterns	Patient will maintain or attain normal elimination patterns
Knowledge deficit related to drug administration and effects	Patient will verbalize why this drug is being used and signs or symptoms to report to the healthcare provider

disease, to decrease salivation, spasticity, and tremors; the treatment of asthma and COPD, as they produce bronchodilation and drying of the respiratory sections; and the treatment of symptomatic bradycardia.

The adverse effects of anticholinergic drugs are closely related to the dose administered. Only a narrow margin separates the therapeutic dose and a toxic dose with these agents. The major adverse anticholinergic drug effects include tachycardia, dried bronchial secretions, dry mouth, blurred vision, and decreased sweating. As noted in Table 5-6, there are specific conditions in which cholinergic antagonists are contraindicated because they may interact with pharmacotherapeutic interventions or worsen symptoms of the underlying pathology.

Individual Cholinergic Antagonists

ATROPINE Atropine is the prototype anticholinergic drug. It is absorbed by the gastrointestinal tract and distributed throughout the body. Atropine crosses the blood–brain barrier. In the CNS, a therapeutic dose produces stimulant effects, whereas toxic doses produce depressant effects. When applied to mucous membranes, atropine is absorbed systemically. This agent has a short duration of action.

According to *Advanced Cardiac Life Support Guidelines*, atropine is the drug of choice in the treatment of symptomatic bradycardia. However, it is no longer recommended for the treatment of pulseless electrical activity or asystole (American Heart Association, 2010).

Atropine given preoperatively can avert the vagal stimulation that often accompanies endotracheal intubation, causing bradycardia and hypotension. This agent is also useful in drying respiratory secretions prior to head and neck surgery.

Atropine is used to treat the excessive cholinergic stimulation caused by anticholinesterase toxicity, mushroom poisoning, some nerve gases (Sarin) used for chemical warfare, and some organophosphate pesticide poisoning.

GLYCOPYRROLATE Glycopyrrolate does not cross the blood–brain barrier and, therefore, is devoid of

central effects. This agent increases heart rate and blood pressure, but to a lesser extent than atropine.

SCOPOLAMINE Scopolamine exerts minimal effects on heart rate and blood pressure. However, it has significant central effects and produces profound mydriasis. In high doses, it can cause central toxicity, which manifests as dry mouth, rubor, cycloplegia, and delirium. Central toxicity is an emergency and may be treated with the anticholinesterase drug physostigmine. Administration of scopolamine by cutaneous patch reduces nausea and vomiting due to anesthesia or motion (sea sickness, car sickness).

IPRATROPIUM Ipratropium (Atrovent) can be used as an inhalation treatment for COPD to produce bronchodilation. It is also used as a nasal spray to relieve rhinorrhea. When ipratropium is administered by spray or inhalation, the bronchial secretions are decreased and there is less risk of mucous plugs forming.

TIOTROPIUM BROMIDE Tiotropium bromide (Spiriva) is a long-acting antimuscarinic, anticholinergic agent that produces bronchodilation. It is administered as a dry-powder capsule with a HandiHaler device. This agent is indicated for use as a daily maintenance treatment in patients with COPD; it is not recommended for treating acute episodes.

BENZTROPINE Benztropine (Cogentin) is a centrally acting anticholinergic drug. It is more selective for muscarinic receptors in the CNS, so it also produces fewer adverse drug effects. Benztropine can be used to decrease the symptoms of Parkinson's disease, such as tremors, spasticity, and salivation. This agent is usually prescribed in the early stages of the disease and in patients who have demonstrated a minimal response to levodopa, which is the treatment of choice for Parkinson's disease.

OXYBUTYNIN Oxybutynin (Ditropan, Ditropan XL, and Oxytrol transdermal) increases bladder capacity and decreases voiding frequency by exerting a direct antispasmodic effect on smooth muscle and anticholinergic effects.

Nursing Process for Cholinergic Antagonists

ASSESSMENT The assessment should identify whether the patient is on any other medications with anticholinergic effects, such as antihistamines, antipsychotic agents, or tricyclic antidepressants, as this combination could cause an adverse interaction. Similarly, the nurse should assess for any condition in which the anticholinergic drug would be contraindicated, such as glaucoma, myasthenia gravis, hyperthyroidism, prostatic hypertrophy, tachyarrhythmia, or myocardial infarction. Female patients of childbearing age should be assessed for pregnancy or breastfeeding, as these drugs should be used in such women only if no other alternatives are available. Elderly patients may be at greater risk for most adverse effects and heat stroke.

During the assessment, note the condition for which the patient was prescribed an anticholinergic drug, such as bradycardia, diarrhea, enuresis, Parkinson's disease, asthma, COPD, or other disorders. Note any indications of adverse drug effects such as tachycardia, dried bronchial secretions, dry mouth, blurred vision, and decreased sweating.

Nursing diagnoses and goals related to anticholinergic drugs are listed in **TABLE 5-8**.

Nursing Interventions

- Teach the patient why the drug is being prescribed and how to take it correctly.
- Teach the patient about the potential adverse drug effects.

TABLE 5-8 Anticholinergic Drugs: Nursing Diagnoses and Goals

Nursing Diagnoses	Nursing Goals
Decreased cardiac output related to bradycardia	Patient will attain a heart rate of 60 to 100 beats per minute
Ineffective airway clearance related to increased respiratory secretions and bronchoconstriction	Patient will maintain effective oxygenation of tissues
Ineffective elimination patterns	Patient will maintain or attain normal elimination patterns
Knowledge deficit related to drug administration and effects	Patient will verbalize why this drug is being used and signs or symptoms to report to the healthcare provider
Risk for noncompliance related to adverse drug effects	Patient will verbalize the need to take the medication as prescribed

- Have the patient protect his or her eyes from the sun with sunglasses.
- To alleviate a dry mouth and to prevent tooth decay, sip on cold water, suck on sugarless hard candies, chew sugarless gum, and use frequent oral hygiene.
- Increase fluid and fiber in the diet to prevent constipation.
- Avoid any over-the-counter or prescription drugs without first checking with the healthcare provider.
- Avoid overheating by staying in air conditioning, drinking fluids, and taking frequent showers or sponge baths.

CHAPTER SUMMARY

- The ANS is composed of three interconnected systems that manage involuntary functions: the SNS, the PNS, and the ENS.

- The SNS is responsible for "fight-or-flight" responses, while the PNS is characterized as the "rest and repair" system; the two work in tandem, and the ENS (which innervates the digestive tract) interacts with both.

- The SNS is also called the thoracolumbar system, and the PNS is called the craniosacral system, reflecting the locations from which preganglionic nerves originate in each of the respective divisions.

- Preganglionic nerves may be sympathetic or parasympathetic, and in both cases they are cholinergic nerves that release acetylcholine.

- The receptors at ganglia for both the SNS and the PNS are nicotinic acetylcholine receptors.

- Postganglionic sympathetic nerves release norepinephrine, which stimulates adrenergic receptors at effector organs.

- Postganglionic parasympathetic nerves release acetylcholine, which stimulates muscarinic acetylcholine receptors at effector organs.

- Medications that affect the ANS often mimic or block the actions of acetylcholine or norepinephrine. These actions can provide therapeutic effects by either reducing stress on effector organs such as the heart, lungs, or kidneys, or increasing the output of these organs in cases where function is sub-par.

- Some medications that have generalized, rather than targeted, effects on receptors can also promote unwanted side effects. Understanding how each type of medication affects the receptors is therefore necessary for optimal disease management.

Case Study 1

A 12-year-old boy is stung by a bee while playing in his backyard. In the past, he has had severe reactions to insect stings, which required emergency room visits and the dispensing of an epinephrine injector (EpiPen). On this occasion, by the time he reaches the door to tell his mother, he is covered in hives, is audibly wheezing, and passes out suddenly in the foyer. His mother immediately calls 911 and administers the prescribed intramuscular epinephrine dose into the boy's thigh with the EpiPen. The child recovers consciousness rapidly; at the arrival of the ambulance, he is breathing easier and complaining of itching all over. Paramedics report normal blood pressure and tachycardia.

Case Questions

1. Given the patient's symptoms, what is the likely medical problem?

2. The administration of epinephrine using the EpiPen caused a rapid improvement in the patient's symptoms. Which adrenergic receptors were likely stimulated by the medication, and what response did these invoke that improved his breathing?

3. Which adrenergic receptors were stimulated to restore the patient's normal blood pressure and return to consciousness, and what response did this invoke?

4. Which adrenergic receptors must be stimulated to relieve the patient's tachycardia, and what response did this invoke?

Case Study 2

Mr. Walker enjoys cooking and prefers to eat locally grown food when it is available. While hiking on a trail through the woods, he finds a new crop of mushrooms growing by a log. Thinking about how good fresh sautéed mushrooms would be with his dinner that evening, Mr. Walker gathers the mushrooms.

When he arrives home, he cleans the mushrooms and eats a few of them as he works. Twenty minutes later, he is salivating and sweating, his vision is blurry, and he has difficulty breathing. He calls 911.

Case Questions

1. Which branch of the ANS has been stimulated?

2. What is causing the symptoms?

3. What is the antidote?

4. Why is the antidote effective in this case of mushroom poisoning?

Discussion Questions

1. What are the components of the ANS? Which functions does the ANS control?

2. What does the SNS control? How does it differ from the PNS?

3. Where is acetylcholine released? Where is norepinephrine released? Which receptors do each of these neurotransmitters utilize?

4. Which types of drugs would have a positive effect on bronchoconstriction? Which drugs should be *avoided* in patients who suffer from bronchoconstriction?

5. Name the adrenergic receptors and identify a key function for each receptor.

6. Which conditions are contraindications for cholinergic antagonists?

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