SECTION 13
OPHTHALMIC AND OTOLARYNGOLOGIC DISORDERS

CHAPTER 97

Glaucoma

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KEY CONCEPTS

1. Primary open-angle glaucoma (POAG) or ocular hypertension (ocular hypertension) is more prevalent than closed- or narrow-angle glaucoma.
2. In any form of glaucoma, reduction of intraocular pressure (IOP) is essential.
3. IOP is a very important risk factor for glaucoma, but the most important considerations are progression of glaucomatous changes in the back of the eye (optic disk and nerve fiber layer) and visual field changes when diagnosing and monitoring for POAG or ocular hypertension.
4. Optic nerve changes often occur before visual field changes are exhibited.
5. Recent studies demonstrate that reduction in IOP prevents progression or even onset of glaucoma.
6. Newer medications simplify treatment regimens for patients. Prostaglandin analogs are considered the most potent topical medications for reducing IOP and flattening diurnal variations in intraocular pressure.
7. Local adverse events are common with topical glaucoma medications, but patient education and reinforcing adherence are essential to prevent glaucoma progression.

The glaucomas are a group of ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disk) that is associated with loss of visual sensitivity and field. Increased intraocular pressure (IOP), a traditional diagnostic criterion for glaucoma, is thought to play an important role in the pathogenesis of glaucoma, but is no longer a diagnostic criterion for glaucoma.[1–10] Two major types of glaucoma have been identified: open angle and closed angle. Open-angle glaucoma accounts for the great majority of cases. Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs, and can lead to serious complications.[11–16] Both primary and secondary glaucomas may be caused by a combination of open-angle and closed-angle mechanisms (Table 97–1).

Learning objectives, review questions, and other resources can be found at **www.pharmacotherapyonline.com.**

BASIC CONCEPTS

AQUEOUS HUMOR DYNAMICS AND INTRAOCULAR PRESSURE

An understanding of IOP and aqueous humor dynamics will assist the reader in understanding the drug therapy of glaucoma.[1,2,17–19]

Aqueous humor is formed in the ciliary body and its epithelium (Figs. 97–1 and 97–2) through both filtration and secretion. Because ultrafiltration depends on pressure gradients, blood pressure and IOP changes influence aqueous humor formation. Osmotic gradients produced by active secretion of sodium and bicarbonate, and possibly other solutes such as ascorbate from the ciliary body epithelial cells into the aqueous humor, result in movement of water from the pool of ciliary stromal ultrafiltrate into the posterior chamber, forming aqueous humor. Carbonic anhydrase (primarily isoenzyme type II), α- and β-adrenergic receptors, and sodium- and potassium-activated adenosine triphosphatases are found on the ciliary epithelium and appear to be involved in this secretion of the solutes sodium and bicarbonate.

Receptor systems controlling aqueous inflow have not been elucidated fully. Pharmacologic studies suggest that β-adrenergic agents increase inflow, whereas α_2-adrenergic blocking, α-adrenergic blocking, β-adrenergic blocking, dopamine-blocking, carbonic, anhydrase-inhibiting, and adenylate cyclase-stimulating agents decrease aqueous inflow. Aqueous humor produced by the ciliary body is secreted into the posterior chamber at a rate of approximately 2 to 3 μL/min. The pressure in the posterior chamber produced by the constant inflow pushes the aqueous humor between the iris and lens and through the pupil into the anterior chamber of the eye (see Fig. 97–2).[1,2,17–22]

Aqueous humor in the anterior chamber leaves the eye by two routes: (a) filtration through the trabecular meshwork (conventional outflow) to the Schlemm canal (80% to 85%) and (b) through the

TABLE 97-1 General Classification of Glaucoma

I. Primary glaucoma
  A. Open angle
  B. Angle closure
    1. With pupillary block
    2. Without pupillary block
II. Secondary glaucoma
  A. Open angle
    1. Pretrabecular
    2. Trabecular
    3. Posttrabecular
  B. Angle closure
    1. Without pupillary block
    2. With pupillary block
III. Congenital glaucoma

ciliary body and the suprachoroidal space (uveoscleral outflow or unconventional outflow). Cholinergic agents such as pilocarpine increase outflow by physically opening the meshwork pores secondary to ciliary muscle contraction. The uveoscleral outflow of aqueous humor is also increased by prostaglandin analogs, and β- and α_2-adrenergic agonists. Constant inflow of aqueous humor from the ciliary body and resistance to outflow result in an IOP great enough to produce an outflow rate equal to the inflow rate (see Fig. 97–2).

The median IOP measured in large populations is 15.5 ± 2.5 mm Hg; however, the distribution of pressures around the mean is skewed to the right (toward higher readings). IOP is not constant and changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture. IOP is measured by tonometry: indentation tonometry, applanation tonometry, or a noncontact method using an air pulse. These methods may result in slightly different pressure readings. IOPs consistently greater than 21 mm Hg are found in 5% to 8% of the general population. The incidence increases with age, such that "abnormal" (i.e., >22 mm Hg) IOP is found in 15% of those 70 to 75 years of age. Intermittently high IOP (>40 mm Hg) is found in patients with closed-angle glaucoma (CAG). The increased IOP in all types of glaucoma results from the decreased facility for aqueous humor outflow through the trabecular meshwork. Aqueous humor production in primary open-angle glaucoma (POAG) is normal.[1,2,17–19]

IOP demonstrates considerable circadian variation (often referred to as *diurnal* IOP or the IOP during the daily 24-hour cycle)

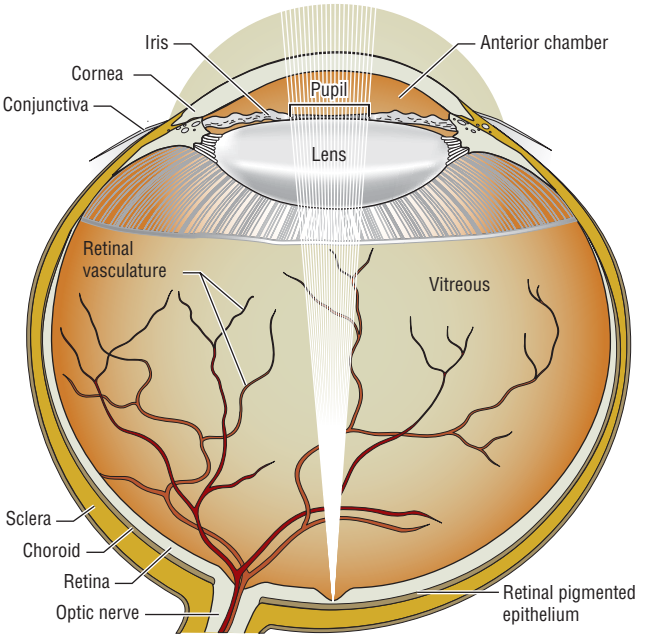

FIGURE 97-1. Anatomy of the eye.

primarily because of changes in the rate of aqueous humor formation. This circadian variation results in a minimum IOP at approximately 6 PM and a maximum IOP at awakening, although some studies suggest that both healthy and glaucoma patients may have their highest IOP at night after falling asleep.[20] Low systemic blood pressure in conjunction with high IOPs (decreased ocular perfusion pressure) at night can result in optic nerve head damage.[20] Generally, the circadian IOP variation is usually less than 3 to 4 mm Hg; however, it may be greater in patients with glaucoma. This circadian variation and the poor relationship of IOP with visual loss make measurement of IOP a poor screening test for glaucoma.

Although increased IOP within any range is associated with a higher risk of glaucomatous damage, it is both an insensitive and nonspecific diagnostic and monitoring tool. Of individuals with IOP between 21 and 30 mm Hg, only 0.5% to 1% per year will develop optic disk changes and visual field loss (i.e., glaucoma) over 5 to 15 years. However, more subtle retinal damage, such as alteration of color vision or decreased contrast sensitivity, occurs in a higher

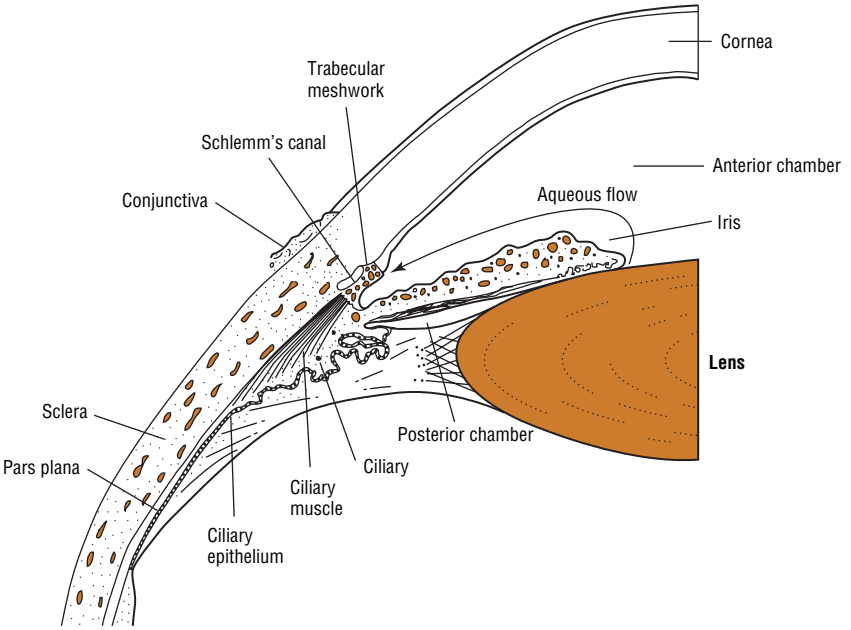

FIGURE 97-2. Anterior chamber of the eye and aqueous humor flow.

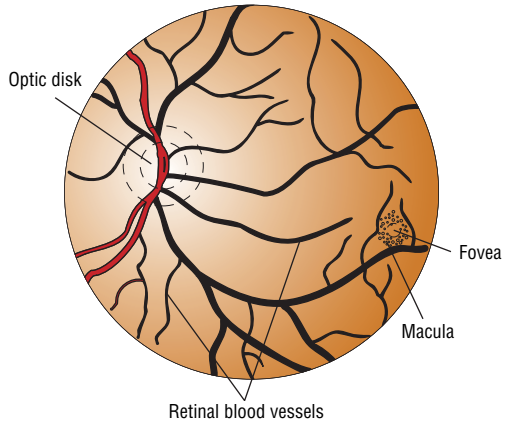

FIGURE 97-3. Normal fundus of the eye and optic disk and cup.

percentage of patients with IOPs greater than 21 mm Hg, and the incidence of visual field defects increases to as high as 28% in individuals with IOPs above 30 mm Hg. For a given abnormal IOP, the incidence of glaucoma increases with age. In patients with preexisting optic nerve damage, the worse the existing damage, the more sensitive the eye is to a given IOP. As many as 20% to 30% of patients with glaucomatous visual field loss have an IOP of less than 21 mm Hg (called *normal-tension glaucoma,* referring to the normal IOP). Thus the absolute IOP is a less-precise predictor of optic nerve damage. More direct measurements of therapeutic outcome, such as optic disk examination and visual-field evaluation, also must be used as monitors of disease progression.[1–7,17–24] Taking the above factors into consideration, glaucoma medications that provide maximal reduction of IOP over 24 hours and have minimal influence on blood pressure may be advantageous in treating glaucoma patients.

OPTIC DISK AND VISUAL FIELDS

The optic disk is the portion of the optic nerve ophthalmoscopically visible as it leaves the eye. It consists of approximately 1 million retinal ganglion nerve cell axons, blood vessels, and supporting connective tissue structures (lamina cribrosa). The small depression within the disk is termed the *cup* (Fig. 97–3). A normal physiologic cup does not extend beyond the optic nerve rim and has a varying diameter of less than one-third to one-half that of the disk (cup-to-disk ratio: 0.33 to 0.5). Table 97–2 lists the common alterations of the optic disk found in glaucoma. These disk changes result from optic nerve axonal degeneration and remodeling of the supporting structures. As the nerve axons die, the cup becomes larger in relation to the whole disk. A loss of retinal nerve fiber layer visibility might be visualized in glaucoma patients with detectable visual field loss. This pattern of changes is consistent with visual field losses and loss of visual sensitivity seen in glaucoma.[1,2,17–24]

Determination of the visual field allows assessment of optic nerve damage and is an important monitoring parameter in treatment. However, visual field changes lag behind optic disk changes, and a loss of 25% to 35% of retinal ganglion cells is usually required before detectable visual field defects are noted. The peripheral visual field is measured using a visual field instrument called a *perimeter.* Characteristic visual field loss occurs in glaucoma (Fig. 97–4; see also Table

TABLE 97-2 Optic Disk and Visual Field Findings

Optic disk
Cup-to-disk ratio >0.5
Progressive increase in cup size
Cup-to-disk ratio asymmetry >0.2
Vertical elongation of the cup
Excavation of the cup
Increased exposure of lamina cribrosa
Pallor of the cup
Splinter hemorrhages
Cupping to edge of disk
Notching of the cup (usually superior or inferior)
Nerve fiber defects
Visual field findings
General peripheral field constriction
Isolated scotomas (blind spots)
Nasal visual field depression ("nasal step")
Enlargement of blind spot
Large arc-like scotomas
Reduced contrast sensitivity
Reduced peripheral acuity
Altered color vision

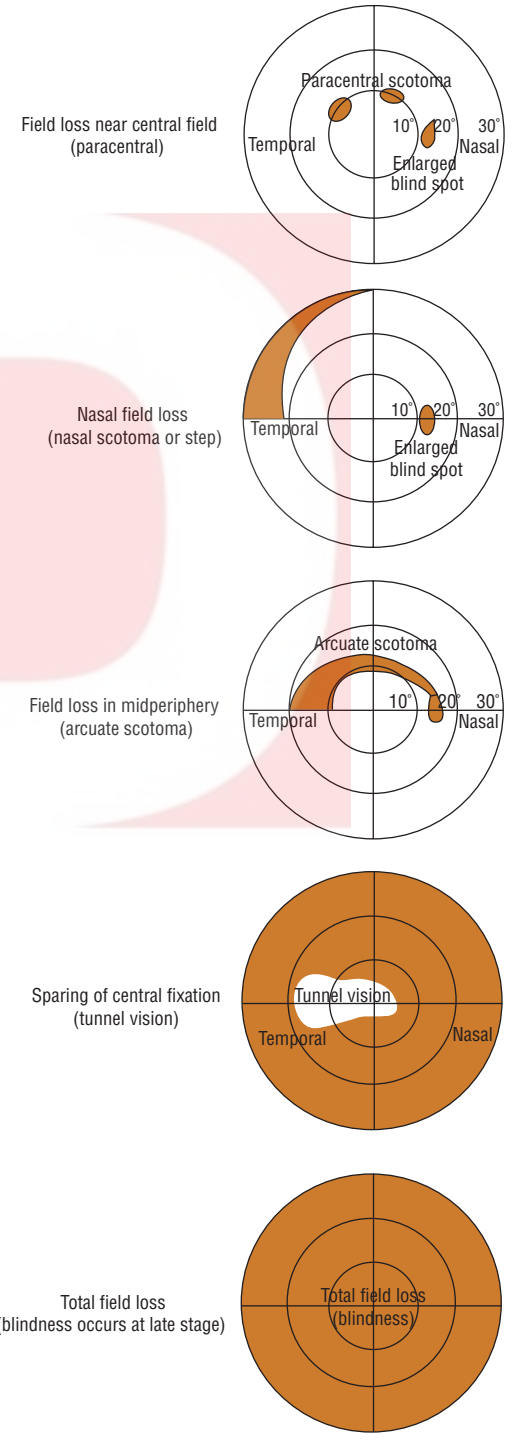

FIGURE 97-4. Schematic of the progression of visual field loss in glaucoma.

97–2), but loss of central visual acuity usually does not occur until late in the disease. Other indicators, such as color vision changes and contrast sensitivity, may allow earlier and more sensitive detection of glaucomatous changes.[1,2]

GENETICS

Glaucoma is often inherited as a complex multifactorial disease, but it can also be inherited as a mendelian autosomal-dominant or autosomal-recessive trait form. The common age-related adult-onset glaucoma, like POAG, although containing heritability of some significance, is more complex and is influenced by environmental factors. Genetic studies have more clearly defined the underlying molecular events responsible for the mendelian forms of the disease. However, the chromosome locations identified may play some factor in the more complex forms. A number of major gene loci associated with POAG have been identified. The molecular mechanism of how mutations in any of these genes result in increased IOP with loss of visual field has not been elucidated. The future of genetic studies in glaucoma will include discovery of new glaucoma genes, determination of clinical phenotypes associated with these genes and mutations, understanding how environmental factors interact, and developing a database that can be used for further testing. It is hoped that improved understanding of the genetic origins of POAG will lead to new diagnostic tools and therapies that target the underlying causes of the disease.[1,2,25,26]

EPIDEMIOLOGY OF OPEN-ANGLE GLAUCOMA

1 Open-angle glaucoma is the second leading cause of blindness, affecting up to 3 million individuals in the United States and up to 60.5 million individuals worldwide by 2010. It is estimated that by 2010, 135,000 persons in the United States, and about 4.5 million in the world, will have bilateral blindness. The prevalence rate varies with age, race, diagnostic criteria, and other factors. In the United States, open-angle glaucoma occurs in 1.5% of the population older than 30 years of age, 1.3% of whites and 3.5% of blacks. The incidence of open-angle glaucoma increases with increasing age. The incidence of the disease in patients 80 years of age is 3% in whites and 5% to 8% in blacks.

ETIOLOGY OF OPEN-ANGLE GLAUCOMA

2 The specific cause of glaucomatous optic neuropathy is presently unknown. Previously, increased IOP was considered to be the sole cause of the damage; however, it is now recognized that IOP is only one of many factors associated with the development and progression of glaucoma.[1–10] Increased susceptibility of the optic nerve to ischemia, a reduced or dysregulated blood flow, excitotoxicity, autoimmune reactions, and other abnormal physiologic processes are likely additional contributory factors. The final outcome of these processes is believed to be apoptosis of the retinal ganglion cells, which results in axonal degeneration, and finally permanent loss of vision.[11–16] Interestingly enough, there appears to be a fair amount of similarity between neuronal cell death by apoptosis in Alzheimer's disease and glaucoma.[13] Indeed, open-angle glaucoma may represent a number of distinct diseases or conditions that simply manifest the same symptoms. Susceptibility to visual loss at a given IOP varies considerably; some patients do not demonstrate damage at high IOPs, whereas other patients have progressive visual field loss despite an IOP in the normal range (normal-tension glaucoma).

Although IOP poorly predicts which patients will have visual field loss, the risk of visual field loss clearly increases with increasing IOP within any range. In fact, recent studies demonstrate that lowering IOP, no matter what the pretreatment IOP, reduces the risk of glaucomatous progression or may even prevent the onset to early glaucoma in patients with ocular hypertension.[3–7]

The mechanism by which a certain level of IOP increases the susceptibility of a given eye to nerve damage remains controversial. Multiple mechanisms are likely to be operative in a spectrum of combinations to produce the death of retinal ganglion cells and their axons in glaucoma. Pressure-sensitive astrocytes and other cells in the optic disk supportive matrix may produce changes and remodeling of the disk, resulting in axonal death. Vasogenic theories suggest that optic nerve damage results from insufficient blood flow to the retina secondary to the increased perfusion pressure required in the eye, dysregulated perfusion, or vessel wall abnormalities, and results in degeneration of axonal fibers of the retina. Another theory suggests that the IOP may disrupt axoplasmal flow at the optic disk.

Recently, focus on the mechanisms of the retinal ganglion cell apoptosis and the role of excessive glutamate and nitric oxide found in glaucoma patients has broadened the focus of drug therapy research to include evaluation of agents that act as neuroprotectants.[12–15] Such agents may be particularly useful in patients with normal-pressure glaucoma, in whom pressure-independent factors may play a relatively larger role in disease progression. These agents would target risk factors and underlying pathophysiologic mechanisms of disease other than IOP.[11–16]

PATHOPHYSIOLOGY OF OPEN-ANGLE GLAUCOMA

3 As stated previously, optic nerve damage in POAG can occur at a wide range of intraocular pressures, and the rate of progression is highly variable. Patients may exhibit pressures in the 20 to 30 mm Hg range for years before any disease progression is noticed in the optic disk or visual fields. That is why open-angle glaucoma is often referred to as the "sneak thief of sight."

CLINICAL PRESENTATION OF GLAUCOMA

General

- Glaucoma can be detected in otherwise asymptomatic patients, or patients can present with characteristic symptoms, especially vision loss. POAG is a chronic, slowly progressive disease found primarily in patients older than 50 years of age, whereas CAG is more typically associated with symptomatic acute episodes.

Symptoms

- POAG: None until substantial visual field loss occurs.
- CAG: Nonsymptomatic or prodromal symptoms (blurred or hazy vision with halos around lights that is caused by a hazy, edematous cornea, and occasionally headache) may be present. Acute episodes produce symptoms associated with a cloudy, edematous cornea, ocular pain or discomfort, nausea, vomiting, abdominal pain, and diaphoresis.

Signs

- POAG: Disk changes and visual field loss (see Table 97–2); IOP can be normal or elevated (>21 mm Hg).
- CAG: Hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally an edematous and hyperemic optic disk; IOP is generally elevated markedly (40 to 90 mm Hg) when symptoms are present.

Laboratory Tests

- None

Other Diagnostic Tests

- Emerging tests include optical coherence tomography, retinal nerve fiber analyzers, and confocal scanning laser tomography of the optic nerve.

CLINICAL PRESENTATION OF OPEN-ANGLE GLAUCOMA

POAG is a bilateral, genetically determined disorder constituting 60% to 70% of all glaucomas and 90% to 95% of primary glaucomas (see Clinical Presentation of Glaucoma above). An increased IOP is not required for diagnosis of POAG. Symptoms do not present until substantial visual field constriction occurs. Central visual acuity typically is maintained, even in the late stages of the disease. Even though POAG is a bilateral disease, it may have greater progression and severity in one eye.

4 Detection and diagnosis involve evaluation of the optic disk and retinal nerve fiber layer, assessment of the visual fields, and measurement of IOP. The presence of characteristic disk changes and visual field loss with or without increased IOP confirms the diagnosis of glaucoma. Typical disk changes and field loss occurring at an IOP of less than 21 mm Hg account for 20% to 30% of patients and are referred to as *normal-tension glaucoma.* Elevated IOP (>21 mm Hg) without disk changes or visual field loss is observed in 5% to 7% of individuals (known as *glaucoma suspects*) and is referred to as *ocular hypertension.* New technologies such as optical coherence tomography, retinal nerve fiber analyzers, or confocal scanning laser tomography of the optic nerve head may allow early identification of signs of glaucomatous retinal changes in ocular hypertensives, thus allowing for earlier initiation of therapy.[1–3,17]

Secondary open-angle glaucoma has many causes, including exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and medications. A system for classifying secondary glaucomas into pretrabecular, trabecular, and posttrabecular forms has been proposed. This classification allows drug therapy to be chosen on the basis of the pathogenic mechanism involved. In pretrabecular forms, a normal meshwork is covered that does not permit aqueous humor outflow. Trabecular forms of secondary glaucoma result from either an alteration of meshwork or an accumulation of material in the intertrabecular spaces. The posttrabecular forms result primarily from disorders causing increased episcleral venous blood pressure.[1,2,15–17]

PROGNOSIS OF OPEN-ANGLE GLAUCOMA

5 In most cases of POAG, the overall prognosis is excellent when it is discovered early and treated adequately. Even patients with advanced visual field loss can have continued visual field loss reduced if the IOP is maintained at low enough pressures (often <10 to 12 mm Hg). Progression of visual field loss still occurs in 8% to 20% of patients despite reaching standard therapy IOP goals. However, in untreated patients and in those who fail to achieve target IOP reduction, up to 80% have continued visual field loss. Estimates of progression to bilateral blindness in treated patients range from 4% to 22%. Thus the keys to medical treatment of POAG are an effective, well-tolerated drug regimen, close monitoring of therapy, and adherence. Medications will control IOP successfully in 60% to 80% of patients over a 5-year period. Availability of newer, highly effective, well-tolerated agents may improve the prognosis further.[1,2,5,17–19,23–28]

EPIDEMIOLOGY OF CLOSED-ANGLE GLAUCOMA

The incidence of closed-angle glaucoma varies by ethnic group, with a higher incidence in individuals of Inuit, Chinese, and Asian-Indian descent. Incidence rates of 1% to 4% have been reported in these populations.[1,2]

ETIOLOGY OF CLOSED-ANGLE GLAUCOMA (ANGLE-CLOSURE GLAUCOMA)

Primary CAG accounts for 5% or less of primary glaucomas; however, when CAG occurs, it may need to be treated as an emergency to avoid visual loss. CAG results from mechanical blockage of the (usually normal) trabecular meshwork by the peripheral iris. Partial or complete blockage of the meshwork occurs intermittently, resulting in extreme fluctuations between normal IOP with no symptoms, and very high IOP with symptoms of acute CAG. Between attacks of CAG, the IOP is usually normal unless the patient has concomitant open-angle glaucoma or nonreversible blockage of the meshwork with synechiae ("creeping" angle closure) that develops over time in the narrow-angle eye. Primary CAG occurs in patients with inherited shallow anterior chambers, which produce a narrow angle between the cornea and iris or tight contact between the iris and lens (pupillary block). The presence of a narrow angle is determined mainly by visualization of the angle by gonioscopy. Other tests for CAG involve provocation of an angle-closure–induced IOP increase. These tests, which attempt to produce angle closure through mydriasis (darkroom test or mydriasis test), or gravity (prone test), are rarely performed in the clinical setting.

Two major types of classic, reversible primary CAG have been described: CAG with pupillary block and CAG without pupillary block. CAG with pupillary block results when the iris is in firm contact with the lens. This produces a relative block of aqueous flow through the pupil to the anterior chamber (pupillary block), resulting in a bowing forward of the iris, which blocks the trabecular meshwork. CAG with pupillary block occurs most commonly when the pupil is in middilation. In this position, the combination of pupillary block and relaxed iris allows the greatest bowing of the iris; however, angle closure may occur during miosis or mydriasis.

CAG can occur without significant pupillary block in patients with an abnormality called a *plateau iris.* The ciliary processes in these cases are situated anteriorly, which indent the iris forward and cause closure of the trabecular meshwork, especially during mydriasis. The mydriasis produced by anticholinergic drugs or any other drug results in precipitation of both types of CAG glaucoma, whereas drug-induced miosis may produce pupillary block.

PATHOPHYSIOLOGY OF CLOSED-ANGLE GLAUCOMA

The mechanism of IOP elevation in CAG is clearer than that of POAG. In CAG, a physical blockage of trabecular meshwork is present. In many cases, single or multiple episodes of excessively high IOP (>40 mm Hg) result in optic nerve damage. Very high IOP (>60 mm Hg) may result in permanent loss of visual field within a matter of hours to days.

One type of CAG, known as "creeping" angle closure, occurs in patients with narrow angles in which the iris adheres to the trabecular meshwork and may result in continuously increased IOP in ranges more similar to those of POAG, and the clinical behavior is similar to POAG, with individuals differing in the degree and rapidity of visual loss from any given elevated IOP.[1]

CLINICAL PRESENTATION OF CLOSED-ANGLE GLAUCOMA

Patients with untreated CAG typically experience intermittent nonsymptomatic or prodromal symptoms brought on by precipitating events (see Clinical Presentation of Glaucoma above). Increased IOP during such prodromal episodes is not great enough or long enough to produce the other symptoms of a full-blown

TABLE 97-3 Drugs That May Induce or Potentiate Increased Intraocular Pressure

Open-angle glaucoma
Ophthalmic corticosteroids (high risk)
Systemic corticosteroids
Nasal/inhaled corticosteroids
Fenoldopam
Ophthalmic anticholinergics
Succinylcholine
Vasodilators (low risk)
Cimetidine (low risk)
Closed-angle glaucoma
Topical anticholinergics
Topical sympathomimetics
Systemic anticholinergics
Heterocyclic antidepressants
Low-potency phenothiazines
Antihistamines
Ipratropium
Benzodiazepines (low risk)
Theophylline (low risk)
Vasodilators (low risk)
Systemic sympathomimetics (low risk)
Central nervous system stimulants (low risk)
Serotonin selective reuptake inhibitors
Imipramine
Venlafaxine
Topiramate
Tetracyclines (low risk)
Carbonic anhydrase inhibitors (low risk)
Monoamine oxidase inhibitors (low risk)
Topical cholinergics (low risk)

attack. Such prodromal attacks last 1 to 2 hours, at which time pupillary block is broken by further mydriasis or miosis; or when miosis or mydriasis occurs in patients with plateau iris. The rate at which IOP increases may be a determinant of when full-blown symptoms occur. Visual fields demonstrate generalized constriction or typical glaucomatous defects. In prolonged attacks, total loss of vision may occur if the IOP is high enough. Tonometry reveals IOPs as high as 40 to 90 mm Hg. Patients who have developed adhesions between the iris and meshwork (anterior synechiae) may have chronic IOP elevation with intermittent spikes of high IOP when angle closure occurs.

DRUG-INDUCED GLAUCOMA

A number of medications are associated with increased IOP or carry labeling that cautions against use of the medication in glaucoma patients. The potential for a medication to produce or worsen glaucoma depends on the type of glaucoma and whether or not the patient is treated adequately.[25]

Patients with treated, controlled POAG are at minimal risk of induction of an increase in IOP by systemic medications with anticholinergic properties or vasodilators; however, in patients with untreated glaucoma or uncontrolled POAG, the potential of these medications to increase IOP should be considered. Topical anticholinergic agents used to produce mydriasis may result in an increase in IOP. Potent anticholinergic agents such as atropine or homatropine are most likely to increase IOP. Weaker anticholinergics, such as tropicamide, that produce less cycloplegia are less likely to increase IOP and are favored, along with phenylephrine, when mydriasis is desired in POAG patients. Inhaled, nasal, topical, or systemic glucocorticoids may increase IOP in both normal individuals and patients with POAG.

Patients with POAG appear to be particularly susceptible to glucocorticoid-induced increases in IOP. Glucocorticoids reduce the facility of aqueous humor outflow through the trabecular meshwork. The decreased facility of outflow appears to result from the accumulation of extracellular material blocking the trabecular channels. The potential of a glucocorticoid to increase IOP is related to its antiinflammatory potency and intraocular penetration. Thus patients should be treated with the lowest potency and dose and for the shortest time possible when steroids are indicated.

In patients predisposed to CAG (i.e., narrow anterior chambers), angle closure may be produced by any drug that causes mydriasis (e.g., anticholinergics). A wide range of sulfa compounds cause idiosyncratic reactions that result in anterior choroidal effusions with anterior movement of the iris and lens, resulting in angle closure. The topical use of anticholinergics or sympathomimetic agents most likely will result in angle closure. Systemic and inhaled anticholinergic and sympathomimetic agents also must be used with caution in such patients. As discussed previously, potent miotic agents such as echothiophate may produce angle closure by increasing pupillary block. Table 97–3 lists the drugs associated with potentiation of glaucoma.

TREATMENT

Ocular Hypertension

Treatment of the patient with possible glaucoma (ocular hypertension; i.e., patients with IOP >22 mm Hg) is less controversial than it was in the past, with the recent results of the Ocular Hypertensive Treatment Study (OHTS).[3] The OHTS helped to identify risk factors for treatment. Patients with intraocular pressures higher than 25 mm Hg, vertical cup-to-disk ratio of more than 0.5, and central corneal thickness of less than 555 micrometers are at greater risk for developing glaucoma. Risk factors such as family history of glaucoma, black ethnicity, severe myopia, and patients with only one eye must also be taken into consideration when deciding which individuals need treatment.

Patients without risk factors typically are not treated and are monitored for the development of glaucomatous changes. Patients with significant risk factors usually are treated with a well-tolerated topical agent such as a β-blocking agent, an α_2-agonist (brimonidine), a topical carbonic anhydrase inhibitor (CAI), or a prostaglandin analog, depending on individual patient characteristics. Optimally, therapy is initiated in one eye to assess efficacy and tolerance. Use of second- or third-line agents (e.g., pilocarpine or dipivefrin) when first-line agents fail to reduce IOP depends on the risk-to-benefit assessment of each patient. The cost, inconvenience, and frequent adverse effects of combination therapies, anticholinesterase inhibitors, and oral CAIs result in an unfavorable risk-to-benefit ratio in patients with possible glaucoma.[29]

The goal of therapy is to lower the IOP to a level associated with a decreased risk of optic nerve damage, usually at least a 20%, if not a 25% to 30%, decrease from the baseline IOP. Greater decreases may be required in high-risk patients or those with higher initial IOPs. Drug therapy should be monitored by measurement of IOP, examination of the optic disk, assessment of the visual fields, and evaluation of the patient for drug adverse effects and compliance with therapy. Patients who are unresponsive to or intolerant of a drug should be switched to an alternative agent rather than given an additional drug. Many clinicians prefer to discontinue all medications in patients who fail to respond adequately to simple topical therapy, closely monitor for development of disk changes or visual field loss, and treat again when such changes occur.[1,2,17–19,29]

More recently risk calculators have been suggested as a means of determining who are at greatest risk in developing glaucoma. It is hoped that with future improvement in such calculators, one would

be able to tailor treatment to those at greatest risk for developing glaucoma.

TREATMENT

Open-Angle Glaucoma

All patients with elevated IOP and characteristic optic disk changes and/or visual field defects not caused by other factors (i.e., glaucoma by definition) should be treated. Recent findings that 1 in 5 patients with "normal" IOP and glaucomatous retinal nerve findings (i.e., normal-tension glaucoma) do not have progression of visual field loss if left untreated have prompted recommendations to monitor normal-tension glaucoma patients without immediate threat of loss of central vision, and treat only when progression is documented. Some controversy exists as to whether the initial therapy of glaucoma should be surgical trabeculectomy (filtering procedure), argon laser trabeculectomy, or medical therapy.[1,2,17,18] Presently, drug therapy remains the most common initial treatment modality. Drug therapy of patients with documented glaucomatous change with either elevated or normal IOP is initiated in a stepwise manner (Fig. 97–5), starting with lower concentrations of a single, well-tolerated topical agent. The goal of therapy is to prevent further visual loss. A "target" IOP is chosen based on a patient baseline IOP and the amount of existing visual field loss. Typically, an initial target IOP reduction of 30% is desired. Greater reductions may be desired in patients with very high baseline IOPs or advanced visual field loss. Patients with normal baseline IOPs (normal-tension glaucoma) may have target IOPs of less than 10 to 12 mm Hg.

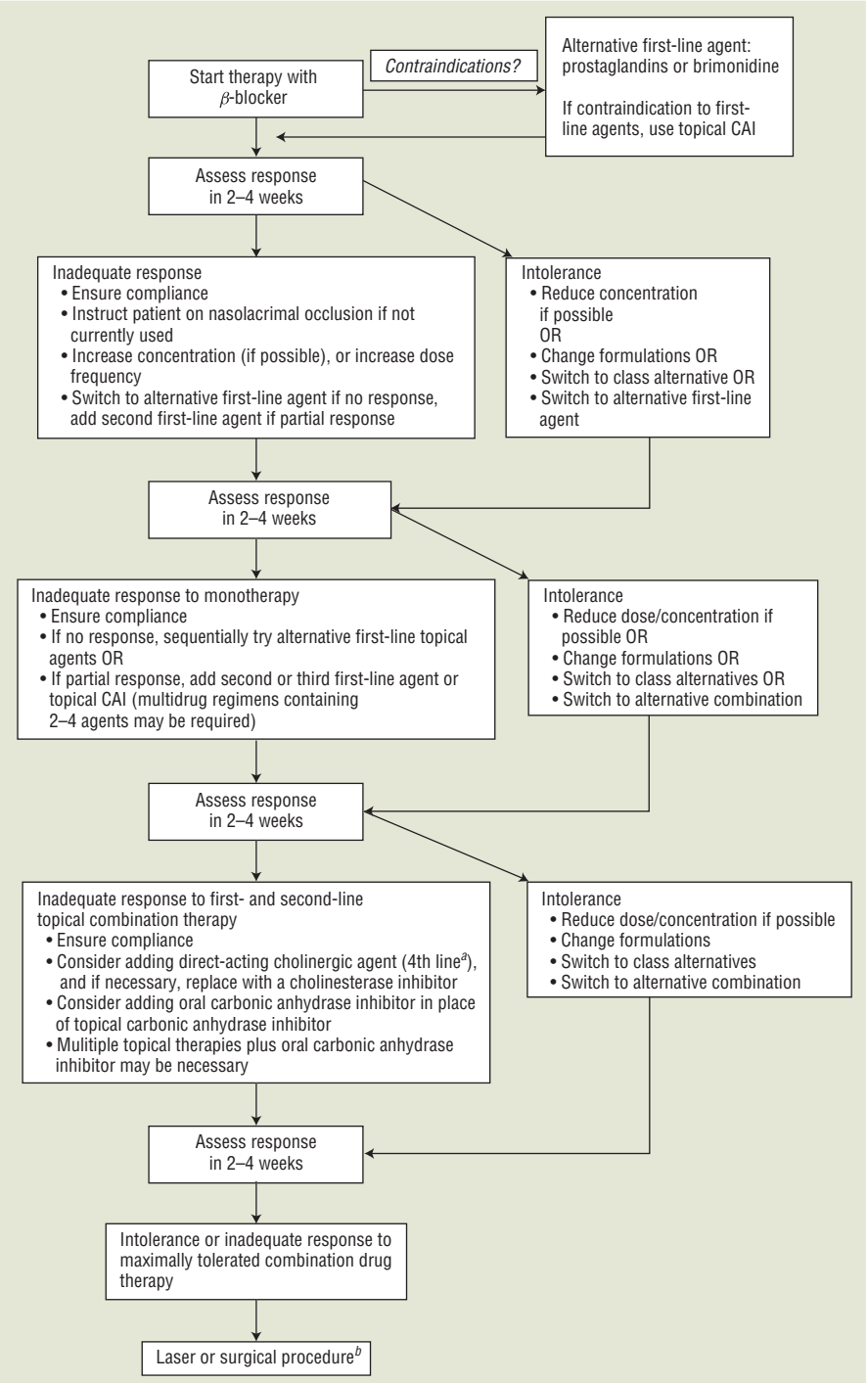

FIGURE 97-5. Algorithm for the pharmacotherapy of open-angle glaucoma. [a]Fourth-line agents not commonly used any longer. [b]Most clinicians believe laser procedure should be performed earlier (e.g., after three-drug maximum, poorly adherent patient). (CAI, carbonic anhydrase inhibitor.)

CLINICAL CONTROVERSY

How much should the IOP be reduced in patients who may have POAG? Although the major clinical trial (OHTS[3]) required a 20% reduction in IOP for patients with ocular hypertension, many clinicians believe a further lowering of IOP may be more beneficial in preventing the progression of ocular hypertension to glaucoma. The American Academy of Ophthalmology Preferred Practice Guidelines suggest 20% to 30% IOP lowering. It remains to be seen if a more aggressive approach earlier in the treatment of the POAG suspect would be more beneficial.

PHARMACOTHERAPEUTIC APPROACH

6 Medications most commonly used to treat glaucoma are the nonselective β-blockers, the prostaglandin analogs (latanoprost, travoprost, and bimatoprost), brimonidine (an α_2-agonist), and the fixed combination product of timolol and dorzolamide.[21–22]

Before 1996, a β-blocker was used provided no contraindications existed, because this class of drugs has a long history of successful use, providing a combination of clinical efficacy and tolerability. The newer agents, in particular the prostaglandin analogs, brimonidine, and topical CAIs, are also considered suitable first-line therapy or alternative initial therapy in patients with contraindications to or other concerns with β-blockers (see Fig. 97–5). Pilocarpine and dipivefrin are used as third-line therapies because of their increased frequency of adverse effects or reduced efficacy.

Therapy optimally is started as a single agent in one eye (except in patients with very high IOP or advanced visual field loss) to evaluate drug efficacy and tolerance. Monitoring of therapy should be individualized: Initial response to therapy is typically done 4 to 6 weeks after the medication is started. A monocular trial of medication is recommended when possible. Once IOPs reach acceptable levels, the IOP is monitored every 3 to 4 months (more frequently after any change in drug therapy).

Visual fields and disk changes are typically monitored annually or earlier if the glaucoma is unstable or there is suspicion of disease worsening. Patients should always be questioned regarding adherence to and tolerance of prescribed therapy. Initial IOP response does not predict long-term IOP control. Using more than one drop per dose does not improve response, but increases the likelihood of adverse effects and the cost of therapy. When using more than one medication, separation of drop instillation of each agent by at least 5 to 10 minutes is suggested to provide optimal ocular contact for each agent.

The value of an agent with which the patient has shown a drop in IOP following an initial response can be measured by discontinuing the medication completely and determining if an increase in IOP occurs. Patients responding to but intolerant of initial therapy may be switched to another drug or to an alternative dosage form of the same medication. For patients failing to respond to the highest tolerated concentrations of an initial drug, a switch to an alternative agent after 1 day of concurrent therapy should be considered. Alternatively, if only a partial response occurs, addition of another topical drug to be used in combination is a possibility. A number of drugs or drug combinations may need to be tried before an effective and well-tolerated regimen is identified. Because of the frequency of adverse effects, carbachol, topical cholinesterase inhibitors, and oral CAIs are considered last-line agents to be used in patients who fail less-toxic combination topical therapy.

CLINICAL CONTROVERSY

The American Academy of Ophthalmology has not designated any agent as the drug of choice for initiation of glaucoma treatment. In recent years, many clinicians have used the prostaglandin analogs because they are dosed once daily and achieve the best pressure reduction. However, others believe that even though the β-blockers are less potent in reducing IOP, they should still be used as initial agents because they are dosed once or twice daily and are available as generic products, and thus are more cost-effective.

NONPHARMACOLOGIC THERAPY: LASER AND SURGICAL PROCEDURES

When drug therapy fails, is not tolerated, or is excessively complicated, surgical procedures such as laser trabeculoplasty (argon or selective) or a surgical trabeculectomy (filtering procedure) may be performed to improve outflow. Laser trabeculoplasty is usually an intermediate step between drug therapy and trabeculectomy. Procedures with higher complication rates, such as those involving placement of draining tubes or destruction of the ciliary body (cyclodestruction), may be required when other methods fail (see Fig. 97–2).[1,2,25]

Surgical methods for reduction of IOP involve the creation of a channel through which aqueous humor can flow from the anterior chamber to the subconjunctival space (filtering bleb), where it is reabsorbed by the vasculature. A major reason for failure of the procedure is healing and scarring of the site.

Modification of the healing process to maintain patency is possible with the use of antiproliferative agents. The antiproliferative agents 5-fluorouracil and mitomycin C are used in patients undergoing glaucoma-filtering surgery to improve success rates by reducing fibroblast proliferation and consequent scarring. Although used most commonly in patients with increased risk for suboptimal surgical outcome (after cataract surgery and a previous failed filtering procedure), use of these agents also improves success in low-risk patients.[30–33]

TREATMENT

Closed-Angle Glaucoma

The goal of initial therapy for acute CAG with high IOP is rapid reduction of the IOP to preserve vision and to avoid surgical or laser iridectomy on a hypertensive, congested eye. Iridectomy (laser or surgical) is the definitive treatment of CAG; it produces a hole in the iris that permits aqueous humor flow to move directly from the posterior chamber to the anterior chamber, opening up the block at the trabecular meshwork. Drug therapy of an acute attack typically involves administration of pilocarpine, hyperosmotic agents, and a secretory inhibitor (a β-blocker, α_2-agonist, prostaglandin $F_2\alpha$ analog, or a topical or systemic CAI). With miosis produced by pilocarpine, the peripheral iris is pulled away from the meshwork. Although traditionally the drug of choice, pilocarpine used as initial therapy is controversial. Miotics may worsen angle closure by increasing pupillary block and producing anterior movement of the lens because of drug-induced accommodation.

At IOPs greater than 60 mm Hg, the iris may be ischemic and unresponsive to miotics; as the pressure drops and the iris responds, miosis occurs. During this time, the urge to use excessive amounts of pilocarpine must be resisted. The dose of pilocarpine commonly used is a 1% or 2% solution instilled every 5 minutes for two or three doses and then every 4 to 6 hours. However, many practitioners withhold application of pilocarpine until the IOP has been reduced by other agents, and then apply a single drop of 1% to 2% pilocarpine to produce miosis. In either case, the unaffected contralateral eye should be treated with the miotic every 6 hours to prevent development of angle closure. An osmotic agent also commonly is administered because these drugs produce the most rapid decrease

in IOP. Oral glycerin 1 to 2 g/kg can be used if an oral agent is tolerated; if not, intravenous mannitol 1 to 2 g/kg should be used. Osmotic agents reduce IOP by withdrawing water from the eye secondary to the osmotic gradient between the blood and the eyes. These drugs are among the first-line agents in the short-term treatment of CAG or other forms of acute very high IOP elevations. Topical corticosteroids often are used to reduce the ocular inflammation and reduce the development of synechiae in CAG eyes. In classic CAG, once the IOP is controlled, pilocarpine may be given every 6 hours until iridectomy is performed. Patients failing therapy altogether will require an emergency iridectomy.

Peripheral iridectomy essentially "cures" primary CAG without significant synechiae. Long-term drug therapy is not used unless IOP remains high because of the presence of synechiae blocking the trabecular meshwork or concurrent POAG. In such cases, the pharmacotherapeutic approach is essentially identical to that for the POAG patient, or laser or surgical procedures are performed.[1,2]

PHARMACOLOGIC AGENTS USED IN GLAUCOMA

β-BLOCKING DRUGS

The topical β-blocking agents are one of the most commonly used antiglaucoma medications (Table 97–4). β-Blockers lower IOP by

TABLE 97-4 Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic blocking agents						
Betaxolol	Relative β_1-selective	Generic	Solution	0.5	1 drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	1 drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	1 drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	1 drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	1 drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol	Solution	0.25, 0.5	1 drop every day–one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	1 drop every day[a]	
Nonspecific adrenergic agonists						
Dipivefrin	Prodrug	Propine	Solution	0.1	1 drop twice a day	Increased aqueous humor outflow
α_2-Adrenergic agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	1 drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow
Brimonidine		Alphagan P	Solution	0.15, 0.1	1 drop two to three times a day	
Cholinergic agonists direct acting						
Carbachol	Irreversible	Carboptic, Isopto Carbachol	Solution	1.5, 3	1 drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.25, 0.5, 1, 2, 4, 6, 8, 10	1 drop two to three times a day 1 drop four times a day	
		Pilopine HS	Gel	4	Every 24 h at bedtime	
Cholinesterase inhibitors						
Echothiophate		Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic anhydrase inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt	Solution	2	Two to three times a day	
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
			Injection	500 mg/vial	250–500 mg	
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin analogs						
Latanoprost	Prostaglandin $F_{2\alpha}$ analog	Xalatan	Solution	0.005	1 drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	Prostamide analog	Lumigan	Solution	0.03	1 drop every night	
Travoprost		Travatan, Travatan Z	Solution	0.004	1 drop every night	
Combinations						
Timolol-dorzolamide		Cosopt	Solution	Timolol 0.5% dorzolamide 2%	1 drop twice daily	
Timolol-brimonidine		Combigan	Solution	Timolol 0.5% brimonide 0.2%	1 drop twice daily	

[a]Use of nasolacrimal occlusion will increase number of patients successfully treated with longer dosage intervals.

20% to 30% with a minimum of local ocular adverse effects. These are commonly one of the agents of first choice in treating POAG if no contraindications exist.[1,2,17–19,34–36]

The β-blocking agents produce ocular hypotensive effects by decreasing the production of aqueous humor by the ciliary body without producing substantial effects on aqueous humor outflow facility. The mechanism by which β-blockers decrease aqueous humor inflow remains controversial, but it is most frequently attributed to β_2-adrenergic receptor blockade in the ciliary body.

Five ophthalmic β-blockers are presently available: timolol, levobunolol, metipranolol, carteolol, and betaxolol. Timolol, levobunolol, and metipranolol are nonspecific β-blocking agents, whereas betaxolol is a relatively β_1-selective agent. Carteolol is a nonspecific blocker with intrinsic sympathomimetic activity. Despite differences in potency, selectivity, lipophilicity, and intrinsic sympathomimetic activity, the five agents reduce IOP to a similar degree, although betaxolol has been reported to produce somewhat less lowering of IOP than timolol and levobunolol. Levobunolol may be more effective than timolol and betaxolol in reducing postcataract surgery IOP increases. Levobunolol solution is more effective in controlling IOP than other agents when given as aqueous solutions on a once-daily schedule (up to 70% of patients). Timolol in the form of a gel-forming solution (Timoptic-XE) provides equivalent IOP control with once-daily administration when compared with the same concentration of the aqueous solution administered twice daily. The choice of a specific β-blocking agent generally is based on differences in adverse effect potential, individual patient response, and cost. Long-term treatment with topical β-blockers results in tachyphylaxis in 20% to 25% of patients. The mean IOP reduction from baseline may be smaller in patients receiving topical β-blockers with concurrent systemic β-blockers.[29]

Local adverse effects with β-blockers usually are tolerable, although stinging on application occurs commonly, particularly with betaxolol solution (less with betaxolol suspension) and metipranolol. Other local effects include dry eyes, corneal anesthesia, blepharitis, blurred vision, and, rarely, conjunctivitis, uveitis, and keratitis. Some local reactions may be a result of preservatives used in the commercially available products. Switching from one agent to another or switching the type of formulation may improve tolerance in patients experiencing local adverse effects.

Systemic effects are the most important adverse effects of β-blockers. Drug absorbed systematically may produce decreased heart rate, reduced blood pressure, negative inotropic effects, conduction defects, bronchospasm, central nervous system effects, and alteration of serum lipids, and may block the symptoms of hypoglycemia. The β_1-specific agents betaxolol and possibly carteolol (as a consequence of intrinsic sympathomimetic activity) are less likely to produce the systemic adverse effects caused by β-adrenergic blockade, such as the cardiac effects and bronchospasm, but a real risk still exists. The use of timolol as a gel-forming liquid or betaxolol as a suspension allows for administration of less drug per day, and therefore reduces the chance for systemic adverse effects compared with the aqueous solutions.

Because of their systemic adverse effects, all ophthalmic β-blockers should be used with caution in patients with pulmonary diseases, sinus bradycardia, second- or third-degree heart block, congestive heart failure, atherosclerosis, diabetes, and myasthenia gravis, as well as in patients receiving oral β-blocker therapy. Use of nasolacrimal occlusion (NLO; see Patient Education below for description) technique during administration reduces the risk or severity of systemic adverse effects, as well as optimizes response. Overall, β-adrenergic blocking agents are well tolerated by most patients, and most potential problems can be avoided by appropriate patient evaluation, drug choice, and monitoring of drug therapy.

In patients failing or having an inadequate response to single-drug therapy with a β-blocking agent, the addition of a CAI, parasympathomimetic agent, prostaglandin analog, or an α_2-adrenergic receptor agonist usually will result in additional IOP reduction. Epinephrine or dipivefrin added to a β-blocking agent (particularly nonspecific β-blockers) usually results in only minimal additional IOP reduction.[1–3,17–19,29]

α_2-ADRENERGIC AGONISTS

Brimonidine and the less lipid-soluble and less receptor-selective apraclonidine are α_2-adrenergic agonists structurally similar to clonidine. Apraclonidine is indicated and brimonidine is effective for prevention or control of postoperative or postlaser treatment increases in IOP. Brimonidine is considered a first-line or adjunctive agent in the therapy of POAG, and apraclonidine is seen as a second-line or adjunctive therapy. Use of apraclonidine has fallen dramatically because of a high incidence of loss of control of IOP (tachyphylaxis) and a more severe and prevalent ocular allergy rate.

α_2-Agonists reduce IOP by decreasing the rate of aqueous humor production (some increase in uveoscleral outflow also occurs with brimonidine). The drugs reduce IOP by 18% to 27% at peak (2 to 5 hours) and by 10% at 8 to 12 hours. Comparative trials demonstrate a reduction in IOP similar to that obtained with 0.5% timolol. Use of brimonidine 0.2% every 8 to 12 hours appears to provide maximum IOP-lowering effects in long-term use. Use of NLO (see Patient Education, below) may improve response and allow the longer dosing frequency (i.e., every 12 hours). Combinations of α_2-agonists with β-blockers, prostaglandin analogs, or CAIs produce additional IOP reduction.

An allergic-type reaction characterized by lid edema, eye discomfort, foreign-object sensation, itching, and hyperemia occurs in approximately 30% of patients with apraclonidine. Brimonidine produces this adverse effect in up to 8% of patients. This reaction commonly necessitates drug discontinuation. Systemic adverse effects with brimonidine include dizziness, fatigue, somnolence, dry mouth, and possibly a slight reduction in blood pressure and pulse. α_2-Agonists should be used with caution in patients with cardiovascular diseases, renal compromise, cerebrovascular disease, and diabetes, as well as in those taking antihypertensives and other cardiovascular drugs, monoamine oxidase inhibitors, and tricyclic antidepressants.

Brimonidine is also contraindicated in infants because of apneic spells and hypotensive reactions. In terms of overall efficacy and tolerability, brimonidine approximates that achieved with β-blockers.[1,2,17–19,29]

Brimonidine-purite 0.15% or 0.1% is a formulation of brimonidine in a lower concentration than the original product, that contains a less-toxic preservative than the most commonly employed benzalkonium chloride. The newer formulations are as effective as the original because the more neutral pH of brimonidine-purite (0.15% pH 7.2; 0.1% pH 7.7) allows for higher concentrations of brimonidine in the aqueous humor with a similar reduction in IOP and a reduced incidence of ocular allergy.[29]

The combination product timolol 0.5%/brimonidine 0.2% (Combigan) may provide additional IOP lowering than either agent alone. A new treatment option, this product is marketed in solution that is dosed twice daily.

CLINICAL CONTROVERSY

Many animal trials demonstrate that brimonidine has excellent neuroprotective properties.[12–15] Some clinicians believe that one of the major advantages of using brimonidine lies in its potential neuroprotective properties. However, neuroprotection has not been demonstrated in human trials.

PROSTAGLANDIN ANALOGS

The prostaglandin analogs, including latanoprost, travoprost, and bimatoprost, reduce IOP by increasing the uveoscleral and, to a lesser extent, trabecular outflow of aqueous humor. Some differences in receptor sites and mechanisms of action may exist between the two prostaglandins (latanoprost and travoprost), the prostamide (bimatoprost). Bimatoprost may be slightly more effective in lowering IOP, getting a larger percentage of patients to lower IOPs, and in patients unresponsive to latanoprost.[29,37–39]

Reduction in IOP with once-daily doses of prostaglandin $F_2\alpha$ analogs (a 25% to 35% reduction) is often greater than that seen with timolol 0.5% twice daily. In addition, nocturnal control of IOP is improved compared with timolol. Interestingly, administration of prostaglandin $F_2\alpha$ analogs twice daily may reduce the IOP comparably to once-daily dosing. The drugs are administered at nighttime, although they are probably as effective if given in the morning.

Prostaglandin analogs are well tolerated and produce fewer systemic adverse effects than timolol. Local ocular tolerance generally is good, but ocular reactions such as punctate corneal erosions and conjunctival hyperemia do occur. Local intolerance occurs in 10% to 25% of patients with these agents.

With prostaglandin analogs, altered iris pigmentation occurs in 15% to 30% of patients, particularly those with mixed-color irises (blue-brown, green-brown, blue-gray-brown, or yellow-brown eyes), which become more brown in color over 3 to 12 months. The change in iris pigmentation will often appear within 2 years, and long-term consequences of this pigment change appear to be mostly cosmetic but irreversible upon discontinuation. Hypertrichosis is fairly common and reverses upon discontinuation of the drug. Hyperpigmentation around the lids and lashes has also been reported and appears to reverse upon discontinuation.

These agents are associated with uveitis, and caution is recommended in patients with ocular inflammatory conditions. Cystoid macular edema also has been reported. Cases of worsening of herpetic keratitis have been reported.

Prostaglandin analogs can be used in combination with other antiglaucoma agents for additional IOP control because of their unique mechanism of action. Given their excellent efficacy and side-effect profile, prostaglandin analogs provide effective monotherapy or adjunctive therapy in patients who are not responding to or tolerating other agents. Many glaucoma experts have advocated the use of prostaglandin analogs as first-line therapy in POAG. Long-term studies of these agents are ongoing, but they appear to be safe, efficacious, and well tolerated in glaucoma therapy.[17–19,29,37,38]

CARBONIC ANHYDRASE INHIBITORS

Topical Agents

CAIs reduce IOP by decreasing ciliary body aqueous humor secretion. CAIs appear to inhibit aqueous production by blocking active secretion of sodium and bicarbonate ions from the ciliary body to the aqueous humor.[1,2,29] Topical CAIs such as dorzolamide and brinzolamide are well tolerated and are indicated for monotherapy or adjunctive therapy of open-angle glaucoma and ocular hypertension. Relatively specific inhibitors of carbonic anhydrase enzyme II such as dorzolamide and brinzolamide reduce IOP by 15% to 26%.

Topical CAIs generally are well tolerated. Local adverse effects include transient burning and stinging, ocular discomfort and transient blurred vision, tearing, and, rarely, conjunctivitis, lid reactions, and photophobia. A superficial punctate keratitis occurs in 10% to 15% of patients. Brinzolamide produces more blurry vision but is less stinging than dorzolamide. Systemic adverse effects are unusual despite the accumulation of drug in red blood cells. Because of their favorable adverse-effect profile, topical CAIs provide a useful alternative agent for monotherapy or adjunctive therapy in patients with inadequate response to or who are unable to use other agents. The drugs may add additional IOP reduction in patients using other single or multiple topical agents. The usual dose of a topical CAI is 1 drop every 8 to 12 hours. Administration every 12 hours produces somewhat less IOP reduction than administration every 8 hours. Use of NLO should optimize response to CAI given at any interval.[1,2,17–19,29,34,36] The combination product timolol 0.5% and dorzolamide 2% (Cosopt) is dosed twice daily and produces equivalent IOP lowering to each product dosed separately.

Systemic Agents

Systemic CAIs are indicated in patients failing to respond to or tolerate maximum topical therapy. Systemic and topical CAIs should not be used in combination because no data exist concerning improved IOP reduction, and the risk for systemic adverse effects is increased. Oral CAIs reduce aqueous humor inflow by 40% to 60% and IOP by 25% to 40%. The available systemic CAIs (see Table 97–4) produce equivalent IOP reduction but differ in potency, adverse effects, dosage forms, and duration of action. Despite their excellent effects on elevated IOP of any etiology, the systemic CAIs frequently produce intolerable adverse effects. As a result, CAIs are considered third-line agents in the treatment of POAG and often used for short-term administration to lower IOP.

On average, only 30% to 60% of patients are able to tolerate oral CAI therapy for prolonged periods. Intolerance to CAI therapy results most commonly from a symptom complex attributable to systemic acidosis and including malaise, fatigue, anorexia, nausea, weight loss, altered taste, depression, and decreased libido. Other adverse effects include renal calculi, increased uric acid, blood dyscrasias, diuresis, and myopia. Elderly patients do not tolerate CAIs as well as younger patients. The available CAIs produce the same spectrum of adverse effects; however, the drugs differ in the frequency and severity of the adverse effects listed.

CAIs should be used with caution in patients with sulfa allergies (all CAIs, topical or systemic, contain sulfonamide moieties), sickle cell disease, respiratory acidosis, pulmonary disorders, renal calculi, electrolyte imbalance, hepatic disease, renal disease, diabetes mellitus, or Addison's disease. Concurrent use of a CAI and a diuretic may rapidly produce hypokalemia. High-dose salicylate therapy may increase the acidosis produced by CAIs, whereas the acidosis produced by CAIs may increase the toxicity of salicylates.[1,2,17–19,21,29,34,35]

PARASYMPATHOMIMETIC AGENTS

The parasympathomimetic (cholinergic) agents reduce IOP by increasing aqueous humor trabecular outflow. The increase in outflow is a result of physically pulling open the trabecular meshwork secondary to ciliary muscle contraction, thereby reducing resistance to outflow. These agents may reduce uveoscleral outflow. Cholinergics agents work well to decrease IOP, but their use as primary or even adjunctive agents in the treatment of glaucoma has decreased significantly because of local ocular adverse effects and/or frequent dosing requirements.

Pilocarpine, the parasympathomimetic agent of choice in POAG, is available as an ophthalmic solution, an ocular insert, and a hydrophilic polymer gel (see Table 97–4). Pilocarpine produces similar (20% to 30%) reductions in IOP as those seen with β-blocking agents. Pilocarpine in POAG or "glaucoma suspects" is initiated as 0.5% or 1% solution, 1 drop three to four times daily. The use of NLO improves response and reduces the need for an every-6-hour dosing frequency. The use of 1 drop of 2% pilocarpine every 6 to 12 hours and NLO provides optimal response in many patients. Both drug concentration and frequency may be increased if IOP reduction is inadequate. Patients with darkly pigmented eyes

frequently require higher concentrations of pilocarpine than do patients with lightly pigmented eyes. Concentrations of pilocarpine above 4% rarely improve IOP control in patients, other than those patients with darkly pigmented eyes.

Pilocarpine 4% gel (Pilopine HS) once daily is equivalent to treatment with pilocarpine solution 4% four times daily or timolol 0.5% twice daily. When using every-24-hour dosing of pilocarpine gel, the adequacy of IOP control late in the dosing interval should be confirmed. Ocular adverse effects of pilocarpine include miosis, which decreases night vision and vision in patients with central cataracts. Visual field constriction may be seen secondary to miosis and should be considered when evaluating visual field changes in a glaucoma patient. Pilocarpine ciliary muscle contraction produces accommodative spasm, particularly in young patients still able to accommodate (prepresbyopic). Pilocarpine also may produce frontal headache, brow ache, periorbital pain, eyelid twitching, and conjunctival irritation or injection early in therapy, which tends to decrease in severity over 3 to 5 weeks of continued therapy.

Cholinergics produce a breakdown of the blood–aqueous humor barrier and may result in a worsening of an ocular inflammatory reaction or condition. Systemic cholinergic adverse effects of pilocarpine—such as diaphoresis, nausea, vomiting, diarrhea, cramping, urinary frequency, bronchospasm, and heart block—are rare but may be seen in patients who are using products with high pilocarpine concentrations (6% to 8%), or in those patients who are using such products overzealously in treatment of acute-angle closure. Other adverse effects associated with direct-acting miotics include retinal tears or detachment, allergic reaction, permanent miosis, cataracts, precipitation of CAG, and, rarely, miotic cysts of the pupillary margin.

Carbachol is a potent direct-acting miotic agent; its duration of action is longer than that of pilocarpine (8 to 10 hours) because of resistance to hydrolysis by cholinesterases. This drug also may act as a weak inhibitor of cholinesterase. Patients with an inadequate response to or intolerance of pilocarpine as a result of ocular irritation or allergy frequently do well on carbachol. The ocular and systemic adverse effects of carbachol are similar to but more frequent, constant, and severe than those of pilocarpine.[1,2,17–19,29,34,35] Clinical use of carbachol is limited and may not be commercially available in the near future.

The cholinesterase inhibitors used most commonly in the treatment of POAG are the long-acting, relatively irreversible agents demecarium and echothiophate (limited commercial availability; see Table 97–4). These agents are potent inhibitors of pseudocholinesterase, but they also inhibit true cholinesterase. Because of the serious ocular and systemic toxic effects of these agents, the cholinesterase inhibitors are reserved primarily for patients who are either not responding to or are intolerant of other therapy. Because of their cataractogenic properties, most ophthalmologists use these agents only in patients without lenses (aphakia) and in patients with artificial lenses (pseudophakia). The ocular and periocular parasympathomimetic adverse effects are more common and more severe than with pilocarpine or carbachol.

In addition to the parasympathomimetic effects, the cholinesterase inhibitors may produce severe fibrinous iritis (particularly with the irreversible inhibitors), synechiae, iris cysts, conjunctival thickening, occlusion of the nasolacrimal ducts, and cataracts. The inhibition of systemic pseudocholinesterase by these agents decreases the rate of succinylcholine hydrolysis, resulting in prolonged muscle paralysis. Cholinesterase inhibitors should be discontinued at least 2 weeks before procedures in which succinylcholine is used.

The role of cholinesterase inhibitors in glaucoma is limited by the frequency and potential toxicity of these agents. In phakic patients, cholinesterase inhibitors should be administered only if intolerance or failure results with other antiglaucoma medications. Cholinesterase inhibitors have been shown to provide additional IOP-lowering effects when used with β-blockers, CAIs, and sympathomimetic (adrenergic) agents. As with all agents for glaucoma, therapy should be initiated with lower concentrations of these agents. A once-daily administration frequency should be used in most patients unless very high IOP is present.

Use of NLO likely improves response and reduces systemic adverse effects and should be performed by all patients administering cholinesterase inhibitors. These agents should be used with caution in patients with asthma, retinal detachments, narrow angles, bradycardia, hypotension, heart failure, Down's syndrome, epilepsy, parkinsonism, peptic ulcer, and ocular inflammation, as well as in those receiving cholinesterase inhibitor therapy for myasthenia gravis or exposure to carbamate or organophosphate insecticides and pesticides.[1,2,17–19,29,34,35]

EPINEPHRINE AND DIPIVEFRIN

The mechanism of action by which epinephrine lowers IOP has not been fully elucidated; however, a β_2-receptor–mediated increase in outflow facility through the trabecular meshwork and the uveoscleral route appears to be the primary mechanism. Compared with β-blockers or miotics, epinephrine and dipivefrin reduce IOP less. With the advent of the better tolerated and more efficacious agents to treat glaucoma, the clinical use of epinephrines has decreased dramatically.

Epinephrine is not commercially available anymore. Use of the prodrug of epinephrine, dipivefrin, allows use of lower concentrations secondary to improved intraocular absorption (10- to 15-fold higher). The 0.1% dipivefrin produces equivalent IOP reduction to 1% to 2% epinephrine. Consequently, dipivefrin may be tolerated by patients who are unable to tolerate epinephrine solutions, and it is often chosen over other epinephrine products when this class of drugs is indicated.

A factor limiting the usefulness of epinephrine was the high frequency of local ocular adverse effects. Tearing, burning, ocular discomfort, brow ache, conjunctival hyperemia, punctate keratopathy, allergic blepharoconjunctivitis, rare loss of eyelashes, stenosis of the nasolacrimal duct, and blurred vision may occur. Prolonged use (>1 year) may result in deposition of pigment (adrenochrome) in the conjunctiva and cornea. Pigment also may deposit in soft contact lenses, turning them black. These adverse effects occur less frequently with dipivefrin. Epinephrine may produce mydriasis (particularly when combined with a β-blocker) and may precipitate acute CAG in patients with narrow anterior chambers. A transient increase in IOP may occur with initial therapy, particularly in patients not using other antiglaucoma medications. A relative contraindication to the use of dipivefrin is aphakia (i.e., after cataract removal) or lens dislocation because of the development of swelling of the macular portion of the retina. The edema is dose dependent and disappears with drug discontinuation.

Systemic adverse effects of epinephrine include headache, faintness, increased blood pressure, tachycardia, arrhythmias, tremor, pallor, anxiety, and increased perspiration. Epinephrine should be used with caution in patients with cardiovascular diseases, cerebrovascular diseases, aphakia, CAG, hyperthyroidism, and diabetes mellitus, as well as in patients undergoing anesthesia with halogenated hydrocarbon anesthetics. Using NLO with epinephrine and dipivefrin will improve therapeutic response and reduce the risk of systemic adverse effects.[1,2,17–19,29,34,35]

FUTURE DRUG THERAPIES

It is hoped that new agents, improved formulations, and novel approaches to the reduction of IOP and other methods of preven-

tion of glaucomatous visual field loss will provide more effective and better-tolerated therapies. Agents that are neuroprotective and act through mechanisms other than IOP reduction are likely to be part of glaucoma therapy in the future.[13–15,40]

EVALUATION OF THERAPEUTIC OUTCOMES

The ultimate goal of drug therapy in the patient with glaucoma is to preserve visual function through reduction of IOP to a level at which no further optic nerve damage occurs. Because of the poor relationship between IOP and optic nerve damage, no specific target IOP exists. Indeed, drugs used to treat glaucoma may act in part to halt visual field loss through mechanisms separate from or in addition to IOP reduction, such as improvements in retinal or choroidal blood flow. Often a 25% to 30% reduction is desired, but greater reductions (40% to 50%) may be desired in patients with initially high IOPs. For patients with glaucoma, an IOP of less than 21 mm Hg generally is desired, with progressively lower target pressures needed for greater levels of glaucomatous damage. Even lower IOPs (possibly even below 10 mm Hg) are required in patients with very advanced disease, those showing continued damage at higher IOPs, and those with normal-tension glaucoma and pretreatment pressures in the low to middle teens. The IOP considered acceptable for a patient is often a balance of desired IOP and acceptable treatment-related toxicity and patient quality of life.

PATIENT EDUCATION

7 An important consideration in patients failing to respond to drug therapy is adherence. Poor adherence or nonadherence occurs in 25% to 60% of glaucoma patients.

A large percentage of patients also fail to use topical ophthalmic drugs correctly. Patients should be taught the following procedure:

1. Wash and dry the hands; shake the bottle if it contains a suspension.
2. With a forefinger, pull down the outer portion of the lower eyelid to form a "pocket" to receive the drop.
3. Grasp the dropper bottle between the thumb and fingers with the hand braced against the cheek or nose and the head held upward.
4. Place the dropper over the eye while looking at the tip of the bottle; then look up and place a single drop in the eye.
5. The lids should be closed (but not squeezed or rubbed) for 1 to 3 minutes after instillation. This increases the ocular availability of the drug.
6. Recap bottle and store as instructed.

Note that many patients are physically unable to administer their own eyedrops without assistance. NLO also should be used to improve ocular bioavailability and reduce systemic absorption.[1,2,17–19,29,34,35] The patient induces NLO for 1 to 3 minutes by closing the eyes and placing the index finger over the nasolacrimal drainage system in the inner corner of the eye. This maneuver, as well as eyelid closure itself, decreases nasolacrimal drainage of drug, thereby decreasing the amount of drug available for systemic absorption by the nasopharyngeal mucosa. The use of NLO may improve drug response significantly, reduce adverse effects, and allow less frequent dosing intervals and the use of lower drug concentrations.

Use of more than 1 drop per dose increases costs, does not improve response significantly, and may increase adverse effects. When two drugs are to be administered, instillations should be separated by at least 3 to 5 minutes (preferably 10 minutes) to prevent the drug administered first from being washed out. The patient should be taught not to touch the dropper bottle tip with eye, hands, or any surface.

Adherence to glaucoma therapy commonly is inadequate, and it always should be considered as a possible cause of drug therapy failure. Assessment of adherence by healthcare providers generally is poor, so all patients should be encouraged continually to administer prescribed therapy diligently as instructed. To improve adherence, the patient, family, and care providers should be fully informed of the expectations of therapy and the need to continue therapy despite a lack of symptoms. Possible adverse effects of the medication and ways to reduce them should be discussed. Adherence will be improved by good communication, close monitoring, and use of well-tolerated and convenient drug regimens.[1,2,17–19,29]

CONCLUSIONS

The glaucomas are a group of primary and secondary diseases, the management of which presents a considerable challenge to the clinician. Successful therapy requires rational use of antiglaucoma medications and patient adherence to the selected regimen, combined with conscientious monitoring for adverse effects and disease progression. The reward for successful therapy is considerable—the maintenance of vision. The overview of the clinical findings, pathology, and drug therapy presented in this chapter provides the clinician with the fundamentals necessary to understand and treat glaucoma.

ABBREVIATIONS

CAG: closed-angle glaucoma

CAI: carbonic anhydrase inhibitor

IOP: intraocular pressure

NLO: nasolacrimal occlusion

OHTS: Ocular Hypertensive Treatment Study

POAG: primary open-angle glaucoma

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