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Age-Related Macular Degeneration and Glaucoma

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Goal. The goal of this lesson is to provide an overview of two common eye disorders: macular degeneration and glaucoma, both of which are age-related and recognized as leading causes of blindness. Basic pathophysiology, risk factors, signs and symptoms, and the role of pharmacologic treatment in these diseases will be presented.

Objectives. At the completion of this activity, the participant will be able to:

1. recognize the basic pathophysiology for age-related macular degeneration (AMD) and glaucoma, as well as patients at risk;
2. demonstrate an understanding of the role of AREDS supplements and vascular endothelial growth factor (VEGF) inhibitors in the treatment of AMD;
3. identify adverse effects and safety concerns associated with VEGF inhibitors; and
4. list medications that may cause or exacerbate glaucoma, as well as the agents used to treat the condition.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD), a disease of the retina, is the leading cause of irreversible blindness in persons 50 years of age or older in the developed world. It is estimated that 30 percent of persons 75 years and older have signs of the disease. As the number of Americans over 65 increases, the incidence of age-related eye diseases will likewise escalate. By the year 2020, nearly three million Americans are expected to suffer from AMD.

Macular degeneration is a degenerative disease that affects the macula, a part of the eye located in the center of the retina. The macula contains the densest concentrations of photoreceptors within the retina, and is responsible for sharp, central vision allowing a person to see fine detail, read, and recognize faces. Posterior to the photoreceptors lies the retinal pigment epithelium, responsible for photoreceptor phagocytosis, nutrient transport, and cytokine secretion. With age, debris may deposit between the retinal pigment epithelium and the Bruch's membrane, a posterior semipermeable exchange barier.

These focal deposits are called drusen and are seen as pale, yellowish lesions in the macula or peripheral retina during a funduscopic examination. Drusen are categorized by size and appearance. The presence of drusen in people over 50 years of age is common, and considered a normal part of aging. Individuals with few, small and "hard" (defined margins) drusen are not considered to have AMD. Alternatively, excess drusen, or large, bilateral, and "soft" (indistinct edges) drusen, is a clinical hallmark of AMD and is usually the first clinical finding. AMD is further classified as dry (atrophic) or wet (neovascular or exudative).

Regular eye exams can detect AMD, but left unnoticed and untreated, AMD can cause irreversible vision loss. Early AMD is often asymptomatic. However, some early symptoms may occur such as blurred vision, visual scotomas (blind spots), decreased contrast sensitivity, abnormal dark adaptation, and the need for brighter light or additional magnification to read small print. Distortion of straight lines is one of the earliest changes with wet AMD.

Once advanced AMD develops in one eye, there is a greater than 40 percent risk of development in the other eye within five years. Although most persons with advanced age-related macular degeneration do not become completely blind, visual loss often markedly reduces quality of life and is associated with disability and clinical depression in up to one-third of patients.

Blindness from AMD is caused by gradual destruction of the macula over time, secondary to oxidative damage. Oxidative stress causes the formation of free radicals that attack rod and cone cells in the eye leading to damage and cell death. Oxidative damage is further enhanced by nutritional deficiencies, such as low serum levels of lutein. Both are thought to contrib-

Table 1
Classification of age-related macular degeneration*

Category	Clinical Features	Management
Early AMD (Dry)	•Presence of a few medium-sized drusen •Pigmentary abnormalities such as hyperpigmentation or hypopigmentation	Lifestyle and dietary modifications (smoking cessation, increased dietary intake of antioxidants, control of blood pressure and body mass index)
Intermediate AMD (Dry)	•Presence of at least one large drusen •Numerous medium-size drusen •Geographic atrophy that does not extend to the center of the macula	•Supplementation according to the ARED Study** •Lifestyle and dietary modifications
Advanced Non-Neovascular AMD (Dry)	Drusen and geographic atrophy extending to the center of the macula	•Supplementation according to the ARED Study** if the other eye has early or intermediate AMD •Lifestyle and dietary modifications
Advanced Neovascular AMD (Wet)	Choroidal neovascularization and of its potential sequelae, including subretinal fluid, lipid deposition, hemorrhage, retinal pigment, epithelium detachment and a fibrotic scar	•Supplementation according to the ARED Study** if the other eye has early or intermediate AMD •Lifestyle and dietary modifications •Antiangiogenic therapy (e.g., intravitreal injection) •Laser therapy

*According to AREDS trial
**AREDS 2 supplement formulation may be appropriate in some populations

ute to the development of the early stages of AMD. For this reason, cumulative photo-oxidative stress and nutritional deficiencies may contribute to the onset and progression of AMD. Well-documented risk factors for AMD include age, smoking, family history, cardiovascular disease, and white race. Other possible risk factors that have been identified with either little or conflicting evidence include diet, cataract surgery, alcohol use, hypertension, sunlight exposure, and obesity.

While the broad categories of AMD are generally considered wet or dry, various classification systems exist in literature to further stage the progression of AMD. The classification proposed by the Age-Related Eye Disease Study (AREDS), a trial sponsored by the National Institutes of Health (NIH) in 1994, is now increasingly used.

In general, wet or neovascular is the most progressed form of the disease, while non-neovascular or dry AMD (90 percent of cases) has been subdivided into early, intermediate, and advanced non-neovascular AMD. Patients are categorized based on the number and size of drusen present, pigmentary abnormalities, as well as extent of atrophy. It should be noted that this classification system is not used universally throughout literature; however, familiarity with these categories can help pharmacists appreciate the progression of AMD and understand those publications that utilize the AREDS categories.

While there is currently no cure for any stage of AMD, current therapies aim to reduce risk factors and curb further progression. Table 1 reviews the categories created and utilized by the AREDS trial, as well as clinical features and management.

Age-Related Eye Disease Study (AREDS). AREDS was a major clinical trial sponsored by the National Eye Institute, which is part of NIH. The trial was designed to learn more about the natural history and risk factors of AMD and cataracts, and to evaluate the effects of high doses of vitamin C, vitamin E, and beta-carotene on the progression of disease. While no significant effect was found in relation to cataracts, the results of the study showed that high levels of antioxidants and zinc significantly reduce the risk of AMD and related vision loss.

The AMD trial included 3640 participants who had at least early disease. The participants were placed in one of four categories as defined in Table 1. The participants were then randomly selected to receive daily oral tablets of one of four treatments: 1) zinc alone; 2) antioxidants alone; 3) a combination of antioxidants and zinc; or 4) placebo. Approximately 90 percent of participants were followed for at least five years. Daily doses of antioxidants and zinc used by the researchers were 500 mg of vitamin C; 400 IU of vitamin E; 15 mg of beta-carotene; 80 mg of zinc oxide; and 2 mg cupric oxide. All three of the treatment arms were found to have varying, yet promising, results in slowing the progression of advanced AMD, and reduction in vision loss in people at high risk of developing advanced AMD. Those at high risk were defined as individuals with intermediate AMD and those with advanced AMD in only one eye. The reduced risk of developing advanced AMD and vision loss was greatest in the antioxidant plus zinc group at 25 percent and 19 percent respectively.

AREDS participants with early AMD did not experience a slowed progression to intermediate AMD. Hence, researchers concluded that the antioxidants and zinc combina-

tion products are not recommended for this group. However, dilated eye examinations should be conducted to determine if the disease is progressing.

Bausch + Lomb markets PreserVision® Eye Vitamin AREDS softgels, which is the original product containing the antioxidant and zinc combination that was tested in AREDS. The product label dosage is one softgel in the morning and one in the evening, with a full glass of water during a meal. This formulation is not suitable as an alternative to multivitamins, and many patients may require both. In AREDS, two-thirds of the study participants took multivitamins along with the AREDS formulation.

Alcon now also markets ICaps Eye Vitamin and Mineral Supplement AREDS Formula softgels, which contain the same formulation used in AREDS. Additionally, Alcon markets ICAPS Eye Vitamin Multivitamin Formula, which is a multivitamin containing some, but not all, of the ingredients studied in AREDS.

The Age-Related Eye Disease Study 2 (AREDS2). Past observational studies have suggested that higher dietary intake of lutein + zeaxanthin, omega-3 long chain polyunsaturated fatty acids (docosahexaenoic acid [DHA], and eicosapentaenoic acid [EPA]), or both, are associated with a decreased risk of developing advanced AMD. Lutein and zeaxanthin are main components of the macula pigment; DHA is a major structural component of the retina, and EPA may play a role in retinal function. Therefore, AREDS2, a sequel to the original study, was designed to determine whether adding lutein + zeaxanthin, DHA + EPA, or both, to the AREDS formulation might further decrease the risk of developing advanced AMD.

The secondary goal was to test the effects of eliminating beta-carotene (replaced with lutein + zeaxanthin) and reducing zinc dose in the AREDS formulation. In past studies, beta-carotene has been associated with an increased risk of lung cancer in smokers. Lutein + zeaxanthin are antioxidants in the same family of nutrients as beta-carotene. The zinc dose was reduced to address concerns that the higher dose may cause minor side effects, such as stomach upset, and may not be fully absorbed.

AREDS2 was a multicenter, randomized, double-blinded, placebo-controlled Phase 3 study conducted from 2006 to 2012, that enrolled 4203 participants aged 50 to 85 years. Participants were at risk for progression to advanced AMD with bilateral large drusen or large drusen in one eye and advanced AMD in the other eye. Participants received one of the following: 1) lutein + zeaxanthin; 2) DHA + EPA; 3) lutein + zeaxanthin and DHA + EPA; 4) or placebo. In addition, study participants were also asked to take the original AREDS formulation, or a secondary randomization to four variations of the AREDS formulation, including elimination of beta-carotene, lowering of zinc dose, or both.

Median follow-up was five years with 1608 participants (1940 study eyes) progressing to advanced AMD established by retinal examination or treatment for advanced AMD. The results of the study indicated that the addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. Adding omega-3 fatty acids or lowering zinc to the AREDS formulation also had no effect on AMD progression.

The authors concluded, however, that lutein + zeaxanthin could be a safe and appropriate carotenoid substitute in the AREDS formulation to address the concern of increased lung cancer in former smokers. It appears that removing beta-carotene from the AREDS formulation did not curb the formulation's protective effect. No clinically or statistically significant differences in the rates of developing neoplasms were noted in the primary randomized treatment groups. However, secondary randomization, excluding participants who were former smokers, showed more lung cancers in the beta-carotene group than in the non-beta-carotene group. While no smokers received beta-carotene in AREDS2, half of all participants were former smokers.

The National Eye Institute recommends that patients over the age of 60 years should get a dilated eye exam at least once a year. Patients with moderate to advanced AMD who are taking either the PreserVision AREDS or PreserVision AREDS2 supplement should consult with their eye care professional. Because of the high levels of vitamins and minerals, patients should also talk with their physician before starting treatment. Bausch + Lomb and Alcon market various other eye supplements containing lutein, zeaxanthin, or omega-3 promoted for general eye health.

Treatment of AMD with VEGF Inhibitors. Table 1 summarizes the proposed management of patients with AMD and of patients for whom an AREDS supplement is recommended. Patients at all stages of this disease may also benefit from lifestyle and dietary modifications, including smoking cessation, increasing dietary intake of antioxidants, and control of blood pressure and body mass index.

The primary effective pharmacological therapy for patients with the most advanced form of the disease, wet age-related macular degeneration, is intravitreous injection of a vascular endothelial growth factor (VEGF) inhibitor. VEGF has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the pathophysiology of the disease. Thus, inhibiting the interaction of VEGF with its receptors on the surface of endothelial cells reduces endothelial cell proliferation, vascular leakage, and new blood cell formation. VEGF inhibitors can limit progression of exudative AMD and stabilize, or

reverse, visual loss. Intravitreal injections are localized to the eye and, therefore, possibly reduce the incidence of systemic adverse effects. Currently, there are four intravitreal agents that are available on the market: pegatanib (2004), bevacizumab (2004), ranibizumab (2006), and aflibercept (2011). While pegatanib was the first VEGF inhibitor to be approved by FDA, clinical trials have found that the other three agents provide greater benefit with less toxicity. Therefore, pegatanib is rarely prescribed or recommended.

Bevacizumab (Avastin®) is a monoclonal antibody to VEGF that was initially approved as an intravenous infusion for systemic therapy of colorectal cancer. Bevacizumab intravitreal injection for AMD is off-label, and has become increasingly used since it is much less expensive than other VEGF inhibitors (ranibizumab is 40 times more expensive per injection). Since it is not FDA-approved for this use, the product information does not specify the preferred intravitreal dosing schedule and associated rates of adverse reactions with intravitreal injection. However, bevacizumab 1.25 mg (0.05 mL) monthly for three months, or as needed, is the dose and regimen most studied in the literature.

Ranibizumab (Lucentis®) is a recombinant humanized monocolonal antibody with specificity for VEGF. Usual dosing of intravitreal ranibizumab is 0.5 mg by intravitreal injection, every month for three injections with scheduled or variable treatment thereafter.

Clinical trials showed that ranibizumab prevented vision loss in nearly 95 percent of patients and significantly improved vision in 40 percent. In 2011, results were published for the Comparison of AMD Treatment Trials (CATT), a head-to-head trial sponsored by the National Eye Institute comparing ranibizumab and bevacizumab. The results showed that bevacizumab and ranibizumab have equivalent efficacy over a one-year period, and that less than monthly or as-needed dosing did not compromise vision. There were no differences between the drugs in rates of death or arteriothrombotic events; however, there were more serious adverse events in patients treated with bevacizumab. Because treatment continues indefinitely for most patients, the trial continued for a second year to study the longer-term effects of these drugs and dosing regimens. For both years, the two agents had similar effects on visual acuity when the dosing regimen was the same. The need for a strict "monthly" dosing regimen compared with a less frequent, as-needed protocol is yet to be determined. Higher rates of serious adverse events with bevacizumab were consistent in the second year, but the interpretation of these results is uncertain.

Aflibercept (Eylea®) is the newest intravitreal injection agent approved for wet AMD. The recommended dose for AMD is 2 mg (0.05 mL) administered by intravitreal injection every four weeks for the first three months, followed by 2 mg (0.05 mL) once every eight weeks.

Aflibercept was approved following two randomized trials showing clinically equivalent efficacy to ranibizumab. It has not been compared directly to bevacizumab. It is less expensive than ranibizumab and may result in less frequent injections.

All of the VEGF inhibitors have similar contraindications, warnings, and adverse effects. Injections in patients with ocular or periocular infections are contraindicated for all agents. Additionally, aflibercept should not be used in patients with active intraocular inflammation. Serious warnings for VEGF inhibitors include the risk of endophthalmitis, retinal detachment, increased intraocular pressure (IOP); and arterial thromboembolic events. Other ocular adverse reactions that have been reported are conjunctival hemorrhage, eye pain, vitreous floaters, punctate keratitis, cataracts, vitreous opacities, anterior chamber inflammation, vision disturbances, corneal edema, and ocular discharge.

The second important issue with VEGF inhibitor use is systemic safety. Ranibizumab and bevacizumab enter systemic circulation which can lead to prolonged suppression of plasma VEGF levels. In theory, this can lead to a higher risk of systemic vascular events. Cardiovascular effects of these medications have been studied, but remain unclear. One study found similar rates of stroke, myocardial infarction, and mortality between the groups treated with ranibizumab and bevacizumab. Clinicians should be aware of the increased risk of stroke in patients treated with VEGF inhibitors.

Intravitreal injection procedures utilizing VEGF inhibitors should be carried out under controlled aseptic conditions, which include the use of sterile gloves, sterile drape, and a sterile eyelid speculum. Adequate anesthesia and a broad-spectrum, topical microbicide should be given prior to the injection. Prior to and 30 minutes following the intravitreal injections, patients should be monitored for elevations in intraocular pressure (IOP). Patients should also be monitored for, and instructed to report, any symptoms suggestive of endophthalmitis without delay following the injection. Each vial should only be used for the treatment of a single eye.

Glaucoma

Glaucoma is defined as an optic neuropathy and is thought to be present when at least one eye has both typical structural and functional defects. Resulting optic disc and optic nerve damage is accompanied with visual field loss. Glaucoma is traditionally characterized by elevated intraocular pressure, but is not, in fact, a defining criteria and is not required for diagnosis.

The two most common forms of glaucoma are open-angle glaucoma and angle-closure glaucoma. Survey data indicate that one in

40 adults older than 40 years has glaucoma with loss of vision function. Therefore, it affects approximately 60 million people worldwide. The prevalence of both open-angle glaucoma and angle-closure glaucoma is low before 40 years of age, and increases exponentially with age. Diagnosis requires a detailed eye examination, including testing of both the structure and function of the eye.

Open-angle glaucoma occurs with slow progression over months to years. The typical onset is after the age of 60, with increasing frequency as persons age. Genetic influences have a role in the occurrence and morbidity. For instance, having a first-degree relative who has open-angle glaucoma raises the likelihood for developing this disorder 10 times. African Americans and Hispanics have a higher incidence rate for this eye disorder. African Americans experience open-angle glaucoma at a rate three times that of Caucasians, and suffer blindness four times more frequently. Persons at risk should get comprehensive eye exams at least every two years, especially: 1) African Americans over age 40 years; 2) persons over age 60, especially Hispanics; and 3) persons with a family history of glaucoma. Secondary causes due to uveitis, trauma, and corticosteroid therapy may occur.

Corticosteroid use (inhaled, injectable, ophthalmic, oral, and topical) can reduce the outflow of aqueous humor in the eye resulting in open-angle glaucoma. The potential for a corticosteroid to increase intraocular pressure is related to anti-inflammatory potency and intraocular penetration. Therefore, the highest risk is associated with ophthalmic corticosteroid formulations. General recommendations include using the lowest potency corticosteroid for the shortest period of time, and to taper corticosteroids as soon as possible if increased intraocular pressure occurs. Product labeling for ophthalmic corticosteroids recommends monitoring IOP when used for ten days or more. Additional monitoring may be required for patients at risk for open-angle glaucoma and those who require chronic steroid use. Those at greater risk of steroid-induced glaucoma include 1) patients with primary open-angle in their first-degree relatives; 2) elderly or young patients (<6 years); and 3) patients with type 1 diabetes, rheumatoid arthritis, or high myopia.

Table 2
Selected topical drugs for glaucoma

Drug	Daily Dose	Common Adverse Effects
Prostaglandin Analogs		
Latanoprost (Xalatan)	1 drop qPM	•conjunctival hyperemia
Bimatoprost (Lumigan)	1 drop qPM	•irreversible darkening of the iris in persons with multicolor irises
Travoprost (Travatan Z)	1 drop qPM	•increases in length, thickness, and number of eyelashes
Tafluprost (Zioptan)	1 drop qPM	•increases in eyelid skin pigmentation •local irritation, itching, dryness, blurred vision and periorbital fat atrophy
Beta Blockers		
Betaxolol (Betoptic S)	1 drop qAM or BID	•stinging, itching, redness, and blurred vision
Levobunolol (Betagan)	1 drop qAM or BID	
Metipranolol (Optipranolol)	1 drop qAM or BID	•systemic effects: fatigue, dizziness, bradycardia, respiratory depression, masking of hypoglycemia, and blocking effects of beta2-agonists in the treatment of asthma
Timolol (Betimol, Istalol)	1 drop qAM or BID	
Timolol (Timoptic, Timoptic Ocudose)	1 drop BID	
Carbonic Anhydrase Inhibitors		
Brinzolamide (Azopt)	1 drop TID	•stinging, redness, burning, conjunctivitis, dry eyes, and blurred vision •bitter taste
Dorzolamide (Trusopt)	1 drop TID	
Alpha2 Agonists		
Apraclonidine (Iodipine)	1 drop TID	•fatigue, somnolence (especially younger children) •local allergic reactions •dry eyes, stinging, conjunctival hyperemia, and foreign body sensation
Brimonidine (Alphagan P)	1 drop TID	
Combinations		
Brimonidine/timolol (Combigan)	1 drop BID	•see individual agents
Timolol/dorzolamide (Cosopt, Cosopt PF)	1 drop BID	•see individual agents
Brimonidine/brinzolamide (Simbrinza)	1 drop TID	•see individual agents

The goal of therapy in open-angle glaucoma is to lower IOP, which has been shown to reduce the risk of disease progression and visual field loss and/or optic disc changes. The higher the IOP, the greater the likelihood of developing the disorder, and the more rapidly it progresses. Lowering of IOP is always recommended in patients with established glaucoma defined as having optic nerve damage, even if IOP is within normal limits. This form of glaucoma is usually bilateral, but asymmetric. Therefore, the decision to treat is made for each eye. On average, there is 50 percent as much damage in the better eye, as in the worse eye. IOP can be lowered by pharmacological therapy, laser therapy, or surgery.

Topical agents most often

used include prostaglandins, beta blockers, carbonic anhydrase inhibitors, and alpha adrenergic agonists. These agents are summarized in Table 2.

Prostaglandin analogs typically lower IOP by 25 to 30 percent, and stabilize it at a lower level throughout the day and night by increasing aqueous outflow. They are usually dosed once daily at night, and are currently the most frequently used eye drop for glaucoma.

Topical beta blockers decrease aqueous humor production. They lower IOP by 20 to 25 percent, and are dosed either once or twice daily. Topical beta blockers rarely cause local irritation, but are limited in use as a first-line agent due to their systemic effects. Therefore, they should be used with caution in patients with asthma, bradycardia, or chronic obstructive pulmonary disease.

Carbonic anhydrase inhibitors (CAIs) decrease IOP by decreasing production of aqueous humor. The oral agents, acetazolamide and methazolamide, reduce IOP by 30 to 50 percent, but have many systemic effects. Alternatively, topical CAIs reduce IOP about 15 to 20 percent throughout the day and night. They are FDA-approved for three times a day dosing. Topical CAIs are better tolerated than beta blockers.

Topical alpha agonists also decrease IOP by decreasing aqueous humor, but may also cause increased uveoscleral outflow (aqueous passage from the anterior chamber into the ciliary muscle and then into the supraciliary and suprachoroidal spaces, before exiting the eye through the intact sclera or along the nerves and the vessels that penetrate it). Brimonidine, a selective alpha2-agonist, typically lowers IOP by 15 to 20 percent during the day, but not during the night. Recently, there was a preservative change and a change in concentration from 0.15 percent to 0.1 percent, which may improve the drug's tolerability.

Combination products are options for patients who require treatment with two of these drug classes, but should not be used for initial therapy. Adherence to topical regimens is not ideal, with only 60 to 70 percent of prescribed doses of eye drops typically administered. Systemic agents such as carbonic anhydrase inhibitors and cholinergic agents have been largely replaced by topical agents, but may still be used.

Angle-closure glaucoma (narrow-angle or closed-angle) is characterized by narrowing or closure of the anterior chamber angle. Worldwide, angle-closure glaucoma accounts for one-third of patients with primary glaucoma. Risk factors include family history of angle-closure glaucoma, age older than 40 to 50 years, female gender, hyperopia (farsightedness), and race. Population-based studies indicate that this eye disorder has a greater prevalence in people of Asian and Indian origin, when compared to those of European and African descent. Secondary angle-closure glaucoma is caused by processes that either push or pull the anterior chamber closed, such as fibrosis, scarring, drug reactions, neovascularization, or a mass. In open-angle glaucoma, optic nerve damage results in a progressive loss of retinal ganglion axons, which manifests initially as visual field loss and can lead to irreversible blindness if untreated. While angle-closure glaucoma occurs less frequently than open-angle glaucoma, vision loss is more frequent.

Patients with acute angle-closure glaucoma have rapid rises in IOP and may experience decreased vision, halos around lights, headache, severe eye pain, and nausea and vomiting. Alternatively, 75 percent of patients do not have an acute attack, but rather experience chronic angle-closure glaucoma where the rise in intraocular pressure is slower and never reaches high levels. Therefore, the patient may be symptom-free and may not notice damage to peripheral vision. Patients with signs or symptoms should undergo emergency ophthalmic examination.

Initial management of an acute attack requires prompt administration of pressure-lowering eye drops which may include a regimen of timolol, apraclonidine, and pilocarpine. Systemic medications such as oral or intravenous (IV) acetazolamide, IV mannitol, or oral isosorbide are also often given. Once the IOP is reduced, the treatment of choice is a procedure called peripheral iridotomy, where a tiny hole in the peripheral iris is created to allow aqueous humor to flow and reach the angle, thus allowing the block to be bypassed. Peripheral iridotomy to relieve the block is the first step in treating chronic angle-closure glaucoma. If elevated IOP remains due to scarring, it is treated like open-angle glaucoma.

Medications that have a direct or secondary effect, either to stimulate sympathomimetic or inhibit parasympathetic activation, cause pupillary dilation, which can precipitate acute angle-closure glaucoma in patients with occludable angles. Specifically, in patients with narrow angles (narrow-angle glaucoma), the dilation leads to a mechanism in which the lens blocks the movement of aqueous fluid through the pupil, leading to fluid accumulation and subsequent increases in IOP. In fact, more than one-third of acute narrow-angle glaucoma results from the use of OTC or prescription medications. Some drugs or drug classes have been noted to either cause or exacerbate this type of glaucoma, such as antidepressants (e.g., SNRIs, SSRIs, TCAs, and monoamine oxidase inhibitors), first-generation antihistamines, typical antipsychotics, cyclobenzaprine, antiparkinsons drugs, antispasmodic drugs, and decongestants. General management recommendations suggest avoiding the use of these agents in uncontrolled narrow-angle glaucoma, but considering initial and periodic eye exams in at-risk patients when these agents are used, or to use alternative agents when feasible. In terms

of antidepressants, drugs that affect both serotonin and norephinephrine may carry greatest risk. Additionally, of the SSRIs, paroxetine appears to be the most likely cause. Patients who have narrow angles who have been treated with laser iridotomy to break or prevent an attack can often safely take these medications.

Various drugs containing sulfa components, such as sulfamethoxazole/trimethoprim, topiramate, hydrochlorothiazide, and acetazolamide, have also been linked to acute attacks in patients with narrow or wide open angles. They produce idiosyncratic bilateral lens swelling, blurred vision, choroidal effusion, and increased IOP unrelated to pupil block. Management includes discontinuation of the inciting drug, lowering of IOP, and surgical intervention.

Summary

Macular degeneration and glaucoma are two age-related eye disorders that can result in loss of vision. Multiple over-the-counter supplements are marketed for eye health or to reduce the progression of age-related macular degeneration (AMD). Pharmacists may be helpful in assisting patients in selecting an appropriate product. Intravitreal injections with VEGF inhibitors may be used in patients with advanced (wet) AMD to limit, stabilize, and possibly reverse visual loss. The mainstay of pharmacologic treatment for glaucoma consists of ophthalmic drops aimed at reducing intraocular pressure. Medications such as corticosteroids, decongestants, and antidepressants may also cause or exacerbate glaucoma.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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Age-Related Macular Degeneration and Glaucoma

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1. A clinical hallmark of age-related macular degeneration (AMD) is:
   a. excess drusen. b. increased IOP.

2. Early symptoms of AMD include all of the following EXCEPT:
   a. blurred vision. c. elevated IOP.
   b. visual scotomas. d. decreased contrast sensitivity.

3. Risk factors for AMD include all of the following EXCEPT:
   a. smoking. c. cardiovascular disease.
   b. family history. d. corticosteroid therapy.

4. The most progressed form of AMD is:
   a. wet. b. dry.

5. AREDS results showed that the reduced risk of developing AMD and vision loss was greatest in which group?
   a. Antioxidant alone c. Antioxidant plus zinc
   b. Zinc alone

6. The CATT study results showed which two VEGF inhibitors had equivalent efficacy over one year?
   a. Aflibercept and bevacizumab
   b. Bevacizumab and ranibizumab
   c. Aflibercept and ranibizumab
   d. Ranibizumab and pegatanib

7. While interpretation of results is uncertain, which VEGF inhibitor was associated with higher rates of serious adverse events in CATT?
   a. Pegatanib c. Ranibizumab
   b. Bevacizumab d. Aflibercept

8. Which of the following VEGF inhibitors is used off-label for the treatment of AMD?
   a. Pegatanib c. Ranibizumab
   b. Aflibercept d. Bevacizumab

9. Serious warnings for VEGF inhibitors include the risk of all of following EXCEPT:
   a. endophthalmitis. c. irreversible darkening of iris.
   b. increased IOP. d. arterial thromboembolic events.

10. Patients treated with VEGF inhibitors may be at increased risk of stroke.
   a. True b. False

11. Elevated intraocular pressure:
   a. is required for diagnosis of glaucoma.
   b. is not required for diagnosis of glaucoma.

12. African Americans experience which form of glaucoma at a higher rate compared to other ethnicities?
   a. Angle-closure c. Open-angle
   b. Narrow-closure

13. Which form of corticosteroids is associated with the highest risk of open-angle glaucoma?
   a. Oral c. Intravenous
   b. Inhaled d. Ophthalmic

14. The most frequently used eye drops for glaucoma are:
   a. alpha adrenergic agonists. c. beta blockers.
   b. carbonic anhydrase inhibitors. d. prostaglandins.

15. All of the following drugs cause or exacerbate angle-closure glaucoma EXCEPT:
   a. ibuprofen. c. TCAs.
   b. SSRIs. d. decongestants.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b]	6. [a] [b] [c] [d]	11. [a] [b]
2. [a] [b] [c] [d]	7. [a] [b] [c] [d]	12. [a] [b] [c]
3. [a] [b] [c] [d]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c]	10. [a] [b]	15. [a] [b] [c] [d]

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4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
5. How long did it take you to read this lesson and complete the quiz? _____
6. Comments/future topics welcome.

To receive CE credit, your quiz must be received no later than December 15, 2017. A passing grade of 80% must be attained. CE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.