

Cholinergic Drugs

Key Terms

acetylcholine

acetylcholinesterase

cholinergic crisis

glaucoma

micturition

myasthenia gravis

parasympathomimetic

drugs

Chapter Objectives

On completion of this chapter, the student will:

- Discuss important aspects of the parasympathetic nervous system.
- Discuss the uses, drug actions, general adverse reactions, contraindications, precautions, and interactions of the cholinergic drugs.
- Identify important preadministration and ongoing assessment activities the nurse should perform on the patient taking cholinergic drugs.
- List some nursing diagnoses particular to a patient taking cholinergic drugs.
- Discuss ways to promote an optimal response to therapy, how to manage common adverse reactions, and important points to keep in mind when educating the patient about the use of cholinergic drugs.

Cholinergic drugs mimic the activity of the parasympathetic nervous system (PNS). They also are called **parasympathomimetic drugs**. An understanding of the PNS is useful in understanding the cholinergic drugs.

PARASYMPATHETIC NERVOUS SYSTEM

The PNS is a part of the autonomic nervous system (see Chap. 22). It helps conserve body energy and is partly responsible for activities such as slowing the heart rate, digesting food, and eliminating body wastes.

Electron microscopic study reveals an incalculably small space between nerve endings and the effector organ (eg, the muscle, cell, or gland) that is innervated (or controlled) by a nerve fiber. For a nerve impulse to be transmitted from the nerve ending (motor end plate) across the space to the effector organ, a neurohormone is needed.

The PNS has two neurohormones (neurotransmitters): **acetylcholine** (ACh) and **acetylcholinesterase** (AChE). ACh is a neurotransmitter responsible for the transmission of nerve impulses to effector cells of the parasympathetic nervous system. ACh plays an important role in the transmission of nerve impulses at synapses and myoneural junctions. ACh is quickly

destroyed by the enzyme AChE, thereby allowing the nerve impulse to pass, but not remain in an excited state.

These two neurohormones are released at nerve endings of parasympathetic nerve fibers, at some nerve endings in the sympathetic nervous system, and at nerve endings of skeletal muscles. These parasympathetic neurohormones are believed to be manufactured by special cells located in the nerve ending. When a parasympathetic nerve fiber is stimulated, the nerve fiber releases ACh, and the nerve impulses pass (travel) from the nerve fiber to the effector organ or structure. After the impulse has crossed over to the effector organ or structure, ACh is inactivated (destroyed) by the neurohormone AChE. When the next nerve impulse is ready to travel along the nerve fiber, ACh is again released and then inactivated by AChE.

CHOLINERGIC DRUGS

Cholinergic drugs have limited usefulness in medicine, partly because of the adverse reactions that may occur during administration. However, in some diseases or conditions cholinergic drugs are either definitely indicated or may be of value.

ACTIONS

Cholinergic drugs may act like the neurohormone ACh or they may inhibit the release of the neurohormone AChE. Cholinergic drugs that act like ACh are called direct-acting cholinergics. If a cholinergic drug inhibits the body's release of AChE, it prolongs the activity of the ACh produced by the body. Cholinergic drugs that prolong the activity of ACh by inhibiting the release of AChE are called indirect-acting cholinergics. Although a specific cholinergic drug may act in either of these two ways, the results of drug action are basically the same.

USES

The major uses of the cholinergic drugs are in the treatment of glaucoma, myasthenia gravis, and urinary retention.

Glaucoma is a disorder of increased pressure within the eye caused by an obstruction of the outflow of aqueous humor through the canal of Schlemm. In the normal eye the aqueous humor flows from the ciliary body to the posterior chamber of the eye, through the pupil, and out the canal of Schlemm into the venous circulation (Fig. 24-1). This flow of aqueous humor keeps the pressure within the eye within normal limits. Glaucoma may be treated by topical application (eg, eye drops) of a cholinergic drug, such as carbachol or pilocarpine (Isopto Carpine). Treatment of glaucoma with a cholinergic drug produces miosis (constriction of the iris). This opens the blocked channels and allows the normal passage of aqueous humor, thus reducing intraocular pressure.

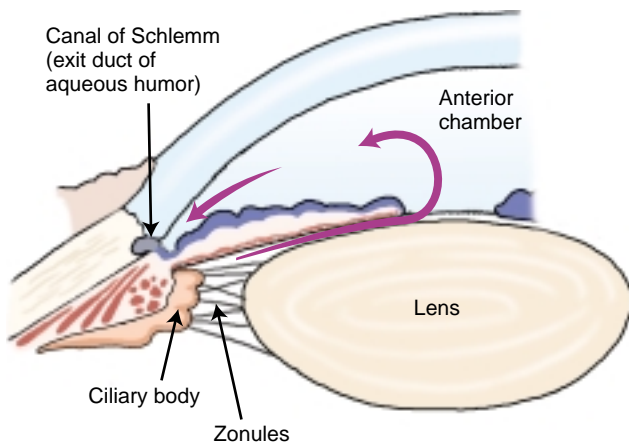


FIGURE 24-1. In the normal eye, aqueous humor flows through the ciliary body into the posterior chamber, through the pupil into the anterior chamber, and out through the trabecular meshwork to the canal of Schlemm into the venous circulation.

Myasthenia gravis is a disease that involves rapid fatigue of skeletal muscles because of the lack of ACh released at the nerve endings of parasympathetic nerve fibers. Drugs used to treat this disorder include ambenonium (Mytelase) and pyridostigmine (Mestinon).

Urinary retention (not caused by a mechanical obstruction, such as a stone in the bladder or an enlarged prostate) results when **micturition** (voiding of urine) is impaired. Micturition is both a voluntary and involuntary act. The PNS partly controls the process of micturition by constricting the detrusor muscle and relaxing the bladder sphincter (see Table 22-1). Treatment of urinary retention with cholinergic drugs, such as ambenonium, bethanechol chloride (Urecholine), or pyridostigmine results in the spontaneous passage of urine.

ADVERSE REACTIONS

Unless applied topically, as in the treatment of glaucoma, cholinergic drugs are not selective in action. Therefore, they may affect many organs and structures of the body, causing a variety of adverse effects. Oral or parenteral administration can result in nausea, diarrhea, abdominal cramping, salivation, flushing of the skin, cardiac arrhythmias, and muscle weakness. Topical administration usually produces few adverse effects, but a temporary reduction of visual acuity (sharpness) and headache may occur. The Summary Drug Table: Cholinergic Drugs lists the adverse reactions that may be seen with specific cholinergic drugs.

CONTRAINDICATIONS

These drugs are contraindicated in patients with known hypersensitivity to the drugs, asthma, peptic ulcer disease, coronary artery disease, and hyperthyroidism. Bethanechol is contraindicated in those with mechanical obstruction of the gastrointestinal or genitourinary tracts. Patients with secondary glaucoma, iritis, corneal abrasion, or any acute inflammatory disease of the eye should not use the ophthalmic cholinergic preparations.

PRECAUTIONS

These drugs are used cautiously in patients with hypertension, epilepsy, cardiac arrhythmias, bradycardia, recent coronary occlusion, and megacolon. The safety of these drugs has not been established for use during pregnancy (Pregnancy Category C), lactation, or in children.

SUMMARY DRUG TABLE CHOLINERGIC DRUGS

GENERIC NAME	TRADE NAME*	USES	ADVERSE REACTIONS	DOSAGE RANGES
ambenonium <i>am-be-noe'-nee-um</i>	Mytelase	Myasthenia gravis	Increased bronchial secretions, cardiac arrhythmias, muscle weakness, urinary frequency	5–75 mg PO TID, QID
bethanechol chloride <i>be-than'-e-kole</i>	Duvoid, Urecholine, <i>generic</i>	Acute nonobstructive urinary retention, neurogenic atony of urinary bladder with urinary retention	Abdominal discomfort, diarrhea, nausea, vomiting, salivation, urgency, flushing, sweating	10–50 mg PO BID to QID; 2.5–5 mg SC TID to QID
carbachol, topical <i>kar'-ba-kole</i>	Isopto Carbachol, Miostat	Glaucoma	Temporary reduction of visual acuity, headache	1–2 drops in eye up to 3 times/d
edrophonium <i>ed-roe-fone'-ee-yum</i>	Enlon, Tensilon	Diagnosis of myasthenia gravis	Increased bronchial secretions, cardiac arrhythmias, muscle weakness, urinary frequency	2–10 mg IV, look for cholinergic reaction
neostigmine <i>nee-oh-stig'-meen</i>	Prostigmin, <i>generic</i>	Myasthenia gravis, urinary retention	Cardiac arrhythmias, vomiting, bowel cramps, increased peristalsis, urinary frequency, flushing, weakness, diaphoresis, nausea, diarrhea, salivation	Myasthenia gravis: maintenance dose 15–375 mg/d PO; 0.5–1 mg IM, SC q4–6h PRN
pilocarpine hydrochloride <i>pye-loe-kar'-peen</i>	Isopto Carpine, Pilocar, <i>generic</i>	Glaucoma	Temporary reduction in visual acuity, headache	1–2 gtts TID in eye 1–6 times/d
pilocarpine ocular therapeutic system <i>pye-loe-kar'-peen</i>	Ocusert	Elevated intraocular pressure	Temporary reduction in visual acuity, headache, redness, burning, iris cysts	1 U placed in the conjunctival sac, replaced as directed by the physician (usually every 7 d)
pyridostigmine bromide <i>peer-id-oh-stig'-meen</i>	Mestinon, Regonol	Myasthenia gravis	Increased bronchial secretions, cardiac arrhythmias, muscle weakness	Average dose is 600 mg/d PO at spaced intervals, with doses as low as 60 mg/d and as high as 1,500 mg/d

*The term *generic* indicates the drug is available in generic form.

INTERACTIONS

When the cholinergic drugs are administered with other cholinergics, there is an increase in the effects of the drugs and greater risk for toxicity. Concurrent use of the anticholinergic drugs antagonizes the effects of the cholinergic drugs. Because of this property, atropine is considered an antidote for overdosage of the cholinergic drugs. Carbachol and pilocarpine produce an additive effect when used concurrently. The effects of the cholinergic drugs, particularly edrophonium, neostigmine, and pyridostigmine, are decreased with possible muscular depression when administered with the corticosteroids.

NURSING PROCESS

● The Patient Receiving a Cholinergic Drug

ASSESSMENT

Preadministration Assessment

The preadministration assessment depends on the drug and the reason for administration.

GLAUCOMA. Before therapy for glaucoma is started, the primary health care provider thoroughly examines the eye. The nurse reviews the primary health care provider's diagnosis and comments, takes a general patient health

history, and evaluates the patient's ability to carry out the activities of daily living, especially if the patient is elderly or has limited vision.

MYASTHENIA GRAVIS. Before the nurse gives a cholinergic drug to a patient with myasthenia gravis, the primary health care provider performs a complete neurologic assessment. The nurse assesses for signs of muscle weakness, such as drooling (ie, the lack of ability to swallow), inability to chew and swallow, drooping of the eyelids, inability to perform repetitive movements (eg, walking, combing hair, using eating utensils), difficulty breathing, and extreme fatigue.

URINARY RETENTION. If a patient receives a cholinergic drug for the treatment of urinary retention, the nurse palpates the abdomen in the pelvis area to determine if distention is present. A rounded swelling over the pelvis usually indicates retention and a distended bladder. The patient may also complain of discomfort in the lower abdomen. In addition, the nurse takes the patient's blood pressure and pulse rate.

Ongoing Assessment

While the patient is receiving a cholinergic drug it is important for the nurse to monitor for drug toxicity or cholinergic crisis.

Nursing Alert

Symptoms of cholinergic crisis (cholinergic drug toxicity) include severe abdominal cramping, diarrhea, excessive salivation, muscle weakness, rigidity and spasm, and clenching of the jaw. Patients exhibiting these symptoms require immediate medical treatment and their condition must be immediately reported to the primary health care provider. In the case of overdose, an antidote such as atropine and other treatment also may be prescribed. The usual dosage of atropine is 0.4 to 0.6 mg IV.

GLAUCOMA. When a cholinergic drug is used to treat glaucoma, the nurse checks the eye and the area around the eye daily for evidence of redness, inflammation, and excessive secretions, particularly if the ocular system is used. If secretions are present around the eye, the nurse removes them with a cotton ball or gauze soaked in normal saline or other cleansing solution recommended by the primary health care provider.

MYASTHENIA GRAVIS. Once therapy is under way, the nurse must document any increase in the symptoms of the disease or adverse drug reactions before giving each dose of the drug. The nurse assesses the patient for the presence or absence of the symptoms of myasthenia gravis before each drug dose. In patients with severe

myasthenia gravis, the nurse can carry out these assessments between drug doses, as well as immediately before drug administration. The nurse documents each symptom, as well as the patient's response or lack of response to drug therapy.

Assessment is important because the dosage frequently has to be increased or decreased early in therapy, depending on the patient's response. Regulation of dosage is important in keeping the symptoms of myasthenia gravis from incapacitating the patient. For many patients, the symptoms are fairly well controlled with drug therapy once the optimal drug dose is determined.

URINARY RETENTION. The ongoing assessment for a patient with urinary retention includes measuring and recording the fluid intake and output. The nurse must notify the primary health care provider if the patient fails to void after drug administration.

If a cholinergic drug is ordered for the prevention of urinary retention, the nurse measures and records the fluid intake and output. If the amount of each voiding is insufficient or the patient fails to void, the nurse palpates the bladder to determine its size and notifies the primary health care provider.

NURSING DIAGNOSES

Drug-specific nursing diagnoses are highlighted in the Nursing Diagnoses Checklist. Other nursing diagnoses applicable to these drugs are discussed in depth in Chapter 4.

PLANNING

The expected outcomes of the patient depend on the reason for administration of the cholinergic drug but may include an optimal response to therapy, management of common adverse drug effects, and an understanding of and compliance with the prescribed therapeutic regimen.

IMPLEMENTATION

Promoting an Optimal Response to Therapy

The care of a patient receiving a cholinergic drug depends on the drug used, the reason for administration, and the patient's response to the drug.

Nursing Diagnoses Checklist

- ✓ **Disturbed Sensory Perception: Visual** related to adverse drug reactions or increased pressure within the eye
- ✓ **Risk for Injury** related to muscular weakness, rigidity, or spasms due to drug overdose
- ✓ **Diarrhea** related to adverse drug reaction

MANAGING GLAUCOMA. The nurse checks the primary health care provider's order and the drug label carefully when instilling any ophthalmic preparation. The drug label must indicate that the preparation is for ophthalmic use. In addition, the nurse should check the name of the drug and the drug dosage or strength as stated on the label against the primary health care provider's orders. The nurse instills the drug in the lower conjunctival sac unless the primary health care provider orders a different method of instillation. The nurse supports the hand holding the dropper against the patient's forehead. The tip of the dropper must never touch the eye.

In some instances, the patient may have been using an ophthalmic preparation for glaucoma for a long time, and the primary health care provider may allow the hospitalized patient to instill his or her own eye drops. When this is stated on the patient's order sheet, the nurse can leave the drug at the patient's bedside. Even though the drug is self-administered, the nurse checks the patient at intervals to be sure that the drug is instilled at the prescribed time using the correct technique for ophthalmic instillation.

Pilocarpine Ocular System. If the pilocarpine ocular system is prescribed for the hospitalized patient, the nurse checks the cheek and eye area several times a day because the system can become displaced from the eye.

Gerontologic Alert

Most patients are usually aware of displacement of the pilocarpine ocular system, but some patients, the elderly in particular, may not realize that the system has come out of the eye. If displacement does occur, the nurse inserts a new system and informs the primary health care provider of the problem.

On occasion, patients cannot insert the system by themselves or cannot retain the system in the eye for the required time. When this occurs, the nurse notifies the primary health care provider because the ocular system should remain in place until it is time for it to be changed. The nurse changes the pilocarpine ocular system every 7 days unless the primary health care provider orders otherwise (Display 24-1).

If patients have a problem retaining the system, placing the system in the upper conjunctival cul-de-sac is preferable. The nurse can manipulate the system from the lower to the upper conjunctival cul-de-sac using gentle massage through the eyelid. The nurse contacts the primary health care provider if the symptoms of glaucoma increase, if the patient is unable to retain the ocular system, or if redness, eye irritation, or excessive secretions are noted.

MANAGING MYASTHENIA GRAVIS. In the beginning, determining the dosage that will control symptoms may be difficult. In many cases, the dosage must be adjusted upward or downward until optimal drug effects are obtained. Patients with severe symptoms of the disease require the drug every 2 to 4 hours even during the night. Sustained-released tablets are available that allow less frequent dosing and help the patient to have longer undisturbed periods during the night.

Nursing Alert

Because of the need to make frequent dosage adjustments, the nurse should observe the patient closely for symptoms of drug overdosage or underdosage. Signs of drug overdosage include muscle rigidity and spasm, salivation, and clenching of the jaw. Signs of drug underdosage are signs of the disease itself, namely, rapid fatigability of the muscles, drooping of the eyelids, and difficulty breathing. If symptoms of drug overdosage or underdosage develop, the nurse should contact the primary health care provider immediately because a change in dosage is usually necessary.

MANAGING URINARY RETENTION. Voiding usually occurs in 5 to 15 minutes after subcutaneous drug administration and 30 to 90 minutes after oral administration. The nurse should place the call light and any other items the patient might need, such as the urinal or the bedpan, within easy reach. However, some patients are not able to reach or handle these aids easily, so the nurse must promptly answer their call light.

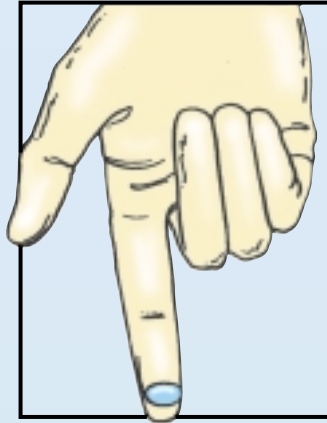
Monitoring and Managing Adverse Reactions

When a cholinergic drug is given by the oral or parenteral route, adverse drug reactions may affect many systems of the body, such as the heart, respiratory and gastrointestinal tracts, and the central nervous system. The nurse observes the patient closely for the appearance of adverse drug reactions, such as a change in vital signs or an increase in symptoms. The nurse documents any complaints the patient may have and notifies the primary health care provider.

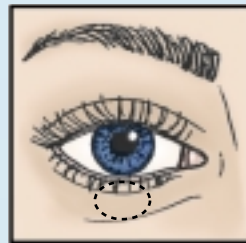
DISTURBED SENSORY PERCEPTION: VISUAL. Because drug-induced myopia (nearsightedness) may occur after instillation of a cholinergic ophthalmic drug for the treatment of glaucoma, the nurse assists the patient in getting out of bed or ambulating. Keeping the patient's room dimly lit at night is helpful because night vision may be decreased. Obstacles that may hinder ambulation or result in falls, such as slippers, chairs, and tables, are placed out of the way, especially during the night.

DISPLAY 24-1 • Inserting the Pilocarpine Ocular System

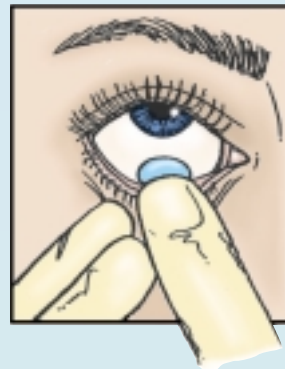
1. Wash hands and put on gloves. Press the disk with the fingertip until it remains on the finger as shown.



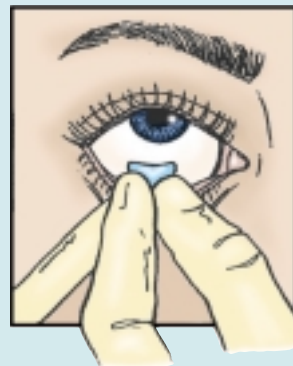
2. Have the patient look up. Pull the lower conjunctiva away from the eye and gently place the disk in the lower conjunctival sac. The disk should float on the sclera.



3. Pull the lower conjunctiva over the disk. Check for correct position. The disk should not be visible. If the disk is still seen, the eyelid must be repositioned by pulling the lower conjunctiva out and over the disk again.



4. Use gloves when removing the disk. Pull the lower eyelid down and use the thumb and first finger of the free hand to lift the disk out of the eye as shown.



(Adapted from Nursing94, June, Intraocular Drug Administration, pp. 44–45, which was adapted from *Giving drugs by advanced techniques* [1993]. Springhouse, PA: Springhouse Corp.)

DIARRHEA. When these drugs are used orally they occasionally result in excessive salivation, abdominal cramping, flatus, and sometimes diarrhea. The patient is informed that these reactions will continue until tolerance develops, usually within a few weeks. Until tolerance develops, the nurse ensures that proper facilities, such as a bedside commode, bedpan, or bathroom, are readily available. The patient is encouraged to ambulate to assist the passing of flatus. If needed, a rectal tube may be used to assist in the passing of flatus. The nurse keeps a record of the fluid intake and output and the number, consistency, and frequency of stools if diarrhea is present. The primary health care provider is informed if diarrhea is excessive because this may be an indication of toxicity.

Educating the Patient and Family

Patients required to take a drug over a long period may incur lapses in their drug schedule. For some, it is a matter of occasionally forgetting to take a drug; for others, a lapse may be caused by other factors, such as failure to understand the importance of drug therapy, inability to instill an eye drug (when the drug is prescribed for glaucoma), the cost of the drug, or unfamiliarity with the consequences associated with discontinuing the drug therapy.

When developing a teaching plan for the patient and family, the nurse emphasizes the importance of uninterrupted drug therapy. The nurse allows the patient and family time to ask questions. The nurse explores any problems that appear to be associated with the prescribed drug regimen and then reports them to the primary health care provider. The nurse reviews the purpose of the drug therapy with the patient and family, as well as the adverse reactions that may occur.

GLAUCOMA. When a cholinergic drug is prescribed for glaucoma, the nurse instructs the patient and a family member in instillation of the eye drops (see Patient and Family Teaching Checklist: Instilling Liquid Eye Medications).

If a family member is to instill the drug, the nurse allows time for instruction as well as supervised practice of the procedure. The nurse warns the patient that the eye drops may sting when instilled into the eye and that this is a normal, but often temporary, discomfort. The nurse advises the patient to observe caution while driving or performing any task that requires visual acuity.

Local irritation and headache may occur at the beginning of therapy. The patient is instructed to notify the primary health care provider if abdominal cramping, diarrhea, or excessive salivation occurs.

PILOCARPINE OCULAR SYSTEM. If the pilocarpine ocular system is prescribed, the primary health care provider must evaluate the patient's ability to insert and remove the system. A package insert is provided with the system



Patient and Family Teaching Checklist

Instilling Liquid Eye Medications

The nurse:

- ✓ Explains the importance of keeping the bottle tightly closed.
- ✓ Stresses that the tip of the dropper should not be washed.
- ✓ States that the dropper should not be put down on a table or other surface.
- ✓ Demonstrates support of the hand holding the dropper against the forehead.
- ✓ Cautions against letting the tip of the dropper touch the eye.
- ✓ States that the dropper should be put back in the bottle immediately after use.
- ✓ Instructs on tilting the head back and instilling the prescribed number of drops in the inner lower eyelid (lower conjunctival sac).
- ✓ Demonstrates applying light finger pressure to the inner corner of the eye (lacrimal sac) for about 1 minute after instillation (teaching the use of this maneuver should be approved by the primary health care provider).
- ✓ Explains that if the patient or caregiver is unable to instill eye drops, the primary health care provider should be contacted immediately.

and the nurse reviews this with the patient. The nurse instructs the patient to remove and replace the system every 7 days or as instructed by the primary health care provider. Replacement is best done at bedtime (unless the primary health care provider orders otherwise) because there is some impairment of vision for a short time after insertion. The nurse tells the patient to check for unit placement before retiring at night and in the morning on arising. The nurse notifies the primary health care provider if eye secretions are excessive or irritation occurs.

MYASTHENIA GRAVIS. Many patients with myasthenia gravis learn to adjust their drug dosage according to their needs because dosages may vary slightly from day to day. The nurse teaches the patient and family members to recognize symptoms of overdosage and underdosage, as well as what steps the primary health care provider wishes them to take if either occurs. The dosage regimen is explained and instruction is given in how to adjust the dosage upward or downward.

The nurse gives the patient a written or printed description of the signs and symptoms of drug overdosage or underdosage. The nurse instructs the patient

to keep a record of the response to drug therapy (eg, time of day, increased or decreased muscle strength, fatigue) and to bring this to each primary health care provider or clinic visit until the symptoms are well controlled and the drug dosage is stabilized. These patients must wear or carry identification (such as a Medic-Alert tag) indicating that they have myasthenia gravis.

EVALUATION

- The therapeutic effect is achieved.
- Adverse reactions are identified, reported to the primary health care provider, and managed successfully through appropriate nursing interventions.
- The patient verbalizes the importance of complying with the prescribed treatment regimen.
- The patient complies with the prescribed drug regimen.
- The patient and family demonstrate understanding of the drug regimen.

● Critical Thinking Exercises

1. Mr. Johnson, age 78 years, has glaucoma and is prescribed the pilocarpine ocular system. On a visit to the outpatient clinic, Mr. Johnson tells you that he is having problems retaining the ocular system. You notice that his right eye is very red and inflamed. Determine how you can investigate this problem further with Mr. Johnson. Provide suggestions that will help Mr. Johnson to retain the system.
2. Mr. Hopkins, aged 32 years, has myasthenia gravis. Explain to Mr. Hopkins the symptoms he should be aware of that would indicate toxicity.
3. Discuss the types of ongoing assessments made when a patient takes a cholinergic drug for urinary retention.

● Review Questions

1. A patient with glaucoma is prescribed pilocarpine eye drops. One adverse reaction that the nurse will expect with the use of this drug is _____.

- A. a temporary loss of visual acuity
 - B. pain in the affected eye
 - C. excessive tearing of both eyes
 - D. mydriasis of the eyes
2. The primary care provider allows the patient to keep pilocarpine eye drops at the bedside and to self-administer the eye drops 4 times daily. The nurse _____.
 - A. need not check with the patient concerning the eye drops because the patient is a responsible adult
 - B. must check the patient to be sure the medication is used properly and at the right time
 - C. is not responsible for monitoring the patient's response to the medication
 - D. does not record the administration of the drug in the patient's chart
 3. Ms. Martin has received a diagnosis of myasthenia gravis and begins a regimen of ambenonium. The nursing assessment is important because the dose of the drug _____.
 - A. usually must be increased every 4 hours early in therapy
 - B. frequently is increased or decreased early in therapy
 - C. is titrated according to the patient's blood pressure
 - D. is gradually decreased as a therapeutic response is achieved

● Medication Dosage Problems

1. The dosage of neostigmine is 0.022 mg/kg. What dosage would the nurse expect the primary care provider to prescribe for a patient who weighs 150 pounds?
2. The primary care provider prescribes 2.5 mg of bethanechol subcutaneously. The drug is available in a solution of 5 mg/mL. The nurse administers _____.