Chapter 114: Glaucoma

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 66, Glaucoma.

KEY CONCEPTS

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1. Primary open-angle glaucoma (POAG) or ocular hypertension is more prevalent outside Asia than primary angle-closure glaucoma (PACG).
2. In any form of glaucoma, reduction of intraocular pressure (IOP) is essential.
3. IOP is an 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. 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 IOP.
7. Local adverse events are common with topical glaucoma medications, but patient education and reinforcing adherence are essential to prevent glaucoma progression.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video from Dr. Henry Jampel, a leading glaucoma specialist, entitled "Using Eye Drops to Treat Glaucoma" from The Wilmer Eye Institute (https://www.youtube.com/watch?v=IR7nH1kXsBY). Proper administration of eye drops is critical prior to discussing glaucoma medication with a patient. The video presents common mistakes associated with eye drop administration, the proper technique for administering eye drops, and frequently asked questions about using eye drops in glaucoma. It is a useful tool for the students to help ensure that the proper use of eye drops in glaucoma in the ASSESS and IMPLEMENT steps for the Patient Care Process.

INTRODUCTION

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) is thought to play an important role in the pathogenesis of glaucoma, but it is not a diagnostic criterion for glaucoma. Consistently elevated IOP without signs or symptoms of glaucoma is called ocular hypertension (OHT).

Two major types of glaucoma have been identified: open angle and closed angle. Primary open-angle glaucoma (POAG) accounts for the great majority of cases in North America, while primary angle-closure glaucoma (PACG) is more prevalent in Asia. Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs and can lead to serious complications. Both primary and secondary glaucomas may be caused by a combination of open-angle and closed-angle mechanisms (Table 114-1 and Fig. 114-1). Patients with consistently high IOP or patients with clinical findings suspicious of early glaucomatous changes are called "glaucoma suspects."[1,2]

FIGURE 114-1

Aqueous humor drainage pathways in normal eyes and eyes with glaucoma. The cross-section demonstrates aqueous humor drainage in the normal healthy eye, and in primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG). The three diagrams indicate the following aqueous humor pathways: (*A*) healthy eye, (*B*) POAG, and (*C*) PACG. Aqueous humor exits the anterior chamber by two routes: The trabecular meshwork (conventional) with approximately 80%-85% of outflow through to Schlemm's canal and the rest of the aqueous humor filtering through the uveoscleral (unconventional) outflow pathway (ciliary body and the suprachoroidal space). POAG is often associated with increased resistance to aqueous humor drainage at the trabecular meshwork. In PACG the drainage pathway is often obstructed by the iris. *(Figure by Lauren Kalinoski, MS, CMI. Courtesy University of Illinois at Chicago Department of Ophthalmology, Chicago, Illinois).*

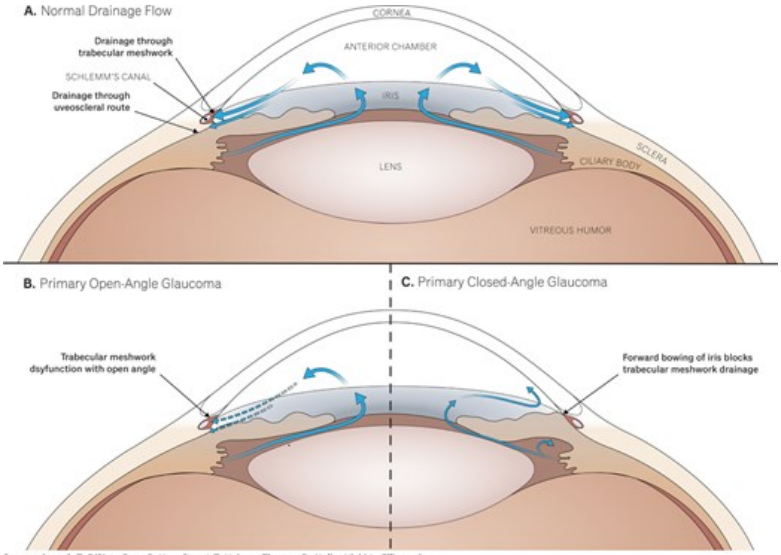


TABLE 114-1

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
IV. Others

BASIC CONCEPTS

Aqueous Humor Dynamics and IOP

An understanding of IOP and aqueous humor dynamics will assist the reader in understanding the drug therapy of glaucoma.[1-6]

Aqueous humor is a clear fluid and ultrafiltrate of the serum that fills and helps to form the anterior and posterior chambers of the eye.[7] It is formed in the ciliary body and its epithelium 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 by other solutes such as ascorbate from the ciliary body epithelial cells into the aqueous humor result in the 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, β-adrenergic blocking dopamine-blocking, carbonic anhydrase-inhibiting, melatonin-1 agonist, 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. 114-1).[1-6]

Aqueous humor in the anterior chamber leaves the eye by two routes: (a) filtration through the trabecular meshwork (conventional outflow) to the Schlemm's canal (80%-85%) and (b) through the ciliary body and the suprachoroidal space (uveoscleral outflow or unconventional outflow) (see Fig. 114-1). Cholinergic agents such as pilocarpine appear to increase outflow by physically opening the meshwork pores secondary to ciliary muscle contraction. The nitric oxide group on latanoprost bunod is believed to cause trabecular relaxation and increased trabecular meshwork outflow. ROCK inhibitors are believed to increase aqueous humor outflow through the trabecular meshwork. Prostaglandins are thought to result in remodeling of extracellular matrix in the meshwork, thereby increasing mainly uveoscleral outflow. The uveoscleral outflow of aqueous humor is increased by prostaglandin analogs, 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. 114-1). Novel adenosine receptor agonists, cannabinoids, serotonin agents, and dopamine agonists also increase aqueous humor outflow and reduce IOP.[1-4,6]

The median IOP measured in large populations is 15.5 ± 2.5 mm Hg (2.1 ± 0.3 kPa); 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. Gender, general health, and lifestyle (eg, smoking) are some factors that may have a long-term effect on the IOP.[5,7-11] The amount of caffeine in one cup of caffeinated coffee (182 mg) increases IOP by about 1 mm Hg (0.1 kPa) after 90 minutes; this increase in IOP is not clinically relevant. Patients who have thinner corneas, have had laser refractive eye surgery (LASIK), or have had cataract surgery demonstrate falsely low IOP readings. IOP is measured by tonometry: indentation tonometry, applanation tonometry, or a noncontact method using an air pulse. Newer methods of tonometry include the Pascal tonometer, Icare™ rebound tonometer, and a contact lens-based investigational device that can remotely monitor 24-hour IOP changes from baseline.[7] These methods may result in slightly different pressure readings. IOPs consistently greater than 21 mm Hg (2.8 kPa) are found in 5% to 8% of the general population. The incidence increases with age, such that “abnormal” (ie, >22 mm Hg [2.9 kPa]) IOP is found in 15% of those 70 to 75 years of age. Intermittently very high IOP (>40 mm Hg [5.3 kPa]) is found in patients with PACG.

IOP demonstrates considerable circadian variation (often referred to as *diurnal* IOP or the IOP during the daily 24-hour cycle) 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.[1-6,8-14] Low systemic blood pressure in conjunction with high IOPs (decreased ocular perfusion pressure) at night can result in optic nerve head damage. Generally, the circadian IOP variation is less than 3 to 4 mm Hg (0.4-0.5 kPa); however, it may be greater for patients with glaucoma. This circadian variation and the variable relationship of IOP with visual loss make measurement of IOP a poor screening test for glaucoma. Controlling circadian increases in IOP is thought to be important in the prevention of disease progression. Prostaglandin analogs and carbonic anhydrase inhibitors (CAIs) reduce nocturnal IOP, whereas beta blockers and alpha-2 adrenergic agents have minimal effects.[1-6,8-15]

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 (2.8-4.0 kPa), only 0.5% to 1% per year will develop optic disk changes and visual field loss (ie, 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 percentage of patients with IOPs greater than 21 mm Hg (2.8 kPa), and the incidence of visual field defects increases to as high as 28% in individuals with IOPs above 30 mm Hg (4.0 kPa). For a given IOP finding, the risk of developing glaucoma increases with older age, family history of glaucoma, lower ocular perfusion pressure, lower blood pressure, thinner central cornea, optic disc hemorrhage, larger cup-to-disk ratio, and specific visual fields findings. For 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 (2.8 kPa) (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. 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.[1-5,8-17]

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*. 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: 0.33-0.5). Table 114-2 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 might be visualized in glaucoma patients with detectable visual field loss (see Fig. 114-2). This pattern of changes is consistent with visual field losses and loss of visual sensitivity seen in glaucoma.[1-6,8-15] Damage to the optic nerve can be documented by optic disk photographs, and disease stability or progression may be monitored by examining sequential photographs. Newer methods of assessing damage to the retinal nerve fiber layer and optic disk have been described. These include scanning laser polarimetry (GDX), confocal laser ophthalmoscopy (Heidelberg retinal tomography, or HRT), and optical coherence tomography (OCT). These methods offer the ability to assess the damage to the optic nerve quantitatively.

TABLE 114-2

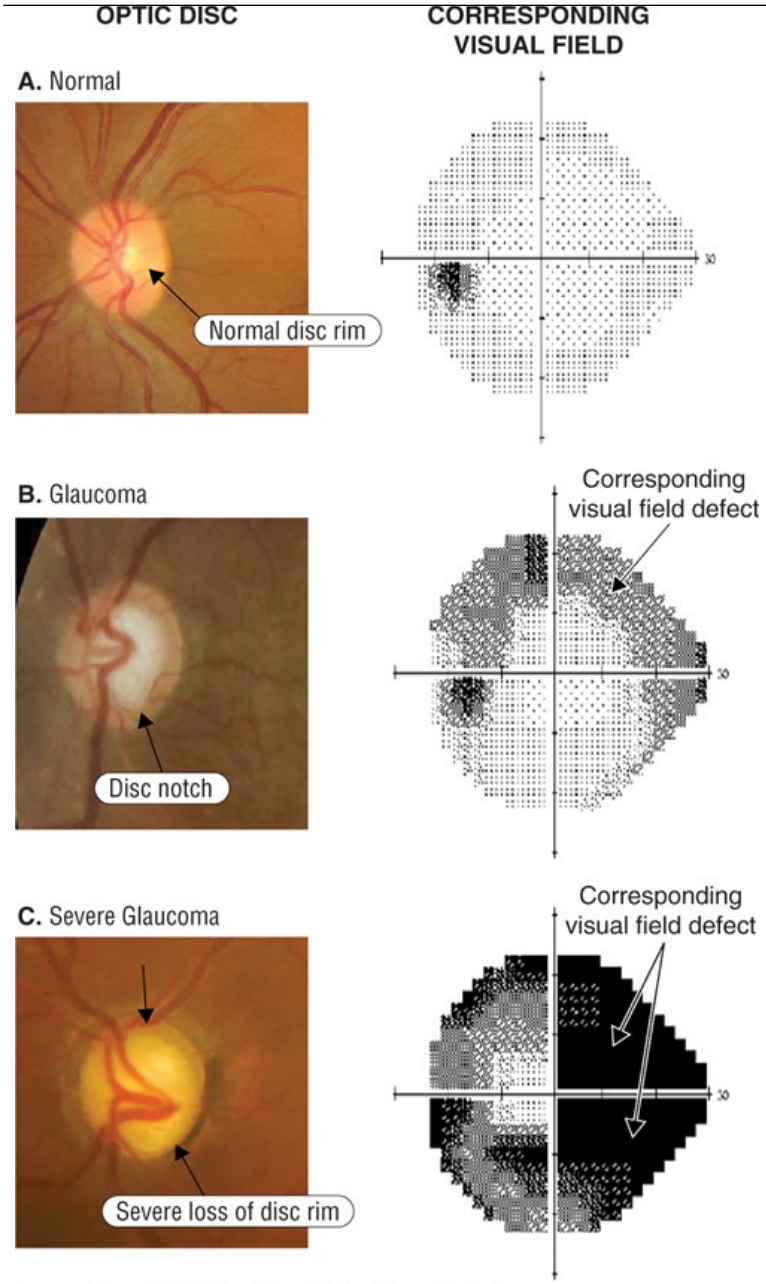
Optic Disk and Visual Field Findings in Patients with Glaucoma

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

Determination of the visual field allows the assessment of optic nerve damage and is an important monitoring parameter in the treatment. However, visual field changes typically 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. 114-2; see also Table 114-2), 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.[1-4]

FIGURE 114-2

Normal, moderate glaucoma, and severe glaucoma disc damage and their corresponding visual fields. (*A*) The photograph shows the normal optic disc, and the corresponding visual field test shows a normal visual field. The physiologic “blind spot” (dark area on the visual field) corresponds to the location of the optic nerve. (*B*) The eye with moderate glaucoma shows an enlarged cup and thinning of the inferior neuro-retinal rim with the arrowhead pointing to the optic disc notch. Note the arrow pointing to the corresponding superior visual field defect. The physiologic “blind spot” corresponds to the location of the optic nerve. (*C*) In severe glaucoma, there is severe loss of the optic disc rim and enlargement of the cup (see arrows). The corresponding visual field shows a significant loss of visual field in both superior and inferior hemifields. *(Courtesy University of Illinois at Chicago Department of Ophthalmology, Chicago, Illinois, and King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

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. Several 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 determined. The future of genetic studies in glaucoma will include the 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.

Genome-wide association studies have identified new loci that are associated with clinically relevant optic disc parameters, including the optic disc area and vertical cup-to-disc ratio. Genes associated with chronic angle-closure glaucoma have also been identified. Improved understanding of the genetic origins of POAG may lead to new diagnostic tools and therapies that target the underlying causes of the disease.[1-4,14,18]

Epidemiology of Ocular Hypertension, Glaucoma Suspects, and Open-Angle Glaucoma

1 Overall, OHT occurs in 4.5% of non-Hispanic Whites in the United States. The frequency increases to 7.7% of those older than 79 years.[19-22] The number of glaucoma suspects (ie, consistently high IOP or suspicious eye findings) is thought to be 3 to 6 million individuals in the United States. Approximately 2% of glaucoma suspects who are left untreated will progress to glaucoma each year.[7]

Open-angle glaucoma (OAG) is the second leading cause of blindness, affecting up to 4 million individuals in the United States and up to 70 million individuals worldwide. More than 135,000 persons in the United States and about 6 to 7 million in the world have glaucoma-related bilateral blindness. The prevalence rate varies with age, race, diagnostic criteria, and other factors. In the United States, OAG occurs in 1.5% of the population older than 30 years, 1.3% of Whites, and 3.5% of Blacks. Data have also suggested that the prevalence of OAG and ocular hypertension is also high among Latinos of Mexican ancestry, with approximately 4.74% and 3.56% of people affected, respectively.[23]

The incidence of OAG increases with increasing age. The incidence of the disease for patients aged 80 years is 3% in Whites and 5% to 8% in Blacks. In addition to increased IOP, age, and ethnicity, the risk of glaucoma increases with family history, thinner central corneal thickness, lower ocular perfusion pressure, Type II diabetes, myopia, and certain genetic mutations.[7,14,18-21]

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 the many factors associated with the development and progression of glaucoma. 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. Damage of the optic nerve ganglion occurs at the point at which ganglion and blood vessels pass through the perforated supportive collagen lamina cribosa of the optic disc. The 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. Neuronal loss also extends beyond the optic nerve to the lateral geniculate nucleus and visual cortex. POAG 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).[1-5,7]

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. 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.[1-4,7,8,10,11]

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.[7]

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. Such agents may be particularly useful for 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.[7,10,24]

Pathophysiology of Open-Angle Glaucoma

3 As stated previously, optic nerve damage in POAG can occur at a wide range of IOPs, and the rate of progression is highly variable. Patients may exhibit pressures in the 20 to 30 mm Hg (2.7-4.0 kPa) range for years before any disease progression is noticed in the optic disk or visual fields. That is why POAG is often referred to as the "sneak thief of sight."

Clinical Presentation of Open-Angle Glaucoma

POAG is a bilateral, often asymmetric, genetically determined disorder constituting 60% to 70% of all glaucomas and 90% to 95% of primary glaucomas in the United States (see the "Clinical Presentation" box). 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 IOP and progression and severity in one eye. As such, each eye is treated individually.[7]

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 (2.8 kPa) account for 20% to 30% of patients and are referred to as *normal-tension glaucoma*. Elevated IOP (>21 mm Hg [2.8 kPa]) without disk changes or visual field loss is observed in 5% to 7% of individuals (*glaucoma suspects*) and is referred to as *ocular hypertension*. New technologies such as OCT, 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.[7]

Secondary OAG 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 and 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.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: 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, whereas PACG is more typically associated with symptomatic acute episodes or may be slowly progressive like POAG

Symptoms

- POAG: None until substantial visual field loss occurs
- PACG: 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 114-2); IOP can be normal or elevated (>21 mm Hg [2.8 kPa])
  - Mild: Optic disk abnormalities with normal visual field with standard perimetry
- Moderate: Optic disk changes plus visual field abnormalities in one hemifield that are not within 5 degrees of central visual fixation
- Severe: Optic disk changes with visual field loss in both hemifields and loss within 5 degrees of central fixation and abnormalities in at least one hemifield
- Acute Angle-Closure Glaucoma (ACG): Acute, hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally an edematous and hyperemic optic disk; IOP is generally elevated markedly (40-90 mm Hg [5.3-12.0 kPa]) when symptoms are present
- Chronic (CACG): Disk changes and visual field loss (see Table 114-2); IOP can be normal or elevated (>21 mm Hg [2.8 kPa])

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. Pachymetry is crucial to detect a thin cornea that has been proved to be associated with visual field progression in open-angle glaucomas

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 <10-12 mm Hg [1.3-1.6 kPa]). Medications will control IOP successfully in 60% to 80% of patients over a 5-year period. Progression of visual field loss still occurs in 8% to 20% of patients despite reaching standard therapy IOP goals. However, for untreated patients and for 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%. Compared to placebo, each 1 mm Hg (0.1 kPa) in IOP reduction reduces the risk of disease progression by at least 10% and up to 19%.[7,24] After 2 years, visual field loss occurred in 25.6% of placebo patients compared to 15.2% of those treated with latanoprost.[25] Thus, the keys to medical treatment of POAG are an effective, well-tolerated drug regimen, close monitoring of therapy, and adherence.[26,27]

Epidemiology of PACG

The incidence of PACG varies by the 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.[7] Because of the high frequency of PACG in populous Asia, PACG accounts for approximately one-third of glaucoma worldwide. PACG accounts for a disproportionately high proportion of blindness (estimated at up to 50%) worldwide.[28-30]

Etiology Primary Angle-Closure Glaucoma (Acute ACG and CACG)

In North America, PACG accounts for a minority of cases of primary glaucoma. When severe acute angle-closure glaucoma (ACG) occurs, it may need to be treated as an emergency to avoid visual loss. PACG results from mechanical blockage of the (usually normal) trabecular meshwork by the peripheral iris. Partial or complete blockage of the meshwork occurs intermittently, potentially resulting in extreme fluctuations between normal IOP with no symptoms and very high IOP with symptoms of acute PACG. Between attacks of PACG, the IOP is usually normal unless the patient has concomitant POAG or nonreversible blockage of the meshwork with synechiae ("creeping" angle closure) that develops over time in the narrow-angle eye. PACG occurs in patients with inherited shallow anterior chambers (often seen in small eyes), which produce a narrow angle between the cornea and iris or tight contact between the iris and lens (pupillary block) (see Fig. 114-1C). The presence of a narrow angle is determined mainly by visualization of the angle by gonioscopy. Other tests for PACG 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 PACG have been described: PACG with pupillary block and PACG without pupillary block. PACG 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. PACG with pupillary block occurs most commonly when the pupil is in mid-dilation. 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.

PACG can occur without significant pupillary block for 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 PACG glaucoma, whereas drug-induced miosis may produce pupillary block.[7,30]

Pathophysiology of PACG

The mechanism of IOP elevation in PACG is clearer than that of POAG. In PACG, a physical blockage of trabecular meshwork is present. In many cases, single or multiple episodes of high IOP that in some patients may exceed 40 mm Hg (5.3 kPa) and result in optic nerve damage. Very high IOP (>60 mm Hg [8.0 kPa]) 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.[30]

Clinical Presentation of Angle-Closure Glaucoma

Most patients with untreated PACG typically experience intermittent nonsymptomatic or prodromal symptoms brought on by precipitating events (see the "Clinical Presentation" box). Increased IOP during such prodromal episodes is not great enough or long enough to produce the other symptoms of a full-blown 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 as seen in POAG. In approximately 25% of patients, severe attacks may occur, and if prolonged, total loss of vision may occur if the IOP is high enough. Tonometry reveals IOPs as high as 40 to 90 mm Hg (5.3-12.0 kPa). 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.[7,30]

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 the patient is treated adequately.[7,31-35] 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, for 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 for POAG patients. Inhaled, nasal, topical, or systemic glucocorticoids may increase IOP for 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 anti-inflammatory 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.

For patients predisposed to CAG (ie, narrow anterior chambers), angle closure may be produced by any drug that causes mydriasis (eg, anticholinergics). A wide range of sulfa compounds causes idiosyncratic reactions that result in lens swelling and 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 114-3 lists the drugs associated with potentiation of glaucoma.

TABLE 114-3

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)
CNS 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)

TREATMENT

Treatment for Glaucoma Suspect and Ocular Hypertension

Treatment of the patients with possible glaucoma (ocular hypertension; ie, patients with IOP >22 mm Hg [2.9 kPa]) is less controversial with the recent results of the Ocular Hypertensive Treatment Study (OHTS) than it was in the past.[10] The OHTS helped to identify risk factors for treatment. Patients with IOPs higher than 25 mm Hg (3.3 kPa), vertical cup-to-disk ratio of more than 0.5, and central corneal thickness of less than 555 µm are at greater risk for developing glaucoma. Risk factors such as family history of glaucoma, Black, Latino/Hispanic 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. The use of risk calculators has

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.

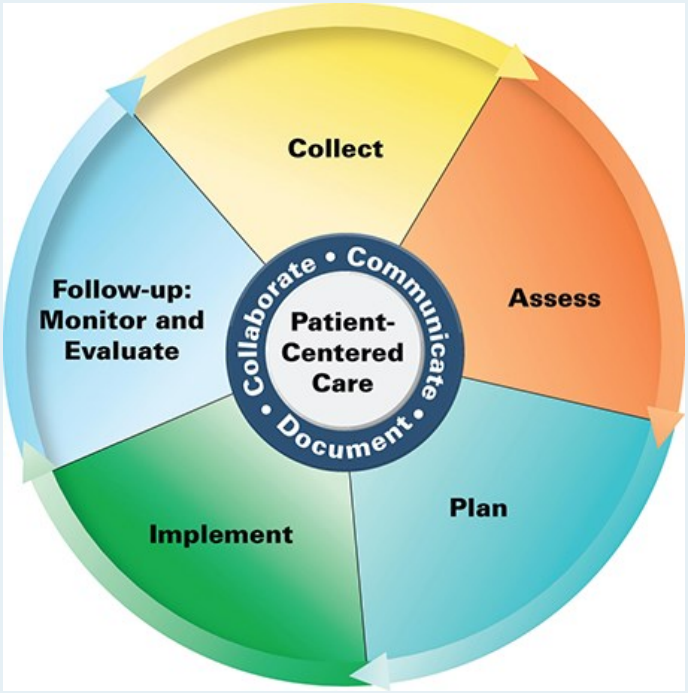
Patients with significant risk factors usually are treated with a well-tolerated topical agent such as a prostaglandin analog or β-blocking agent. Other options include a α_2-agonist (brimonidine), a topical carbonic anhydrase inhibitor (CAI), or netarsudil, depending on individual patient characteristics.

Therapy may be initiated in one eye to assess tolerance and efficacy compared to the contralateral eye; however, because each eye may respond differently to a medication as well as possible contralateral effects, IOP response may be compared to baseline in individual eyes.

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. Partial responders may be treated with combinations of well-tolerated topical medications (prostaglandins, beta-blockers, brimonidine, or a CAI). The use of multiple combinations of topical agents or when first-line agents fail to reduce IOP depends on the risk-to-benefit assessment of each patient. Some clinicians prefer to discontinue all medications for patients who fail to respond adequately to simple topical therapy, closely monitor for the development of disk changes or visual field loss, and treat again when such changes occur. The cost and inconvenience of frequent adverse effects of multiple-combination therapies, pilocarpine, cholinesterase inhibitors, and oral CAIs generally result in an unfavorable risk-to-benefit ratio for glaucoma suspect patients.[3,4,7,32-34,36,37]

PATIENT CARE PROCESS

Patient Care Process for the Management of Glaucoma



Collect

- Patient characteristics (eg, age, race, sex, and pregnant)
- Patient history (past medical, family history of glaucoma, social, and date and results of past eye examinations)
- Changes in vision (see Fig. 114-2)

- Current medications, including nonprescription agents and topically applied products, including eye drops (see Table 114-3 for agents that affect intraocular pressure [IOP])
- Objective data (see the "Clinical Presentation" box)
  - IOP measurements
  - Disc changes and abnormalities—bilateral, symmetrical?
  - Visual field changes and losses

Assess

- If PACG is suspected, manage or refer as ophthalmologic emergency
- Presence of conditions that can produce secondary cases of open-angle glaucoma (eg, exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and medications [see Table 114-3])
- Current medications that may contribute to or worsen glaucoma (see Table 114-3)
- Past history of adverse effects to agents used in the treatment of glaucoma
- Identify target IOP goal based on past history and current situation

Plan*

- Drug therapy regimen designed to achieve target IOP, including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Fig. 114-3 and Table 114-4)
- Monitor IOP for target reductions (usually at least 20% reduction from baseline IOP, if not a reduction of 25% to 30%, at 4 to 6 weeks after therapy begins, and for adverse effects [eg, local intolerance or reactions, altered iris pigmentation within 2 years of treatment initiation, hypertrichosis, hyperpigmentation of lids or lashes]
- Referrals to other providers when appropriate (eg, ophthalmologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Provide extensive education about administration of eye drops, separation of doses, and reinforcement of importance of adherence to preservation of vision
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, usually 4 to 6 weeks after therapy starts and every 3 to 4 months once target IOPs are achieved

Follow-up: Monitor and Evaluate

- Measure IOP
- Optic disc and visual fields
- Adverse effects to medications
- Adherence to treatment and drug administration technique

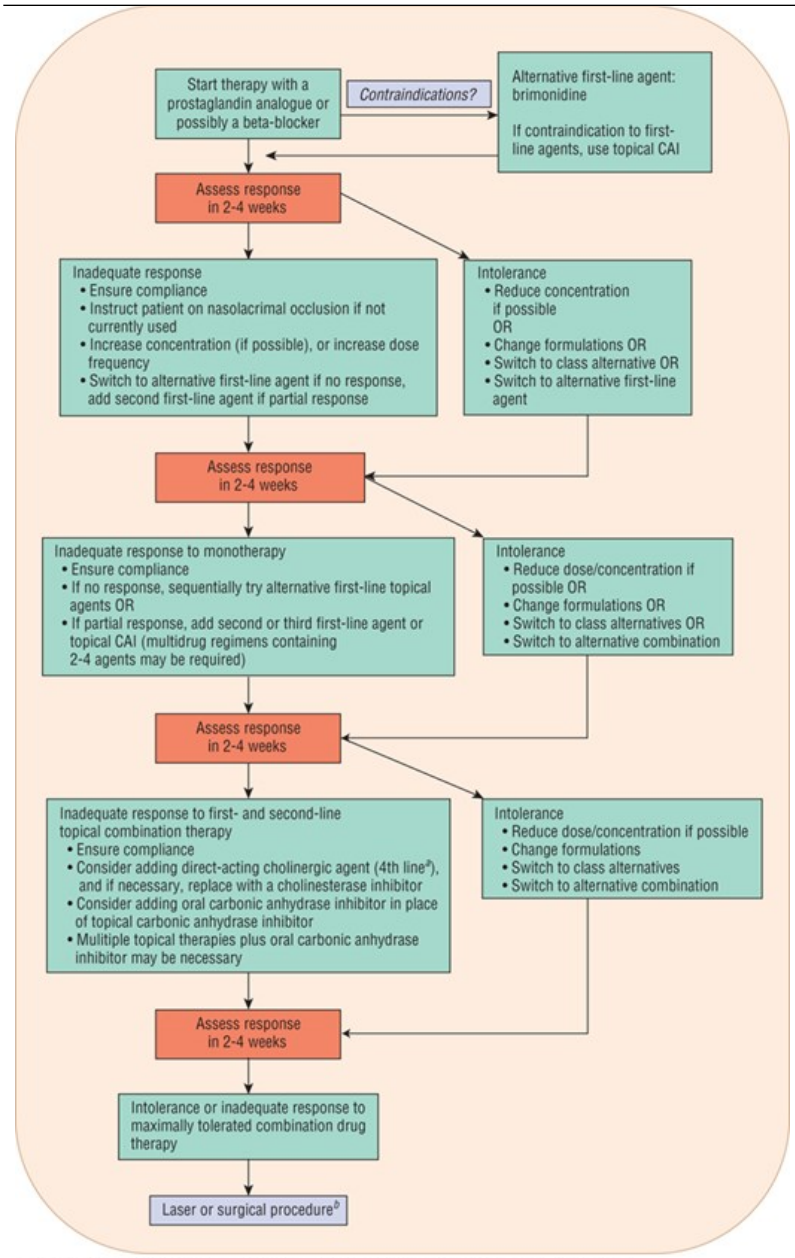
****Collaborate with patient, caregivers, and other healthcare professional.***

Treatment for Open-Angle Glaucoma

All patients with elevated IOP and characteristic optic disk changes and/or visual field defects not caused by other factors (ie, glaucoma by definition) should be treated. Recent findings that one in five patients with "normal" IOP and glaucomatous retinal nerve findings (ie, 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 to treat only when progression is documented. Some controversy exists as to whether the initial therapy of glaucoma should be surgical trabeculectomy (filtering procedure), argon or selective laser trabeculectomy, or medical therapy.[7,32-34,36-43] 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. 114-3), starting with 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 25% to 30% is desired. Greater reductions may be desired for 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 (1.3-1.6 kPa).[7]

FIGURE 114-3

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



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Pharmacotherapeutic Approach

6 Medications most commonly used to treat glaucoma are the prostaglandin analogs, nonselective β-blockers, brimonidine (a α_2-agonist), the topical CAIs, and the fixed combination products of timolol/dorzolamide, timolol/brimonidine, brimonidine/brinzolamide, or timolol/prostaglandins (non-United States). Effective and acceptable safety profiles include latanoprostene bunod and netarsudil.[7,32-34,36,37]

The prostaglandin analogs are often recommended as first-line therapy. They offer once-daily dosing, better IOP reduction, better 24-hour IOP control, good tolerance, and availability of lower-cost generics (see Fig. 114-3). The topical β-blockers have a long history of successful use, providing a combination of clinical efficacy and general tolerability. Brimonidine and topical CAIs are also well tolerated and effective agents, but often considered second-line agents (to prostaglandins and beta blockers).[7] The role of newer agents such as latanoprostene bunod and netarsudil are not established but will likely be used (individually or in combination) in patients not inadequately responding to or intolerant of other agents. Therapy optimally is started as a single agent; it can be started in one eye (except for patients with very high IOP or advanced visual field loss) to evaluate drug efficacy and

tolerance, although response may differ between contralateral eyes. Monitoring of therapy should be individualized. Initial check for IOP response to therapy is typically done 4 to 6 weeks after the medication is started. Once IOPs reach acceptable levels, the IOP is monitored every 3 to 4 months or longer if there is prolonged control (over 6-12 months) without progression. More frequent monitoring is necessary if IOP target is not achieved, disease progression is noted, and after any change in drug therapy.[7]

Visual fields and disk changes are typically monitored every 6 to 12 months 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, as tachyphylaxis to IOP reduction and or disease progression may occur.

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. For patients failing to respond to an initial drug, a switch to an alternative agent should be considered. 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. Prostaglandin agonists, beta blockers, brimonidine, CAI, and pilocarpine may be used in various combinations. Generally adding a second drug results in a less than additive reduction in IOP. Using more than one drop per dose does not improve response, and it 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 minutes is suggested to provide optimal ocular absorption. Combination products reduce the number of daily doses, possibly improving adherence and preventing washout effect seen when a second medication is administered too soon after the initial medication. The use of combination products also reduces exposure to ophthalmic preservatives. Ocular surface disease (OSD) secondary to glaucoma therapy will often manifest as superficial punctate keratitis, tear-film instability, or allergy.[44] In-vivo and animal studies have demonstrated the toxic effects of preservatives, often benzalkonium chloride through various mechanisms. However, extrapolating these results to clinical use is difficult because these studies must control for effects such as blinking, tear dilution and turn over, buffering capabilities, etc., of the human eye. While many crossover clinical trials show benefit to preservative-free therapies, there are a multitude that demonstrate no improvement. Patients with medication-related OSD may try treatment with artificial tears, anti-inflammatory therapy, or possibly preservative-free therapy if feasible.

The IOP response to ocular hypotensive medication may vary with corneal thickness. The response might be better in those with normal or thin corneas than in those with thicker structures.

Because of the frequency of adverse effects, carbachol, topical cholinesterase inhibitors, and oral CAIs are considered last-line agents to be used for patients who fail less-toxic combination topical therapy.

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. The newer selective laser trabeculoplasty (SLT) procedure has demonstrated similar IOP reduction as argon laser trabeculoplasty (ALT) and may be repeatable. Recent studies have demonstrated good efficacy for this procedure in comparison with medical treatment options for POAG.

A multicenter randomized clinical trial (LiGHT Study) conducted at six hospitals in the United Kingdom compared the use of eye drops versus the use of selective laser trabeculoplasty as a first-line treatment in patients with POAG or OHT.[45] The primary outcome was health-related quality of life (HRQoL) at 3 years. Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety. Of the patients in the SLT group, 74.2% (95% CI 69.3-78.6) required no eye drops at 36 months to maintain IOP at target. IOPs within the target range were achieved in slightly more eyes of those in the SLT group (93.0%) than among those using eye drops (91.3%). Glaucoma surgery was needed for 11 patients in the eye drops group versus none of those who received SLT initially. The HRQoL and cost-effectiveness were also more favorable in the SLT group.[45,46]

A real-world outcomes study in the United Kingdom assessed baseline factors associated with treatment success in patients undergoing their first recorded SLT. The main outcome measures were change from baseline in IOPs and glaucoma medication use with failure defined as any further glaucoma procedure post-SLT or IOP of greater than 21 mm Hg (2.8 kPa), IOP reduction of less than 20%, or an increase in glaucoma medications from baseline. The majority failed SLT within 1 year, and efficacy was better in patients with higher baseline IOP but did not differ by glaucoma severity or concurrent use of IOP-lowering medication.[46] As these studies show, many factors must be considered for patients with glaucoma when choosing a

laser treatment option.

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 Figs. 114-1 and 114-2).[7]

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. The use of aqueous shunts or valves to manage glaucoma has been increasing, and the results of a recent study have demonstrated improved safety and efficacy of these devices. However, glaucoma surgery is still plagued with the shortcomings despite modifications and improvements over the past century, including potentially vision-threatening complications like hypotony, wound leaks, and infections.[40,41,47] MIGS (Minimally Invasive Glaucoma Surgery) offers micro incisions and implants that reduce IOP by targeting various areas of the outflow pathway.[47] These can be approached from either inside the eye (ab-interno) (eg, iStent, Hydrus, Trabectome, XEN 45, suprachoroidal shunts) or outside the eye (ab-externo) (eg, canaloplasty, Gold micro shunt, and Stegman Canal Expander).[47] MIGS can be considered as an alternative to medical therapy in an effort to address adherence challenges, adverse events, and quality-of-life (QOL) issues with topical medications. They are usually performed in combination with cataract surgery (eg, iStent, Hydrus) or as a solo procedure (XEN 45).

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 for patients undergoing glaucoma-filtering surgery to improve success rates by reducing fibroblast proliferation and consequent scarring. Although used most commonly for patients with increased risk for suboptimal surgical outcome (after cataract surgery and a previous failed filtering procedure), the use of these agents also improves success in low-risk patients.[40,41,47] A standardized formulation of mitomycin C (MMC) that is prepacked in a kit with a fixed dose and concentration was approved by the US Food and Drug Administration in 2012 and is commercially available under the name “Mitosol.” Off-label use of mitomycin C prepared by compounding pharmacies is also common.

Treatment for Acute Angle-Closure Crisis (AACC)

The goal of initial therapy for acute AACC 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 PACG; 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 AACC typically involves administration of one or more topical antiglaucoma medications including miotics (eg, pilocarpine), secretory inhibitors (β-blockers, α_2-agonist, or topical/systemic CAIs), or a prostaglandin agonist.[6,30] The miosis produced by pilocarpine pulls the peripheral iris away from the meshwork. However, miotics may worsen angle closure by increasing pupillary block and producing anterior movement of the lens because of drug-induced accommodation. The aqueous secretory inhibitors and pilocarpine may not be effective due to ischemia of the ciliary body and pupillary sphincter, respectively. Now, the urge to use excessive amounts of topical agents must be resisted. A hyperosmotic agent such as mannitol or glycerin may be needed to temporarily reduce IOP and restore response to the topical agents.

An osmotic agent also is commonly 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, IV 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 eye. These drugs are among the first-line agents in the short-term treatment of an AACC 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 PACG eyes. Patients failing therapy altogether will require an emergency iridectomy. Once the IOP is controlled, iridectomy is performed on the affected eye as well as the contralateral eye (if narrow angles are present). As reported in the EAGLE study, for patients who are older than 50 years and with other specific inclusion criteria, an alternative approach involves crystalline lens extraction since it plays a role in PACG pathology.[48]

Laser peripheral iridotomy can prevent acute angle closure glaucoma in patients at risk. However, its role on preventing the conversion of an angle-closure suspect to PACG is modest.[31,49] 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.[30]

PHARMACOLOGIC AGENTS USED IN GLAUCOMA

Prostaglandin Analogs

The prostaglandin analogs, including latanoprost, travoprost, bimatoprost, and tafluprost, 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, travoprost, and tafluprost) and the prostamide (bimatoprost). However, both classes appear to produce collagen changes in the matrix of the ciliary body and trabecular meshwork. Bimatoprost may be slightly more effective in lowering IOP, getting a larger percentage of patients to lower IOPs, and for patients unresponsive to latanoprost. If the patient does not respond to one prostaglandin agonist, a switch to another may be beneficial.[39,42,50] Generic forms of some prostaglandin analogs are now available, reducing the cost to patients for these agents. Tafluprost is available as a preservative-free solution, which may be useful in patients intolerant of common ophthalmic preservatives or those with corneal surface disorders.

Reduction in IOP with once-daily doses of prostaglandin analogs (a 25%-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.[7,42,50] 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.[7,33,36,37,51]

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 browner 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 common and reverses upon discontinuation of the drug. Hyperpigmentation around the lids and lashes has also been reported and appears to reverse upon discontinuation. Loss of periorbital fat has been reported, which may lead to apparent enophthalmos and sunken eye, especially when used unilaterally.

Topical prostaglandin analogs may produce rates of corneal thinning that are slightly higher than ongoing age-related changes. This effect is unlikely to be clinically relevant.[24,33,36,37,51,52]

These agents have occasionally been associated with uveitis, and caution is recommended for patients with ocular inflammatory conditions. Cases of cystoid macular edema and 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 for patients who are not responding to or tolerating other agents. Long-term studies demonstrate that these agents are safe, efficacious, and well tolerated in glaucoma therapy.[24,33,36,37,51,52] Various fixed combination prostaglandin products, often with timolol, are available in Canada and overseas.

Latanoprostene bunod is a newer agent approved for use in patients with OAG and OHT.[50,51,53] This agent is a prodrug of latanoprost and is also metabolized to a nitric-oxide–donating moiety, thus providing dual mechanisms for increasing aqueous outflow. This agent produces IOP reduction similar to or greater than that with timolol. Adverse effects are similar to that seen with pure prostaglandin analogs.

The first intraocular biodegradable, implant of bimatoprost (Durysta), is another newer product indicated for patients with OAG and OHT. It is administered intracamerally (into the anterior chamber of the affected eye). The bimatoprost implant has potential to improve adherence and reduce treatment burden in glaucoma. In a randomized, 20-month, evaluator-masked, phase 3 clinical study, efficacy (IOP lowering) and safety of bimatoprost 10- and 15-mcg implants were evaluated. Bimatoprost implants 10 mcg (n = 198) or 15 mcg (n = 198) on day 1 were noninferior to timolol in IOP lowering after administration at baseline and weeks 16 and 32 of the trial. Corneal and inflammatory treatment-emergent adverse events of interest (eg, corneal endothelial cell loss, iritis) were higher with bimatoprost implants than timolol and highest with the 15-µg dose implants. One year after the third administration of bimatoprost implants, IOP was controlled in most study participants. The risk-benefit assessment favored the commercial approval for the 10-mcg implant, and the US Food and Drug Administration approved that dose for a single administration in each eye for the life of the patient. Ongoing studies are evaluating other administration regimens.[26,47] The bimatoprost implant has potential for improving adherence and

reducing treatment burden in glaucoma.

β-Blocking Drugs

The topical β-blocking agents are one of the most commonly used antiglaucoma medications (Table 114-4). β-Blockers lower IOP by 20% to 30% with a minimum of local ocular adverse effects. Beta blockers have minimal effects on nocturnal IOP. These are commonly one of the agents of first choice—along with prostaglandin analogs—in treating POAG if no contraindications exist.[7,33,36,37,51]

TABLE 114-4

Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names/Generic	Dosage Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic blocking agents						
Betaxolol	Relative β_1 selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan/Generic	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol/Generic	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE/Generic	Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic agonists						

α_2-Adrenergic agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine		Alphagan P 0.1/Generic 0.2, 0.15	Solution	0.2, 0.15, 0.1	One drop two to three times a day	
Cholinergic agonists direct acting						
Carbachol	Direct and indirect acting	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day[a]	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Direct acting	Isopto Carpine, Pilocar/Generic	Solution	1, 2, 4	One drop two to three times a day[a]	
					One drop four times a day	
Cholinesterase inhibitors						
Echothiophate	Indirect acting cholinesterase inhibitor	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/Generic	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	Prostanoid agonist	Xalatan/Generic	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Latanoprostene Bunod	Prostanoid agonist	Vyzulta	Solution	0.024	One drop every night	
Bimatoprost	Prostamide agonist	Lumigan 0.01/Generic 0.03	Solution	0.01, 0.03	One drop every night	
		Durysta 10 mcg	Intracameral biodegradable implant	One implant per eye for the life of the patient		
Travoprost	Prostanoid agonist	Travatan Z/GenericTravoprost	Solution	0.004	One drop every night	
Tafluprost	Prostanoid agonist	Zioptan/Saflutan	Preservative free solution	0.0015	One drop every night	
Rho Kinase Inhibitors						

Netarsudil	Rho Kinase Inhibitor	Rhopressa	Solution	0.02	One drop every night	
Combinations						
Timolol –dorzolamide		Cosopt Generic	Solution	Timolol 0.5/Dorzolamide 2	One drop twice daily	
Timolol –brimonidine		Combigan	Solution	Timolol 0.5/Brimonidine 0.2	One drop twice daily	
Brinzolamide –brimonidine		Simbrinza	Suspension	Brinzolamide 1/Brimonidine 0.2	One drop three times daily	
Netarsudil-latanoprost		Rocklatan	Solution	Netarsudil 0.02/Latanoprost 0.005	One drop every night	

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

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, which possesses alpha-adrenergic effects, may be more effective than timolol and betaxolol in reducing postcataract surgery IOP increases and may be 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. Treatment with topical β-blockers may result in tachyphylaxis (short-term escape and long-term drift) in 20% to 25% of patients. The mean IOP reduction from baseline may be smaller for patients receiving topical β-blockers with concurrent systemic β-blockers.[33,36,37]

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, CNS 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 fewer drugs 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 for patients with pulmonary diseases, sinus bradycardia, second- or third-degree heart block, congestive heart failure, atherosclerosis, diabetes, and myasthenia gravis, as well as for patients receiving oral β-blocker therapy. The use of the nasolacrimal occlusion (ELC; 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. For patients failing or having an inadequate response to single-drug therapy with a β-blocking agent, the addition of a topical CAI, prostaglandin analog, or the α_2-adrenergic receptor agonist brimonidine usually will result in additional IOP reduction.[7,33,36,37,51]

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 has a primary indication in open-angle glaucoma and is considered a second-line agent (often after a prostaglandin or beta blocker) or adjunctive agent. Apraclonidine is generally used only in short term after ocular surgery due to high incidence of loss of control of IOP (tachyphylaxis) and a more severe and prevalent ocular allergy rate.

Alpha-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 (2-5 hours) and by 10% at 8 to 12 hours. Comparative trials demonstrate a reduction in IOP similar to that obtained with 0.5% timolol. The use of brimonidine 0.2% every 8 to 12 hours provides maximum IOP-lowering effects in long-term use. The use of ELC (see Patient Education below) may improve response and allow the longer dosing frequency (ie, every 12 hours). These agents have minimal effects on nocturnal IOP. 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 for 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.[7,33,36,37,51]

Brimonidine Purite 0.15% or 0.1% is a formulation of brimonidine in a lower concentration than the original product that contains a less corneal-toxic preservative than the 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.

A randomized clinical trial of topical brimonidine 0.2% twice daily preserved visual field better than treatment with topical timolol maleate 0.5% in patients with OAG and statistically normal IOP.[23] The IOP-lowering efficacy was similar between the two medications, suggesting that this finding was consistent with a non-IOP-related mechanism, possibly a neuroprotective action. However, validation of a neuroprotective role for brimonidine requires further research to confirm these results.[23,54] The combination product timolol 0.5% and brimonidine 0.2% (Combigan) may provide additional IOP lowering than either agent alone.

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.[7,33,51] The topical CAIs dorzolamide and brinzolamide are well tolerated and are considered second line (after prostaglandins and beta blockers) for monotherapy or adjunctive therapy of POAG and ocular hypertension. These drugs 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 for patients with inadequate response to or who are unable to use other agents. The drugs may add additional IOP reduction for patients using other single or multiple topical agents. The usual dose of a topical CAI is one drop every 8 to 12 hours. Administration every 12 hours produces somewhat less IOP reduction than administration every 8 hours. The use of ELC should optimize response to CAI given at any interval.[7,33] The combination product timolol 0.5% and dorzolamide 2% (Cosopt) is dosed twice daily and produces equivalent IOP lowering to each product dosed separately. Both dorzolamide and timolol/dorzolamide (Cosopt) are now available as generic formulations. The combination product brimonidine 0.2% and brinzolamide 1% (Simbrinza) is available dosed three times daily.

Systemic CAI Agents

Systemic CAIs are indicated for 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 114-4) produce equivalent IOP reduction but differ for 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 some caution in patients with sulfa allergies (all CAIs, topical or systemic, contain sulfonamide moieties, although cross-sensitivity is thought to be very low), 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.[7,33,36,37,51]

Rho Kinase Inhibitors

Netarsudil is the first approved agent in a new class of antiglaucoma medications, Rho kinase inhibitors.[51,53] Netarsudil reduces IOP by increasing trabecular meshwork outflow. Once-daily (in the evening) administration of a 0.02% solution reduces both daytime and nighttime IOP. Efficacy appears to be similar to that of beta blockers. Netarsudil may be used in combination with other antiglaucoma agents. The most common local side effects are conjunctival hyperemia, conjunctival hemorrhage, and corneal verticillate. Systemic effects are rare. Patients with OAG or OHT who are taking as many as four ocular hypotensive medications showed modest IOP reduction when netarsudil was added to their regimen.[13]

A combination of netarsudil/latanoprost ophthalmic solution 0.02%/0.005% (Rocklatan) was approved in the United States. Rocklatan provided superior IOP reduction compared to either netarsudil or latanoprost products alone. However, discontinuation rates at 12 months occurred in 20.6%, 23.0%, and 1.7% of patients receiving netarsudil/latanoprost, netarsudil, and latanoprost, respectively.[28]

Parasympathomimetic Agents

The parasympathomimetic (cholinergic) agents reduce IOP by increasing aqueous humor trabecular outflow. The increase in outflow is a thought to be a result of physically pulling open the trabecular meshwork secondary to ciliary muscle contraction, thereby reducing resistance to outflow. These agents may actually reduce uveoscleral outflow. 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 (see Table 114-4). Pilocarpine produces similar (20%-30%) reductions in IOP as those seen with β-blocking agents. Pilocarpine in POAG is initiated as 1% solution, one drop three to four times daily. The use of ELC improves response and reduces the need for an every 6-hour dosing frequency. The use of one drop of 2% pilocarpine every 6 to 12 hours and ELC 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.

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 may also 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 can be seen. 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 (8-10 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.[33] Clinical use of carbachol is limited.

Echothiophate is a cholinesterase inhibitor and is used in the treatment of POAG. It is a long-acting, relatively irreversible agent (limited commercial availability; see Table 114-4). This agent is a potent inhibitor of pseudocholinesterase, but also inhibits true cholinesterase. Because of the serious ocular and systemic toxic effects of echothiophate, it is reserved primarily for patients who are either not responding to or are intolerant of other therapy. Because of its cataractogenic properties, most ophthalmologists use this agent only for patients without lenses (aphakia) and for 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, echothiophate 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 echothiophate decreases the rate of succinylcholine hydrolysis, resulting in prolonged muscle paralysis. Echothiophate should be discontinued at least 2 weeks before procedures in which succinylcholine is used.

The role of echothiophate in glaucoma is limited by its frequency and potential toxicity. For phakic patients, cholinesterase inhibitors should be administered only if intolerance or failure results with other antiglaucoma medications. Echothiophate provides additional IOP-lowering effects when used with β-blockers, CAIs, and sympathomimetic (adrenergic) agents. Only one concentration of this agent (0.125%) is currently available. A once-daily administration frequency should be used for most patients unless very high IOP is present.

The use of ELC likely improves response, reduces systemic adverse effects, and should be performed by all patients administering echothiophate. The drug should be used with caution for 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.

Future Drug Therapies

It is hoped that new agents, improved formulations, and novel approaches to the reduction of IOP and other methods of prevention of glaucomatous visual field loss will provide more effective and better-tolerated therapies. Most areas of glaucoma development continue to focus on drugs that reduce IOP by either reducing aqueous production or increasing outflow. The efficacy and safety of omidenepag isopropyl (OMDI) 0.002%, a selective, nonprostaglandin, prostanoid EP2 receptor agonist, were evaluated in comparison with latanoprost 0.005% in participants with POAG or OHT. OMDI 0.002% was noninferior to latanoprost 0.005% in reducing IOP and was well tolerated.[7]

Classes of drugs in development include adenosine-1 receptor agonists, cannabinoids, serotonin agonists, dopamine agonists, nitric oxide/carbon dioxide modulators, and hydroxysteroid dehydrogenase inhibitors. Agents that are neuroprotective and act through mechanisms other than IOP reduction are also in development and are likely to be part of glaucoma therapy in the future.[24,52-54]

Development of new long-acting topical formulations (such as nanoparticulates), implants, ocular inserts, and drug-eluting punctal plugs may provide improved patient convenience and medication adherence in the future.[28]

EVALUATION OF THERAPEUTIC OUTCOMES

The ultimate goal of drug therapy for 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%-50%) may be desired for patients with initially high IOPs. For patients with glaucoma, an IOP of less than 21 mm Hg (2.8 kPa) generally is desired, with progressively lower target pressures needed for greater levels of glaucomatous damage. Even lower IOPs (possibly even below 10 mm Hg [1.3 kPa]) are required for 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 of patient quality of life.

PATIENT EDUCATION

7 An important consideration for 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 5 minutes after instillation. This increases the ocular availability of the drug and reduces systemic absorption.
6. Recap bottle and store as instructed.

Note that many patients are physically unable to administer their own eye drops without assistance. ELC also should be used to improve ocular bioavailability and reduce systemic absorption.[7] The patient induces ELC for 5 minutes by gently closing the eyes. ELC decreases nasolacrimal drainage of drug, thereby decreasing the amount of drug available for systemic absorption by the nasopharyngeal mucosa. The use of ELC may improve drug response significantly, reduce adverse effects, and allow less-frequent dosing intervals and the use of lower drug concentrations.

The use of more than one 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 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 usually 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, simplified and well-tolerated dosing regimens, reminder devices, education, close monitoring, and individualized care planning.[7,43]

ABBREVIATIONS

CAG	closed-angle glaucoma
CAI	carbonic anhydrase inhibitor
IOP	intraocular pressure
ELC	eyelid closure
OAG	open-angle glaucoma
OHT	ocular hypertension
OHTS	Ocular Hypertensive Treatment Study
POAG	primary open-angle glaucoma

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SELF-ASSESSMENT QUESTIONS

1. All the following are typical optic disc changes seen in primary open-angle glaucoma (POAG) *except*:

   A. Nerve fiber layer defects

   B. Cup-to-disc ratio of >0.5

   C. Splinter hemorrhages

   D. Papilledema

2. All the following are typical visual field findings in primary open-angle glaucoma (POAG) *except:*

   A. Enlargement of the blind spot

   B. General central field constriction

   C. Reduced contrast sensitivity

D. Altered color vision

3. The following are typical symptoms of primary angle-closure glaucoma (PACG) *except*:

   A. Blurred or hazy vision with halos around lights

   B. Acute ocular pain or discomfort

   C. Nausea, vomiting, abdominal pain, and diaphoresis

   D. Double vision

4. Patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) do not often exhibit which of the following signs?

   A. Optic disc abnormalities

   B. Cloudy cornea

   C. Elevated intraocular pressure

   D. Visual field loss

5. Which of the following is not normally considered a risk factor for OHT or POAG?

   A. Family history

   B. Black and Latino/Hispanic ethnicity

   C. Elevated intraocular pressure (IOP)

   D. Central corneal thickness greater than 555 microns

   E. Severe myopia

6. All of the following have been associated with drug-induced glaucoma in closed-angle glaucoma *except*:

   A. Topical anticholinergic agents

   B. Inhaled or topical glucocorticoids

   C. Miotic agents such as echothiophate

   D. Systemic antidepressants

7. Current recommendations for initiation of primary therapy for POAG may include all the following *except*:

   A. Timolol maleate

   B. Latanoprost

   C. Acetazolamide

   D. Brimonidine

   E. Dorzolamide

8. Recommendations for administration of systemic agent for acute angle-closure crisis would be which of the following?

   A. Timolol maleate

B. Latanoprost

C. Acetazolamide

D. Brimonidine

E. Dorzolamide

9. Which of the following is often considered the most reasonable initial therapy for POAG or OHT?

A. Latanoprost

B. Pilocarpine

C. Dorzolamide/timolol

D. Apraclonidine

E. Netarsudil

10. Which of the following agents would be most appropriate as adjunctive therapy for a patient currently treated with timolol for POAG?

A. Acetazolamide

B. Echothiophate

C. Betaxolol

D. Bimatoprost

11. Which of the following is not considered a reasonable treatment option in a patient with POAG?

A. Selective laser trabeculoplasty (SLT)

B. Trabeculectomy

C. Minimally invasive glaucoma devices (MIGS)

D. Peripheral iridectomy

12. Which of the following is *not* considered a reasonable treatment option for acute angle-closure crisis (AACC)?

A. Topical agents (eg, beta blockers, brimonidine)

B. Intravenous acetazolamide

C. Selective laser trabeculoplasty (SLT)

D. Intravenous mannitol

E. topical corticosteroids

13. All the following are ocular side effects related to prostaglandin analogs *except*:

A. Altered iris pigmentation or iris darkening

B. Miosis

C. Hypertrichosis or eyelash growth

D. Hyperemia

E. Loss of periorbital fat

14. Topical beta blockers have been associated with all of the following systemic side effects *except*:

A. Increased heart rate

B. Bronchospasm

C. Alteration of serum lipids

D. CNS effects

E. Reduced blood pressure

15. Eyelid closure (ELC) after ocular drug administration is an important technique that should be explained to all glaucoma patients for the following reasons *except*:

A. It is an easy technique for patients to learn.

B. It may improve ocular bioavailability.

C. It may reduce systemic absorption and thereby reduce some local and systemic adverse events associated with topical glaucoma therapy.

D. The patient is only required to gently close the eyes for 1 minute.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Papilledema is not exhibited in POAG (see Table 114-2).

2. **B.** General peripheral field constriction is prominent in POAG. Loss of central vision is more prominent in other ocular diseases (eg, Adult Macular Degeneration) (see Table 114-2).

3. **D.** Double vision would generally not be exhibited in most cases of PACG and only one eye is affected (see the "Clinical Presentation" box.)

4. **B.** A cloudy cornea is often exhibited in primary angle-closure glaucoma because of the acute IOP rise experienced in these patients. Patients with POAG or ocular hypertension (OHT) often do not exhibit highly elevated IOP and therefore their cornea often appear normal (see the "Clinical Presentation" Box).

5. **D.** Central corneal thickness that is less than 555 microns is considered for patients at greater risk for developing glaucoma. Thinner corneas may reflect a higher IOP than exhibited by tonometry (see the "Glaucoma Suspect and Ocular Hypertension" section).

6. **B.** Inhaled or topical corticosteroids often reduce aqueous humor outflow through the trabecular meshwork by accumulating extracellular material that block the outflow. The medication associated with PACG often causes acute changes in the lens/iris structures that allow for the angle to close and block aqueous outflow, thus resulting in an acute elevated IOP.

7. **C.** Acetazolamide for POAG is a systemic agent and not used in current practice to initiate therapy in a POAG patient (see the "Pharmacotherapeutic Approach" section).

8. **C.** Acetazolamide is the only systemic agent listed that is available for intravenous administration for an acute IOP elevation in a patient (see the "Acute Angle-Closure Crisis" section).

9. **A.** Latanoprost is the most commonly used agent, dosed once daily at bedtime. Pilocarpine is an older agent that has generally fallen out of use;

apraclonidine does not have a primary indication and is seldom used except acutely; a combination product is not often considered initial therapy; netarsudil is a new product that has been considered adjunctive therapy (see the "Pharmacologic Agents Used in Glaucoma" section).

10. **D.** Echothiophate is considered a fourth-line agent with significant ocular side effects. Acetazolamide as an oral agent is not often considered for adjunctive therapy because of significant systemic side effects; betaxolol is another beta blocker and would not be used concurrently with timolol; bimatoprost is a PGA that would be most appropriate for additional IOP lowering benefit (see the "Pharmacologic Agents Used in Glaucoma" section).

11. **D.** A peripheral iridectomy is performed in a patient as a treatment for acute angle-closure glaucoma or as a preventive procedure for a patient at risk for AACC (see "Nonpharmacologic Therapy: Laser and Surgical Procedures" under section "Open-Angle Glaucoma").

12. **C.** SLT is a laser procedure used in POAG. A laser iridectomy is the procedure performed for AACC (see the "Acute Angle-Closure Crisis" section).

13. **B.** While PGAs may have an effect on iris pigmentation, they do not often exhibit any effect on iris constriction (miosis) (see the "Prostaglandin Analogs" section).

14. **A.** topical beta blockers are known to cause many of the same side effects seen with systemic beta blocker administration including bradycardia or decreased heart rate (see the "β-Blocking Drugs" section).

15. **D.** It is important for the patient to keep the eyelid closed for 5 minutes following ocular drug administration. One minute is not enough time to provide a benefit to the patient. Some have suggested 3 minutes may be enough time, but 5 minutes is the preferred time (see the "Patient Education" section).