Review Article

Drug Therapy

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MEDICAL MANAGEMENT OF GLAUCOMA

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GLAUCOMA is the leading cause of irreversible blindness in the world. It is estimated that by the year 2000, 66.8 million people will be affected, of whom 6.7 million will be blind in both eyes.[1] Glaucoma is an optic neuropathy in which the axons of the optic nerve die and the plates of lamina cribrosa collapse, leading to loss of optic-nerve tissue and excavation, or "cupping," of the ophthalmoscopically visible optic-nerve head. When sufficient axonal loss occurs, peripheral vision declines; loss of central vision occurs much later. Most forms of glaucoma are painless, and the loss of vision is insidious.

DIAGNOSIS

Glaucoma can readily be diagnosed before vision loss occurs by ophthalmoscopic examination of the optic nerve to detect cupping. This is particularly important in the case of patients who have one or more of the four major risk factors for primary open-angle glaucoma (the most common type of glaucoma): advanced age, black race, a family history of glaucoma, and elevated intraocular pressure.[2] The last is not part of the definition of glaucoma but is a risk factor for its development. Intraocular pressure is measured most accurately by determination of the force required to flatten the central cornea (a process known as applanation). Applanation tonometry can be performed with an optical measuring device (Goldmann's tonometer) or an electrical strain gauge; both are accurate but relatively expensive. Alternatively, one can measure how far a fixed, weighted plunger can indent the cornea. Although less accurate than applanation tonometers, the Schiøtz indentation tonometer is inexpensive and frequently used in hospitals and clinics. The mean intraocular pressure in normal adults is 15 to 16 mm Hg; the normal range (mean ±2 SD) is 10 to 21 mm Hg.[3,4] The distribution of intraocular pressures is not a true Gaussian curve but, rather, is skewed toward high intraocular pressures. Up to 10 percent of people over the age of 40 years have intraocular pressures above 21 mm Hg[2]; those who have such high pressures but no optic-nerve damage are considered to have ocular hypertension.

If the optic nerve appears abnormal, formal visual-field testing (perimetry) should be performed with attention to glaucomatous visual-field defects. In patients who have or are suspected to have glaucoma, the optic nerves and visual fields are examined periodically to determine whether there is evidence of progressive damage that would indicate the need for treatment. If identified early and managed appropriately, glaucoma is amenable to therapy, and the majority of patients with this condition retain good visual function.

There is currently no proven direct treatment for the optic neuropathy of glaucoma. Instead, treatment is focused on lowering intraocular pressure, the one risk factor that can be modified. Reduction of intraocular pressure has been demonstrated to protect against further damage to the optic-nerve head.[5-7]

To understand how drugs alter intraocular pressure, it is helpful to understand the dynamics of the flow of aqueous humor. The lens and cornea do not contain blood vessels but are nourished by a clear aqueous humor that is produced in the ciliary body and circulates around the lens, through the pupil, and throughout the anterior chamber. It flows out of the anterior chamber primarily through the trabecular meshwork into the venous system (Fig. 1). A smaller amount of fluid (approximately 4 to 18 percent) drains by way of the uveoscleral pathway through the iris root and ciliary body.[8,9] Elevated intraocular pressure is due to inadequate outflow of aqueous humor.

The types of glaucoma are classified, according to the reason for poor aqueous outflow, into three broad categories: congenital, open-angle, and closed-angle. Each of these categories is subdivided into primary and secondary types (Table 1). Although primary open-angle glaucoma is by far the most common type in the United States,[2] primary closed-angle glaucoma is common among Asian patients. Secondary glaucoma due to the exfoliation syndrome, pigment dispersion syndrome, inflammation, or neovascularization is fairly common. The other types of glaucoma (Table 1) are less common.

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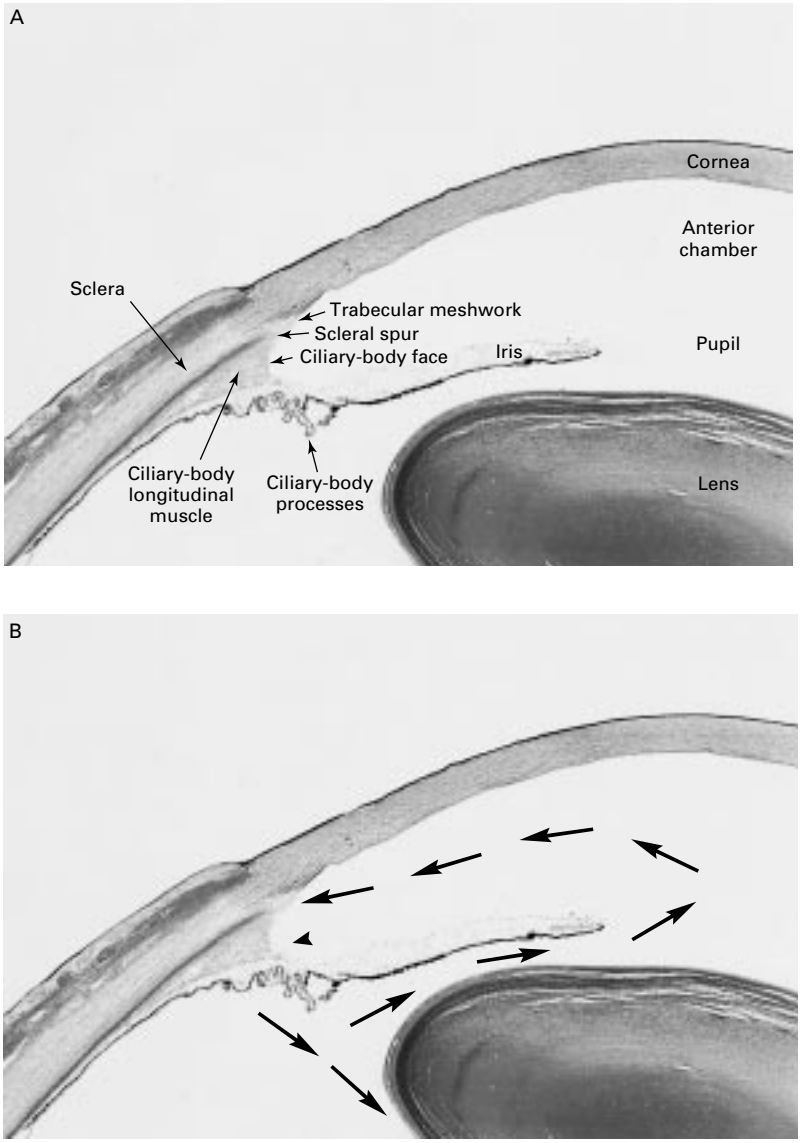

Figure 1. The Anterior Segment of the Eye.

Panel A shows the major structures. The scleral spur is the posterior boundary of the trabecular meshwork and the point of attachment of the longitudinal muscle of the ciliary body. Contraction of the longitudinal muscle can open the trabecular meshwork and increase aqueous outflow. Panel B shows the flow of aqueous humor through the anterior segment. Aqueous humor is produced by the ciliary-body processes. It flows around the lens, then passes through the pupil and into the anterior chamber, where it nourishes the cornea before leaving the eye through the trabecular meshwork into the venous system. A small amount of aqueous humor (arrowhead) exits by way of uveoscleral channels through the iris root and ciliary body.

TREATMENT

Intraocular pressure is reduced either by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow through the trabecular meshwork, through the uveoscleral pathway, or through a surgically created pathway. Treatment is begun or intensified when the patient has new or worsening optic-nerve damage or visual-field loss. A high intraocular pressure, without optic-nerve damage, may be treated, particularly if the patient has other risk factors for glaucoma. Before instituting therapy, the ophthalmologist establishes a target pressure that is thought to be safe for the optic nerve. The target is based on the current amount of damage to the optic nerve and the pressure at which the damage occurred.

TABLE 1. A PARTIAL LIST OF TYPES OF GLAUCOMA.

Open-angle glaucoma
Primary
Normal-tension
Juvenile open-angle
Secondary
Due to angle recession
Due to aphakia or pseudophakia
Due to corticosteroid use
Due to elevated episcleral venous pressure
Due to exfoliation (pseudoexfoliation) syndrome
Due to ghost cells
Due to hemorrhage
Due to inflammation*
Due to iridoschisis*
Due to phacolytic changes in the lens
Due to pigment dispersion syndrome
Closed-angle glaucoma
Primary
Pupillary-block
Due to plateau iris syndrome
Secondary
Due to aqueous misdirection (malignant glaucoma)
Due to ciliary-body swelling
Due to ectopia lentis
Due to epithelial downgrowth
Due to Fuchs' endothelial dystrophy
Due to inflammation*
Due to iridocorneal–endothelial syndrome
Due to iridoschisis*
Due to phacomorphic changes in the lens
Due to posterior polymorphous corneal dystrophy
Congenital glaucoma
Primary
Primary, associated with a syndrome
Associated with aniridia
Associated with Axenfeld–Rieger syndrome
Associated with neurofibromatosis
Associated with Peters' anomaly
Associated with Sturge–Weber syndrome
Secondary
Due to aphakia
Due to retinoblastoma
Due to retinopathy of prematurity

*This type of glaucoma has both open-angle and closed-angle mechanisms and is listed in both categories.

Treatment is usually begun with a topical drug. If necessary, other topical or systemic drugs are added. When drugs fail to control the intraocular pressure, laser energy applied to the trabecular meshwork (laser trabeculoplasty) may be used to increase aqueous outflow. When drugs and laser trabeculoplasty fail to control the intraocular pressure, a new route for aqueous egress can be created surgically.

Most drugs for glaucoma are applied topically. Because of the brief contact time and the strong protective barrier of the eye, the drug solutions need to be concentrated. Excess drug drains through the nasolacrimal duct into the nose, where it may be absorbed into the systemic circulation. For example, timolol administered to one eye enters the bloodstream in a concentration sufficient to cause a measurable decrease in intraocular pressure in the opposite eye.[10,11] Patients who use topical drugs should be taught to occlude the nasolacrimal duct with either digital pressure or simple eyelid closure for about five minutes; this maneuver increases intraocular drug concentrations and decreases systemic concentrations.[12]

In most patients, topical drugs are well tolerated. However, systemic side effects can occur and can be severe. Side effects of ocular drugs should always be considered when a patient presents with new systemic problems. It is not unusual for a patient to be treated with a bronchodilator drug for new-onset bronchospastic disease without the physician's considering that the topical β-adrenergic antagonist used for glaucoma treatment may be contributing to the condition.

In the remainder of this article, I will review the drugs commonly used to treat patients with glaucoma. With the exception of the cannabinoids, all are available in the United States. The systemic side effects of drugs for glaucoma are highlighted because these effects may cause the patient to present to a physician who is not an ophthalmologist.

Drugs used for the long-term management of glaucoma fall into five classes: β-adrenergic antagonists, prostaglandin analogues, adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agonists. Hyperosmotic drugs such as glycerol, isosorbide, and mannitol are given to lower intraocular pressure from very high levels in emergency situations, but they are not given for long-term management and will not be considered in this review.

The drug given initially to patients with most types of glaucoma is a topical β-adrenergic–antagonist drug, such as timolol maleate, because of the excellent pressure-lowering efficacy, long duration of action, and few ocular side effects of this class of drugs. A second drug, if needed, might be a prostaglandin analogue (such as latanoprost), an α_2-adrenergic agonist (such as brimonidine or apraclonidine), or a topical carbonic anhydrase inhibitor (such as dorzolamide or brinzolamide). When therapy with a topical drug is instituted, it is often applied to one eye, with the opposite, untreated eye used as a control. This method makes it possible to determine whether any change in intraocular pressure is due to the drug or to the normal variation of intraocular pressure. If there is no response, the drug should be discontinued in order to avoid unnecessary cost and side effects. If there is a substantial decrease in intraocular pressure but the pressure remains high, another drug should be added. Different classes of drug have additive effects on intraocular pressure.[13-16] Exceptions are nonselective β-adrenergic–antagonist drugs and nonselective adrenergic-agonist drugs, which have little additive effect when given together.[16,17] Whether cholinergic drugs and prostaglandins have additive actions is not clear.[18,19]

Many patients do not know the names of the drugs they are using and refer to them by the color of the bottle caps. For example, if a patient states that his or her bottle of eye drops has a yellow or blue top, that patient is probably using a β-adrenergic antagonist. Cholinergic agonists often come in green-capped bottles, adrenergic agonists in purple-capped bottles, and carbonic anhydrase inhibitors in orange-capped bottles.

β-ADRENERGIC–ANTAGONIST DRUGS

The exact mechanism by which β-adrenergic–antagonist drugs lower intraocular pressure is not known, but their ability to do so suggests that the formation of aqueous humor in the ciliary body is mediated by tonic sympathetic stimulation.[20,21] β-adrenergic antagonists decrease the production of aqueous humor by about one third.[22] Most are antagonists of both β_1 and β_2 receptors, but betaxolol is a selective β_1-adrenergic antagonist. Propranolol was the first β-adrenergic–antagonist drug found to decrease intraocular pressure.[23] Unfortunately, it caused corneal anesthesia, which prevented its use for topical therapy. Timolol was released in the United States in 1978 and quickly became the most popular drug for the treatment of glaucoma. When applied twice daily, it results in a sustained reduction in intraocular pressure, and it has minimal ocular side effects. Drugs of this class that are used to treat glaucoma are listed in Table 2.

Ophthalmic preparations of β-adrenergic–antagonist drugs often have systemic side effects (Table 2).[24,25,29,42] β_2-Blockade can cause the contraction of bronchial smooth muscles, leading to bronchospasm[43]; respiratory failure and death due to bronchospastic complications have been reported, particularly in patients with asthma or chronic obstructive pulmonary disease.[24,25,29,30] In a large study of patients with Medicaid coverage in New Jersey, patients who were receiving bronchodilator drugs and using timolol were 47 percent more likely to need an additional bronchodilator drug than patients not using timolol.[31] Conversely, pulmonary function improved in asymptomatic elderly patients who were switched from timolol to a topical cholinergic agonist or a selective β_1-adrenergic antagonist.[32]

Cardiac side effects of β-adrenergic–antagonist therapy include hypotension, decreased myocardial contractility, worsening of congestive heart failure, syncope, and bradycardia.[24,25,29,33] Bradycardia can be especially severe in patients taking verapamil[34] or quinidine[35,44]; quinidine inhibits the cytochrome P-450 enzyme CYP2D6 that is responsible for the metabolism of timolol.[44] Like oral β-adrenergic–antagonist drugs, their topical counterparts may have an adverse effect on serum lipids. Serum triglyceride concentrations increased and serum high-density lipoprotein cholesterol concentrations decreased in two studies of patients treated with topical timolol,[41,45] but not in another study.[46] Among nonselective β-adrenergic antagonists, carteolol has less effect on serum cholesterol concentrations than does timolol.[45]

Betaxolol is a relatively selective β_1-adrenergic antagonist. Because it has less activity against β_2 receptors, it has less tendency to cause pulmonary problems than nonselective drugs,[47,48] although it can do so in patients with severe asthma or other pulmonary disease.[49,50] Its cardiac side effects are similar to those of the nonselective drugs,[50] although exercise

TABLE 2. β-ADRENERGIC–ANTAGONIST DRUGS USED TO TREAT PATIENTS WITH GLAUCOMA AND THEIR SYSTEMIC SIDE EFFECTS.

DRUG			
TYPE AND NAME	FORMULATION	DOSAGE	U.S. TRADE NAME
Nonselective			
Carteolol	Solution (1%)	Twice a day	Ocupress
Levobunolol	Solution (0.25% or 0.5%)	Twice a day	AKBeta, Betagan
Metipranolol	Solution (0.3%)	Twice a day	OptiPranolol
Timolol hemihydrate	Solution (0.25% or 0.5%)	Twice a day	Betimol
Timolol maleate*	Solution (0.25% or 0.5%)	Twice a day	Timoptic
Timolol maleate	Gel (0.25% or 0.5%)	Once a day	Timoptic XE
β_1-Selective			
Betaxolol	Solution (0.5%)	Twice a day	Betoptic
Betaxolol	Suspension (0.25%)	Twice a day	Betoptic S

SYSTEMIC SIDE EFFECTS OF β-ADRENERGIC–ANTAGONIST DRUGS

General
- Lethargy[24]
- Weakness[24]

Central nervous system
- Anxiety[25]
- Confusion[24,26]
- Decreased libido[27]
- Depression[24,26-28]
- Emotional lability[27]
- Erectile dysfunction[24,27]
- Hallucinations[26]
- Psychosis[26]

Pulmonary
- Bronchospasm[29-31]
- Reduced pulmonary function[31,32]

Cardiovascular
- Bradycardia[33-35]
- Inability to increase heart rate during vigorous exercise[33,36,37]
- Hypotension[24,33]
- Decreased myocardial contractility[33]
- Worsening of congestive heart failure[38]
- Heart block[25]
- Syncope[25]

Gastrointestinal
- Cramps[24]
- Diarrhea[24]
- Nausea[24]

Other
- Exacerbation of myasthenia gravis[39]
- Masking of hypoglycemic symptoms in patients with diabetes[40]
- Reduced glucose tolerance in patients with diabetes[40]
- Decreased serum high-density lipoprotein cholesterol concentrations[41]

*A combination of timolol maleate and dorzolamide is available (Cosopt).

tolerance may be better[36] and central nervous system symptoms are less common, though some have been reported.[28] However, betaxolol lowers intraocular pressure less than do the nonselective drugs.[51]

PROSTAGLANDIN ANALOGUES

Prostaglandins are locally acting hormones, found in most tissues,[52] which have been of interest to ophthalmologists because they cause an increase in intraocular pressure, marked inflammation, and a breakdown of the blood–aqueous barrier when injected into the eyes of laboratory animals.[53] Increased concentrations of prostaglandins are found in the anterior chambers of inflamed eyes.[54] At low concentrations, however, prostaglandin $F_{2\alpha}$ reduces intraocular pressure and does not cause ocular inflammation.[55] Prostaglandin $F_{2\alpha}$ increases uveoscleral outflow through the iris root and ciliary body, either by decreasing the extracellular matrix that surrounds the muscle bundles[56] or by relaxing the ciliary musculature.[18] A 0.005 percent solution of latanoprost (Xalatan) is the only drug in this class that is available in the United States, although other prostaglandin analogues are available in other countries.

Latanoprost has been available for only a few years, and the full range of its systemic side effects may not yet be known. The amount of latanoprost that reaches nonocular tissues through the systemic circulation is very small as compared with endogenous concentrations of prostaglandins,[55,57] and systemic side effects are uncommon. The most frequent systemic side effects are muscle and joint pain and allergic reactions of the skin.[55,57] Latanoprost does not alter the pulse rate or blood pressure.[55,57,58] It has the interesting side effect of causing the color of the iris to darken in up to 10 percent of patients,[55,57] usually those with green–brown or blue–brown irises, and in some patients the eyelashes become longer, thicker, and more heavily pigmented.[59]

ADRENERGIC-AGONIST DRUGS

Adrenergic-agonist drugs used to treat glaucoma are listed in Table 3. Epinephrine is a nonspecific adrenergic-agonist drug that lowers intraocular pressure through a complex series of interactions between α-adrenergic and β-adrenergic stimulation.[66,67] α-Adrenergic stimulation causes an early decrease in the production of aqueous humor by constricting the vessels supplying the ciliary body and decreasing ultrafiltration. Later, there is an increase in aqueous-humor outflow mediated by α-adrenergic and β_2-adrenergic stimulation.[68] Epinephrine has little efficacy when given with a β-adrenergic–antagonist drug and has many side effects (Table 3). For example, in a five-year study of epinephrine in patients with ocular hypertension, 80 percent discontinued it because of systemic or ocular side effects.[60] It is rarely prescribed now.

Dipivefrin, an epinephrine prodrug, represented an important breakthrough in ophthalmic-drug development. The esterification of two pivalic acid chains to epinephrine increased the ability of the drug to penetrate the cornea by a factor of 17.[69,70] The pivalic acid chains are removed as the drug passes through the cornea. Because the drug is inactive until converted by the corneal enzymes and is effective in low concentrations, the systemic side effects are limited.[61,70] Unfortunately dipivefrin has many of the same ocular side effects as epinephrine.[71]

Apraclonidine and brimonidine are relatively selective α_2-adrenergic–agonist drugs available for the treatment of glaucoma. These drugs were derived from the systemic antihypertensive drug clonidine, which was found to decrease intraocular pressure by decreasing the production of aqueous humor.[72,73] Unfortunately, clonidine markedly lowered systemic blood pressure and ocular perfusion pressure, even when applied topically.[72] Apraclonidine is similar to clonidine but does not cross the blood–brain barrier and therefore does not cause systemic hypotension.[64] Initially, 1 percent apraclonidine in a single-use dis-

TABLE 3. ADRENERGIC-AGONIST DRUGS USED TO TREAT PATIENTS WITH GLAUCOMA AND THEIR SYSTEMIC SIDE EFFECTS.

	DRUG		
TYPE AND NAME	FORMULATION	DOSAGE	U.S. TRADE NAME
Nonselective			
Epinephrine borate	Solution (0.5% or 1%)	Twice a day	Epinal
Epinephrine hydrochloride*	Solution (0.1%, 0.5%, 1%, or 2%)†	Twice a day	Epifrin, Glaucon
Nonselective prodrug			
Dipivefrin	Solution (0.1%)	Twice a day	Propine
α_2-Selective			
Apraclonidine	Solution (0.5% or 1%)‡	Three times a day	Iopidine
Brimonidine	Solution (0.2%)	Three times a day	Alphagan

SYSTEMIC SIDE EFFECTS OF ADRENERGIC-AGONIST DRUGS

Nonselective drugs
- General
  - Headaches (epinephrine)[60]
- Cardiovascular
  - Arrhythmia (epinephrine)[60]
  - Hypertension (epinephrine)[61,62]
  - Tachycardia (epinephrine)[62]

α_2-Adrenergic–agonist drugs
- General
  - Lethargy (brimonidine)[63]
  - Fatigue (brimonidine)[63]
  - Drowsiness (brimonidine)[63]
  - Dry mouth[63,64]
  - Dry nose[64]
- Cardiovascular
  - Mild decrease in blood pressure (brimonidine)[65]

*Epinephrine is also available in combination with pilocarpine (E-Pilo).

†Not all concentrations are supplied by all manufacturers.

‡Apraclonidine 1 percent solution comes in single-use vials and is used to treat patients before ophthalmic laser surgery.

penser was approved for the prevention of the increase in intraocular pressure that often occurs after anterior-segment laser procedures.[74,75] Long-term application of 0.5 percent apraclonidine drops effectively lowers intraocular pressure.[64] It has no cardiovascular side effects.[76] Dry nose and dry mouth are the most common nonocular side effects.[64] Upper-eyelid retraction can occur,[77] and follicular conjunctivitis is a frequent ocular side effect.[78]

Brimonidine, a recently released drug, is similar to apraclonidine but is more selective for α_2-adrenergic receptors.[79] Many patients report that it causes dry mouth,[63] but ocular side effects are less frequent than with apraclonidine.[79] Unlike apraclonidine, brimonidine crosses the blood–brain barrier and can cause mild systemic hypotension[65] and lethargy.[63]

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase catalyzes the conversion of carbon dioxide to bicarbonate. Within the ciliary body, the formation of bicarbonate is responsible for the movement of sodium into the eye, accounting for about 70 percent of the sodium that enters the posterior chamber. Water follows the sodium to form the aqueous humor. Carbonic anhydrase inhibition decreases bicarbonate production and therefore the flow of bicarbonate, sodium, and water into the posterior chamber. In order to decrease intraocular pressure, more than 98 percent of carbonic anhydrase activity must be inhibited.[80] Acetazolamide was first developed as an antihypertensive drug (Table 4). Shortly thereafter it was found to decrease intraocular pressure through a decrease in aqueous-humor production.[92] Until recently, acetazolamide and other oral carbonic anhydrase inhibitors were mainstays of glaucoma treatment, but they have many side effects. As a result they have become less popular recently, particularly since the development of drugs that can be used topically. The introduction of topical carbonic anhydrase inhibitors has brought this class of drugs back into favor for patients with glaucoma.

Oral carbonic anhydrase inhibitors include acetazolamide, methazolamide, and dichlorphenamide. Acetazolamide is available in a sustained-release formulation and for intravenous administration, and it can be made into a syrup for children. Systemic side effects are common (Table 4). In one study of 92 patients, 42 (46 percent) had the symptom complex of generalized malaise, fatigue, weight loss, depression, anorexia, and decreased libido.[81] Gastrointestinal side effects include nausea, a metallic taste in the mouth, cramps, epigastric burning, and diarrhea.[81] There is an increased incidence of nephrolithiasis in patients who take drugs of this type, particularly acetazolamide.[85] Renal failure can occur without nephrolithiasis and has been described as similar to the nephropathy induced by sulfonamides.[86,87] The most worrisome side effects are blood dyscrasias. Twenty-six cases of fatal

TABLE 4. CARBONIC ANHYDRASE INHIBITORS USED TO TREAT PATIENTS WITH GLAUCOMA AND THEIR SYSTEMIC SIDE EFFECTS.

	DRUG		
TYPE AND NAME	FORMULATION	DOSAGE	U.S. TRADE NAME
Oral			
Acetazolamide	Tablets (125 mg or 250 mg)	125 mg twice a day to 250 mg four times a day	Diamox, Dazamide
	Sustained-release capsules (500 mg)	Twice a day	Diamox
	Powder for injection (500 mg/vial)	250 to 500 mg four times a day	Diamox
Dichlorphenamide	Tablets (50 mg)	25 to 50 mg one to three times a day	Daranide
Methazolamide	Tablets (25 mg or 50 mg)	25 mg twice a day to 50 mg three times a day	Neptazane, Glauctabs, MZM
Topical			
Brinzolamide	Suspension (1%)	Three times a day	Azopt
Dorzolamide*	Solution (2%)	Three times a day	Trusopt

SYSTEMIC SIDE EFFECTS OF CARBONIC ANHYDRASE INHIBITORS

General
- Anorexia and weight loss[81]
- Fatigue[81]
- Malaise[81]
- Paresthesias of fingers and toes[81]

Central nervous system
- Depression[81]
- Loss of libido[81,82]
- Erectile dysfunction[83]

Pulmonary
- Respiratory decompensation in patients with chronic obstructive pulmonary disease[84]

Gastrointestinal
- Cramps[81]
- Diarrhea[81]
- Epigastric burning[81]
- Metallic taste[81]
- Nausea[81]

Renal or genitourinary
- Nephrolithiasis (calcium oxalate and calcium phosphate)[85]
- Renal failure[86,87]

Hematologic
- Acute leukopenia[88]
- Agranulocytosis[88]
- Aplastic anemia[88,89]
- Hemolytic anemia[88]
- Neutropenia[88]
- Pancytopenia[88]
- Thrombocytopenia[88]

Other
- Hirsutism[90]
- Hypokalemia (particularly with concomitant thiazide-diuretic therapy)[81]
- Metabolic acidosis (especially when given with salicylates and in patients with diabetes mellitus, renal, adrenal, pulmonary, or hepatic disease)[84]
- Stevens–Johnson syndrome[91]

*A combination of dorzolamide and timolol maleate is available (Cosopt).

blood dyscrasias in the United States,[88] including aplastic anemia, agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, hemolytic anemia, and acute leukopenia,[89,93] have been attributed to carbonic anhydrase inhibitors. Systemic acidosis can result from carbonic anhydrase–inhibitor therapy, especially in patients taking salicylates or those with diabetes mellitus, renal disease, adrenal disease, hepatic disease, or chronic obstructive pulmonary disease.[84] These drugs are structurally related to sulfonamides and should be used with caution in patients who are allergic to sulfonamides.

Oral carbonic anhydrase inhibitors have been displaced to a large degree by topical carbonic anhydrase inhibitors, which can lower intraocular pressure by up to 26 percent[94,95] and have few systemic side effects. Some patients report a bitter taste in the mouth.[96] Because some of the blood dyscrasias associated with the use of oral carbonic anhydrase inhibitors are not dose-related, these dyscrasias could theoretically occur in a patient treated with topical drugs.

CHOLINERGIC AGONISTS

Cholinergic agonist (parasympathomimetic) drugs have been used for the treatment of glaucoma since the 1870s, making them the oldest of the glaucoma drugs.[97] They act by stimulating parasympathetic receptors at neuromuscular junctions. One result of this stimulation is contraction of the longitudinal muscle of the ciliary body, which pulls on the scleral spur, opens the trabecular meshwork, and thereby increases aqueous outflow from the eye.[98] Another result is contraction of the circular muscle, leading to myopia, and contraction of the sphincter of the iris, leading to pupillary constriction.

Acetylcholine, the natural postganglionic mediator of the cholinergic nervous system, is not used for the treatment of glaucoma because it is rapidly hydrolyzed by acetylcholinesterase. The cholinergic agonists act by either stimulating acetylcholine at the neuromuscular junction (as in the case of direct-acting cholinergic agonists) or inhibiting acetylcholinesterase, thereby potentiating the action of endogenous acetylcholine (cholinesterase inhibitors). Drugs of this class that are used to treat glaucoma are listed in Table 5.

Pilocarpine, the most commonly used cholinergic agonist, is available in concentrations ranging from 0.25 percent to 10 percent, but there is minimal added benefit, if any, in using concentrations above 4 percent.[104] Because the cholinesterase inhibitors are more potent than the direct cholinergic agonists, most patients who are switched from a direct-acting cholinergic drug to a cholinesterase inhibitor have a further reduction in intraocular pressure.[105]

The chief ocular side effects of cholinergic agonists are fixed, small pupils and induced myopia, and they are the main reasons for the decreasing popu-

TABLE 5. CHOLINERGIC-AGONIST DRUGS USED TO TREAT PATIENTS WITH GLAUCOMA AND THEIR SYSTEMIC SIDE EFFECTS.

	DRUG		
TYPE AND NAME	FORMULATION	DOSAGE	U.S. TRADE NAME
Direct-acting cholinergic agonists			
Carbachol*	Solution (0.75%, 1.5%, 2.25%, or 3%)†	Three times a day	Carboptic, Isopto-Carbachol
Pilocarpine hydrochloride‡	Solution (0.25%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 8%, or 10%)†	Four times a day	Adsorbocarpine, Akarpine, IsoptoCarpine, Pilocar, Pilogel, Piloptic, Pilostat
	Gel 4%	At bedtime	Pilopine HS Gel
Pilocarpine nitrate‡	Solution (1%, 2%, or 4%)	Four times a day	Pilagan
Pilocarpine‡	Sustained-release system (20 or 40 μg/hr)	Once a week	Ocusert
Cholinesterase inhibitors			
Demecarium	Solution (0.125% or 0.25%)	Twice a day	Humorsol
Echothiophate	Solution (0.03%, 0.06%, 0.125%, or 0.25%)	Twice a day	Phospholine Iodide
Physostigmine	Ointment (0.25%)	Three times a day	Eserine Sulphate

SYSTEMIC SIDE EFFECTS OF CHOLINERGIC-AGONIST DRUGS

General
- Diaphoresis[99]
- Headache[99]
- Tremor[99]
- Salivation[99]

Central nervous system
- Deterioration of mental status in patients with Alzheimer's disease[100]§

Pulmonary
- Bronchospasm[101]
- Pulmonary edema[102]

Cardiovascular
- Hypertension[99]
- Hypotension[99]
- Bradycardia[99]

Gastrointestinal
- Cramps[99]
- Diarrhea[99,101]
- Nausea[99]
- Vomiting[99]

Other
- Prolonged respiratory paralysis when given with succinylcholine (cholinesterase inhibitors)[101]
- Decreased ability to metabolize some local anesthetic drugs (cholinesterase inhibitors)[103]

*Carbachol also causes some cholinesterase inhibition.

†Not all concentrations are supplied by all manufacturers.

‡Pilocarpine is also available in combination with epinephrine (E-Pilo).

§This effect was reported in three patients.

larity of these drugs. The cholinesterase-inhibitor drugs have similar but more severe ocular side effects. In addition, they can cause cataracts, and they are therefore usually reserved for patients who have already undergone cataract extraction.[106]

Direct-acting cholinergic drugs are very safe when administered systemically, and nonocular side effects usually occur only when they are used repeatedly, as during an acute attack of closed-angle glaucoma.[99] Cholinesterase-inhibitor drops are more likely than direct-acting cholinergic-agonist drops to cause systemic symptoms, especially diarrhea and abdominal cramps.[101] These drugs can also interfere with the metabolism of succinylcholine, and the administration of succinylcholine in patients using a cholinesterase inhibitor can result in prolonged respiratory paralysis.[101] The metabolism of procaine and other local anesthetic drugs is also inhibited.[103]

Two alternative drug-delivery systems for pilocarpine have been developed to reduce some of its ocular side effects. A pilocarpine gel can be used once a day, although it may lose some effect in the last few hours before the next dose.[107] Because it is applied before bedtime, the worst pupillary constriction and accommodative spasms occur while the patient is sleeping. A sustained-delivery wafer (Ocusert), which is placed under the lid once a week, delivers a small, steady dose of pilocarpine.[108] This is an excellent way of administering the drug to patients who are dexterous enough to insert and remove the wafer. The pupillary constriction is less profound with this method of delivery, and the induced myopia is less extreme and less variable.

CANNABINOIDS

Marijuana and its component cannabinoid compounds are not available for the treatment of glaucoma in the United States, but because of the frequency with which they are mentioned in the media they deserve some discussion here. In 1971 it was discovered that smoking marijuana cigarettes could lower intraocular pressure by up to 45 percent.[109] The primary active ingredients in marijuana are derivatives of tetrahydrocannabinol, which lower intraocular pressure when inhaled,[110] ingested orally,[111] or given intravenously.[112] The results with topical tetrahydrocannabinol have varied. In one study, application to one eye lowered intraocular pressure in both eyes, suggesting that this drug may exert its effect through the cardiovascular or central nervous system.[113] In other studies, however, topical tetrahydrocannabinol had no effect on intraocular pressure.[114,115]

Systemically administered tetrahydrocannabinol has profound side effects. Most patients have alterations in mental status.[110,111] Tachycardia, palpitations, and systemic hypotension are also common, and hypotension can occur even in patients treated with topical tetrahydrocannabinol.[113] There is concern that a deleterious effect on optic-nerve blood flow, resulting from systemic hypotension, might offset any benefit of reduced intraocular pressure.[116]

NEW DRUGS

Some drugs now used for the treatment of glaucoma have been suggested to have direct neuroprotective capability (as in the case of brimonidine)[79] or beneficial effects on blood flow to the optic-nerve head (as in the case of betaxolol)[117]; further study of these actions may lead to the development of new drugs. In addition, studies of the molecular genetics of glaucoma should uncover the basic biochemical abnormalities that cause this disorder. For example, mutations of the *GLC1A* gene have been found in 3 percent of patients with primary open-angle glaucoma.[118] Although gene-replacement therapy is an appealing concept, a more immediate hope is that studies of *GLC1A* and its protein product, myocilin, will lead to effective and specific medication for some patients with primary open-angle glaucoma. As more genes for glaucoma are discovered, one can envision a series of drugs tailored to specific molecular abnormalities.

CONCLUSIONS

Glaucoma is a family of diseases that can usually be treated successfully with a variety of topical drugs. Although most physicians do not ordinarily treat patients with glaucoma, they need to be aware of the drugs used and their potential side effects.

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