

Current Treatment Strategies for Age-Related Ocular Conditions

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Abstract

Treatment for several major age-related ocular diseases has undergone a paradigm shift in recent years. Advances in basic science and clinical research have led to a more thorough understanding of the complex pathophysiology underlying common ocular diseases of aging, and to the development of highly effective new therapies for these conditions. The use of intraocular anti-angiogenic drugs, for example, has transformed the management of neovascular age-related macular degeneration and diabetic retinopathy. Many patients achieve impressive and durable gains in vision with these agents that were unattainable with older treatments. For glaucoma and dry eye disease, clinicians have a variety of pharmacologic and surgical options to choose from. However, significant challenges remain: not all patients respond to treatment, many older patients have difficulty complying with complex drug regimens, frequent office visits put a substantial strain on patients and caregivers, and therapies may cause unpleasant side effects. This article reviews the current treatment landscape for 4 major age-related ocular diseases: age-related macular degeneration, glaucoma, diabetic retinopathy, and dry eye.

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For author information and disclosures, see end of text.

The prevalence of age-related eye diseases in the United States continues to increase as society ages. Vision loss associated with ocular diseases puts a tremendous burden on patients, caregivers, and society as a whole. There have been a number of notable recent advances in the treatment of ocular diseases of aging, such as the development of agents that inhibit the proliferation of abnormal blood vessels in the retina, a characteristic feature of certain retinal conditions, including wet age-related macular degeneration (AMD) and proliferative diabetic retinopathy (DR).

Age-Related Macular Degeneration

Agents that inhibit vascular endothelial growth factor (VEGF) have revolutionized the treatment of wet AMD in recent years. Intravitreal anti-VEGF injection therapy has largely supplanted older, less effective wet AMD therapies, including ocular photodynamic therapy and laser photocoagulation.¹ The 2 primary anti-VEGF agents approved by the US Food and Drug Administration (FDA) for wet AMD are ranibizumab (Lucentis), a humanized anti-VEGF monoclonal antibody fragment (fab) developed specifically for the eye,² and aflibercept (Eylea), a soluble VEGF receptor decoy that binds to VEGF-A, VEGF-B, and placental growth factor.³ Bevacizumab (Avastin), a full-length anti-VEGF monoclonal antibody, is approved as an antiangiogenic cancer agent but has been successfully used off-label to treat wet AMD.¹ Ranibizumab sells for \$1950 per dose, compared with \$1850 for aflibercept; bevacizumab can be prepared for wet AMD in doses that cost about \$50.⁴

The safety and efficacy of ranibizumab for wet AMD was demonstrated in 2 prospective, randomized, phase 3 clinical trials, the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD)⁵ and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD)⁶ studies, which involved a total of 1139 patients. In both studies, significantly more patients treated with monthly intraocular ranibizumab either maintained vision (<15 letters lost in best corrected visual acuity) or had improved vision (gain of ≥15 letters) versus sham injections ($P < .001$).^{5,6} Approximately 95% of ranibizumab-treated patients had their vision stabilize or improve

during the first year. Ranibizumab was approved by the FDA for the treatment of wet AMD in June 2006.⁷

Once-monthly dosing of ranibizumab was evaluated in the ANCHOR and MARINA studies. This dosing regimen places a significant burden on patients and their caregivers. Furthermore, intravitreal injections carry a risk for infectious endophthalmitis, a potentially devastating complication. A recent single-center, prospective case series and case-control study identified 23 cases of presumed infectious endophthalmitis out of 27,736 intravitreal injections of ranibizumab or bevacizumab (0.083% incidence), although only 7 of the cases were culture-positive.⁸ The rates of presumed endophthalmitis in the MARINA and ANCHOR studies, including patients treated and untreated for possible infection, were 0.18% and 0.22%, respectively.⁸ Therefore, clinicians are evaluating less frequent dosing schedules for intravitreal anti-VEGF therapy. A randomized, controlled phase 3b trial (PIER) assessed the efficacy of intraocular ranibizumab administered quarterly (every 3 months) following 3 initial monthly injections.⁹ Although visual outcomes were significantly improved versus sham injections for both monthly and quarterly ranibizumab dosing, the degree of visual improvement achieved with quarterly dosing at 2 years was markedly worse than that which was obtained with monthly ranibizumab in ANCHOR and MARINA.¹⁰ In those studies, patients who received monthly ranibizumab injections gained 5 to 11 letters from baseline, compared with an approximate 2-letter loss with quarterly ranibizumab in PIER. Between 25% and 41% of patients from ANCHOR and MARINA gained at least 15 letters from baseline at 2 years, compared with 15% in the PIER study.

A second randomized, controlled phase 3b study (EXCITE) was conducted to determine whether quarterly maintenance dosing of ranibizumab for wet AMD was non-inferior to monthly dosing.¹¹ Patients were randomized 1:1:1 to receive intravitreal ranibizumab 0.3 mg monthly or quarterly, or ranibizumab 0.5 mg quarterly. Quarterly ranibizumab was clinically inferior to monthly dosing: patients gained 8.3 letters with monthly injections compared with 4.9 and 3.8 letter gains for quarterly ranibizumab 0.3 mg and 0.5 mg, respectively.

In a prospective, non-controlled trial (Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab [PrONTO]), an as-needed dosing schedule of ranibizumab 0.5 mg was used in 40 patients with wet AMD.¹² Patients received 3 initial monthly injections followed by monthly evaluation and re-treatment if certain clinical criteria were met. During year 2, the study protocol was amended to treat patients at the first sign of fluid re-accumulation. Of 37

patients who completed 2 years of treatment, mean visual acuity improved by 11.1 letters with an average of 9.9 injections. By comparison, patients gained 7.2 letters in MARINA and 11.3 letters in ANCHOR.

In May 2011, results from a widely anticipated non-inferiority comparative trial of ranibizumab and bevacizumab—the Comparison of Age-related Macular Degeneration Treatment Trial (CATT)—were published.¹³ CATT was conducted because a high proportion of ophthalmologists use bevacizumab off-label to treat wet AMD. A total of 1208 patients with previously untreated wet AMD were randomized to intraocular ranibizumab or bevacizumab either monthly or as needed. At 1 year, patients in the monthly treatment arms of both drugs were randomly reassigned to continue monthly therapy or switch to as-needed dosing. The main finding from CATT was that ranibizumab and bevacizumab were similarly effective for wet AMD.^{13,14} Among patients who received the same treatment regimen for 2 years, the difference in mean visual acuity improvement for bevacizumab relative to ranibizumab was -1.4 letters (95% confidence interval, -3.7 to 0.8 ; $P = .21$).¹⁴ In terms of dosing regimens, monthly dosing of either drug was statistically superior to as-needed dosing (mean -2.4 letters for monthly versus as-needed dosing at 2 years; $P = .046$). Improvement in visual acuity ranged from a mean of $+5.0$ letters for bevacizumab as needed (worst performing group) to $+8.8$ letters for monthly ranibizumab (best performing group). Switching from monthly to as-needed dosing resulted in a greater mean decrease in vision during year 2 (-2.2 letters; $P = .03$). Patients in the monthly treatment arms also generally had better secondary outcomes than those in the as-needed arms, such as less visible fluid on optical coherence tomography, less fluorescein dye leakage, lower mean retinal thickness, and smaller AMD lesions. Interestingly, a greater proportion of patients receiving fixed monthly therapy had geographic atrophy (GA) at year 2. The highest occurrence of GA among all 6 treatment groups (fixed monthly, as needed, switched) was in the monthly ranibizumab arm (25.8%); by comparison, 12.9% of patients in the bevacizumab as-needed arm had GA at 2 years (the lowest incidence). The reasons for this finding and its clinical significance are not clear.

The rate of arteriothrombotic events at 2 years was similar between the ranibizumab and bevacizumab arms (4.7% vs 5.0%; $P = .89$).¹⁴ Notably, the proportion of patients who experienced at least 1 serious adverse event was statistically greater for bevacizumab than ranibizumab (39.9% vs 31.7%; $P = .004$). This discrepancy was also notable for gastrointestinal events, which occurred in 1.8% of ranibizumab-treated patients and 4.8% of bevacizumab-treated patients ($P = .005$). Whether these findings may be attributable to greater systemic

Reports

distribution of bevacizumab relative to ranibizumab requires further study. The newest anti-VEGF therapy for wet AMD is aflibercept (Eylea), which was approved by the FDA in November 2011. The clinical efficacy of aflibercept was demonstrated in 2 parallel, randomized, controlled phase 3 clinical trials: VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD)¹ (North America) and VIEW2 (Europe, Asia, Latin America, Australia), involving a total of 2419 patients with wet AMD.¹⁵ Aflibercept 0.5 mg monthly, 2.0 mg monthly, or 2.0 mg dosed every 2 months following 3 initial monthly injections was compared with monthly ranibizumab 0.5 mg. At 1 year, all 3 aflibercept treatment groups in VIEW1 and VIEW2 were found to be statistically non-inferior and clinically equivalent to monthly ranibizumab with respect to the primary end point of maintenance of vision (94% for ranibizumab and 95% to 96% for aflibercept). For the secondary end point of mean change in best corrected visual acuity, only the once-monthly aflibercept dosing group in VIEW1 was statistically superior to ranibizumab (+10.9 letters vs +8.1 letters; $P < .05$). After year 1, the dosing protocol in the VIEW trials was modified so that all patients were treated at least every 3 months, with monthly evaluations and interim treatment as needed. An integrated analysis at 96 weeks found that all treatment groups maintained baseline vision to a similar degree (91%-92%); however, patients in the original bimonthly aflibercept treatment arm received 5 fewer injections on average. Additionally, aflibercept was equivalent to ranibizumab on anatomic measures, including reduction in central retinal thickness and the proportion of patients with fluid-free retinas.

Because dosing frequency is such an important issue in the care of patients with wet AMD, results from the CATT and VIEW studies have generated considerable discussion within the ophthalmology community.⁴ While acknowledging that monthly intraocular ranibizumab is still considered the “gold standard” in wet AMD therapy, most retinal specialists use treat-and-extend or treat-and-observe strategies to try to maximize intervals between injections.⁴ Randomized, prospective studies that compare less frequent dosing schedules between the 3 drugs are needed to determine whether the greater VEGF-binding affinity of aflibercept relative to ranibizumab and bevacizumab confers a longer duration of action.

Glaucoma

Although glaucoma is a complex and poorly understood disorder, the primary goal of therapy is lowering intraocular pressure (IOP), which remains the only modifiable and clinically validated risk factor that has been shown to delay disease onset and reduce the risk of progression.¹⁶ Controlled

clinical studies have demonstrated the efficacy of a variety of different IOP-lowering interventions (eg, medications, laser treatment, surgery) for reducing the risk of optic nerve damage, vision loss, and disease progression in patients with advanced glaucoma, newly diagnosed glaucoma, and those with elevated IOP at risk for developing glaucoma.¹⁶

Despite these findings, the role of IOP in the initiation and progression of glaucoma is controversial and not completely understood. Some research suggests that fluctuations in IOP between office visits may be of more clinical importance than absolute measurements, particularly for glaucoma patients with IOPs in the normal range (normal-tension glaucoma).¹⁶⁻¹⁸ While differences in study design, patient populations, and treatments may account for some of the discrepancies in IOP findings, it is also possible that the eyes of some individuals may be inherently more susceptible than others to damage from fluctuations in IOP.¹⁶⁻¹⁸

Treatment of open-angle glaucoma (OAG) begins with an assessment of baseline IOP.^{19,20} A target IOP is then individualized for the patient based on patient-specific factors, including the extent of optic nerve damage, risk factors for progression (eg, family history, age, presence of disc hemorrhages), and rate of progression.²⁰ Lowering IOP by 20% to 40% reduces the average rate of progressive visual field loss by half.¹⁹ Data from randomized clinical studies indicate that IOP should be lowered by at least 25% from baseline to reduce the risk of progression of OAG and associated vision loss.²¹⁻²³ A less or more aggressive pressure target may be indicated depending on the severity of optic nerve damage and rate of progression. Once a treatment plan is chosen, patients should receive regular follow-up to monitor treatment response, according to the schedule in [Table 1](#).

The treatment modalities for OAG include eye drops, laser trabeculoplasty, and incisional surgery, which can be used alone or in combination. A number of factors are considered when choosing a treatment, including cost, side effects, dosing schedules, and patients' preference, risk tolerance, and likelihood of compliance.¹⁵ Older patients with glaucoma and cognitive impairment, for example, may have difficulty complying with multi-drop medication regimens or may have comorbidities that may make surgery problematic.^{16,20}

For most patients with glaucoma seen in clinical practice, first-line therapy consists of topical agents, typically prostaglandin analogues or β -adrenergic receptor blockers.¹⁹ Other medication classes that may be considered include α -2 adrenergic agonists, parasympathomimetic agents, and carbonic anhydrase inhibitors. A comparison of the different medication classes is shown in [Table 2](#).²⁰ Recent studies have suggested that 24-hour assessments of IOP in patients with

■ Table 1. Recommended Guidelines for Follow-Up Glaucoma Status Evaluations With Optic Nerve and Visual Field Assessment^{20,a}

Target IOP Achieved	Progression of Damage	Duration of Control (months)	Approximate Follow-up Interval (months) ^b
Yes	No	≤6	6
Yes	No	>6	12
Yes	Yes	NA	1-2
No	Yes	NA	1-2
No	No	NA	3-6

IOP indicates intraocular pressure; NA, not applicable.

^aLevel BIII evidence (moderately important; obtained from 1 of the following: descriptive studies, case reports, reports of expert committees/organizations [eg, Preferred Practice Pattern panel consensus with external peer review]). Evaluations consist of clinical examination of the patient, including optic nerve head assessment (with periodic color stereophotography or computerized imaging of the optic nerve and retinal nerve fiber layer structure) and visual field assessment.

^bPatients with more advanced damage or greater lifetime risk from primary open-angle glaucoma may require more frequent evaluations. These intervals are the maximum recommended time between evaluations.

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glaucoma may provide a more complete clinical picture than daytime pressures alone.²⁴ A meta-analysis of randomized, controlled clinical studies of different medication types used for primary OAG found that prostaglandin analogues were associated with the greatest mean 24-hour reduction in IOP from baseline (24%-29%), of which bimatoprost and travoprost showed the greatest efficacy.²⁴ The carbonic anhydrase inhibitor dorzolamide and the β -adrenergic blocker timolol both demonstrated mean 24-hour IOP reductions of 19%. The α -adrenergic agonists (eg, brimonidine, dosed twice daily) produced a 24-hour pressure decrease of 14%. As the efficacy of brimonidine has been observed to diminish toward the end of the dosing cycle in the late afternoon or evenings, it is recommended that it be dosed 3 times daily to provide better late-day IOPs.

Patient adherence to glaucoma medications is a significant problem—patients with glaucoma generally take 70% or less of their prescribed regimen.²⁵ In a large analysis of pharmacy data and patient and physician interviews, compliance with topical glaucoma treatments was found to be generally poor and on par with that observed in other chronic diseases. More than 55% of patients with glaucoma who were followed for at least 1 year failed to consistently refill their prescriptions.²⁶ Another study in patients with glaucoma and a history of low medication adherence showed that a multifaceted approach comprising education and reminder systems improved eye drop adherence to 73% from 54% ($P < .001$).²⁵

Laser trabeculoplasty is often used as an alternative to medication in selected patients with glaucoma who cannot or will not use eye drops reliably due to cost, adherence problems, side effects, or other factors.²⁰ Laser procedures are performed on an outpatient basis with local anesthesia to relieve IOP. Traditional laser trabeculoplasty uses a thermal argon laser (ALT) with a 50- μ m laser spot that is aimed at

the trabecular meshwork to stimulate opening of the mesh to allow more outflow of aqueous fluid. Usually, half of the angle is treated at a time. A newer type of laser trabeculoplasty (selective laser trabeculoplasty) uses a nonthermal/cold, 532-nm, frequency-doubled, Q-switched Nd:YAG laser to selectively target melanin pigment in the trabecular meshwork to stimulate drainage. This newer procedure is as effective as ALT for lowering eye pressure and may be repeated 3 to 4 times, whereas ALT can usually be repeated only once.²⁰

Laser peripheral iridotomy (LPI) may be used in patients with angle closure or narrow angle glaucoma or pigment dispersion syndrome. Nd:YAG laser energy is used to make a small, full-thickness opening in the iris to equalize the pressure between the front and back of the iris. LPI reduces the risk of developing an attack of acute angle closure in individuals with narrow angles. In most cases, it also reduces the risk of developing chronic angle closure or adhesions of the iris to the trabecular meshwork.

The most commonly used surgical procedure for OAG is trabeculectomy, in which a partial thickness flap is made within the scleral wall of the eye and a window opening is made under the flap to remove a portion of the trabecular meshwork. The scleral flap is then sutured loosely back in place to allow aqueous fluid to drain from the anterior chamber to the space between the sclera and conjunctiva. This process creates a fluid-filled blister called a bleb on the surface of the eye underneath the upper eyelid, where the trabeculectomy surgery is most commonly performed.²⁷ Late complications of trabeculectomy include fluid leakage through the bleb, accompanied by abnormally low IOP or bacterial infection.¹⁹ Worsening of cataracts is common in patients with glaucoma undergoing trabeculectomy.¹⁹ Scarring and failure of the bleb can also occur.

For patients refractory to or who are considered less likely to benefit from trabeculectomy, a variety of aqueous drainage

■ **Table 2.** Glaucoma Medications²⁰

Drug Classification	Methods of Action	IOP Reduction ^a	Side Effects	Contraindications
Prostaglandin analogues	Increase uveoscleral and/or trabecular outflow	25%-33%	Cystoid macular edema Conjunctival injection Increased eyelash growth Periocular hyperpigmentation Iris color change Uveiti Possible herpes virus activation	Macular edema History of herpetic keratitis
Beta-adrenergic antagonists (beta-blockers)	Decrease aqueous production	20%-25%	Corneal toxicity Allergic reactions CHF (classic teaching, although cardiologists use beta-blockers as first line treatment in CHF) Bronchospasm (seen with nonselective) Bradycardia Depression Impotence	Chronic obstructive pulmonary disease (nonselective) Asthma (nonselective) CHF (check with cardiologist) Bradycardia Hypotension Greater than first degree heart block
Alpha-adrenergic agonists	Nonselective: improve aqueous outflow Selective: decrease aqueous production; decrease episcleral venous pressure or increase uveoscleral outflow	20%-25%	Conjunctival injection Allergic reactions Fatigue Somnolence Headache	Monoamine oxidase inhibitor therapy Infants and children younger than 2 years
Parasympathomimetic agents	Increase trabecular outflow	20%-25%	Increased myopia Eye or brow ache/pain Decreased vision Cataract Periocular contact dermatitis Corneal toxicity Paradoxical angle closure	Neovascular, uveitic, or malignant glaucoma Need to regularly assess fundus
Carbonic anhydrase inhibitors (mainly with systemic use)	Decrease aqueous production	15%-20%	With topical route: Metallic taste Allergic dermatitis/conjunctivitis Corneal edema With oral route: Stevens-Johnson syndrome Malaise, anorexia, depression Serum electrolyte imbalance Renal calculi Blood dyscrasias (aplastic anemia, thrombocytopenia) Metallic taste	Sulfonamide allergy Kidney stones Aplastic anemia Thrombocytopenia Sickle cell disease

CHF indicates congestive heart failure; IOP, intraocular pressure.

^aData from the European Glaucoma Society. Terminology and Guidelines for Glaucoma. 3rd ed. Savona, Italy: Editrice Dogma S.r.l.; 2008:127. www.eugs.org/eng/EGS_guidelines.asp. Accessed May 28, 2010.

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devices (tube-shunt surgery) can be implanted into the anterior chamber to relieve IOP.²⁰ A recent randomized, multicenter study compared the efficacy and safety of tube-shunt surgery against trabeculectomy in 212 patients with medically uncontrolled glaucoma (IOP ≥ 18 mm Hg and ≤ 40 mm Hg on maximum tolerated therapy) who had undergone prior cataract surgery with an intraocular lens implant and/or had failed prior trabeculectomy.²⁸ The 2 procedures produced similar reductions in IOP at 3 years (mean IOP: 13.0 mm Hg for tube-shunt vs 13.3 mm Hg for trabeculectomy; $P = .78$). However, the cumulative probability of treatment failure was significantly higher for patients who received trabeculectomy compared with tube-shunt surgery (30.7% vs 15.1%; $P = .010$). Further, significantly more treatment-related complications were reported in the trabeculectomy arm versus the tube-shunt arm (60% vs 39%; $P = .004$). Other surgical options for OAG include cyclodestructive surgery of the ciliary body using a diode laser or cryogenic laser to reduce aqueous production, deep sclerectomy, viscocanalostomy, and canaloplasty.^{19,20}

Diabetic Retinopathy

Treatment of DR is quite similar to that for wet AMD, and focuses on alleviating the macular edema associated with the proliferation of leaky capillaries in the retina. The safety and efficacy of ranibizumab for the treatment of diabetic macular edema (DME) was demonstrated in 2 parallel, randomized, controlled phase 3 clinical studies (RISE and RIDE) involving a total of 759 patients with type 1 or type 2 diabetes and vision loss from DME.²⁹ Patients were randomized to monthly intravitreal injections of ranibizumab 0.3 mg or 0.5 mg or sham injections. After 3 months, patients were eligible for laser photocoagulation therapy if they met certain clinical criteria during monthly evaluations.

At 2 years in the RISE study, 18.1% of sham-treated patients gained at least 15 letters in best corrected visual acuity versus 44.8% of patients treated with ranibizumab 0.3 mg ($P < .0001$) and 39.2% treated with ranibizumab 0.5 mg ($P < .001$).²⁹ In RIDE, the results were 12.3%, 33.6%, and 45.7% for sham injection, ranibizumab 0.3 mg, and ranibizumab 0.5 mg, respectively, which reached statistical significance. Ranibizumab-treated patients also underwent significantly fewer macular laser procedures than sham-treated patients over the 2-year period. Ranibizumab 0.3 mg was approved by the FDA for the treatment of DME in August 2012.³⁰

Aflibercept was evaluated for DME in a randomized, controlled phase 2 study (DME And VEGF Trap-Eye: INvestigation of Clinical Impact [DA VINCI]) involving 221 patients using 4 different dosing schemes: 0.5 mg monthly, 2.0 mg monthly, 2.0 mg every 2 months, or 2.0 mg

as needed.³¹ A fifth treatment group received monthly sham injections plus laser photocoagulation as needed. Compared with the laser group, aflibercept produced significantly greater improvements in all treatment groups at 24 and 52 weeks. Improvement in visual acuity with aflibercept ranged from +8.5 to +11.4 letters at week 24 (versus +2.5 letters for control; $P \leq .0085$), and +9.7 to +13.1 letters at week 52 (versus -1.3 letters for control; $P \leq .0001$). The most common ocular adverse events were characteristic of intravitreal injections (eg, conjunctival hemorrhage, eye pain, increased IOP, ocular hyperemia, cataracts, and vitreous floaters).

Some research suggests that modification of diabetes risk factors through medical intervention may reduce the risk of progression of DR.³² One of largest studies to investigate this was the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Eye study, a subset of 2856 participants from the ACCORD trial in patients with type 2 diabetes.³² The study found that intensive treatment for glycemia (targeting a glycated hemoglobin [A1C] level $< 6.0\%$) was significantly more effective than standard glycemic therapy (targeting an A1C level of 7.0%-7.9%) for reducing the risk of progression of DR at 4 years (7.3% vs 10.4%; $P = .003$). Adding fenofibrate to simvastatin also significantly lowered the risk of progression of DR (6.5% vs 10.2% with placebo; $P = .006$); more intensive blood pressure control, however, did not demonstrate a significant effect versus standard therapy at 4 years (10.4% vs 8.8%; $P = .29$).

Dry Eye

Treatment for dry eye is determined by the severity of signs and symptoms (ie, mild, moderate, or severe; see [Table 3](#)) and the underlying cause, with the goal of alleviating symptoms, maintaining or improving visual function, and preventing structural damage to the ocular surface.^{33,34} Patients with dry eye symptoms should undergo a full ophthalmic examination (eg, visual acuity measurement, external examination, slit-lamp biomicroscopy), as well as a review of systemic conditions.³³ Diagnostic tests may be performed to characterize the type and severity of dry eye (aqueous versus evaporative tear deficiency; see [Table 4](#)).³³ Patients with positive findings (eg, dry mouth, joint pain, fatigue, family history of autoimmune diseases) in their review of systems may need to undergo a systemic workup to uncover a possible underlying immunologic disease.³⁵

For patients with mild dry eye, the first step is to identify and address potential exogenous exacerbating factors, such as exposure to cigarette smoke, medications that may cause dry eye, low humidity or high elevation environments, or sources of eye strain or low blinking rate, such as reading or

Table 3. Treatment Recommendations for Dry Eye Syndrome by Disease Severity Level³³

Mild	<ul style="list-style-type: none"> • Education and environmental modifications^[A:III] • Elimination of offending topical or systemic medications^[A:III] • Aqueous enhancement using artificial tear substitutes, gels/ointments^[A:III] • Eyelid therapy (warm compresses and eyelid hygiene)^[A:III] • Treatment of contributing ocular factors such as blepharitis or meibomianitis^[A:III] (see Blepharitis PPP^a)
Moderate	<p>In addition to the above treatments:</p> <ul style="list-style-type: none"> • Anti-inflammatory agents (topical cyclosporine^{b,c [A:I]} and corticosteroids^{d-g [A:III]}), systemic omega-3 fatty acids supplements^{h,i [A:III]} • Punctal plugs^[A:III] • Spectacle side shields and moisture chambers^[A:III]
Severe	<p>In addition to the above treatments:</p> <ul style="list-style-type: none"> • Systemic cholinergic agonists^{j-l [A:I]} • Systemic anti-inflammatory agents^[A:III] • Mucolytic agents^[A:III] • Autologous serum tears^{m,n [A:III]} • Contact lenses^[A:III] • Correction of eyelid abnormalities^[A:III] • Permanent punctal occlusion^[A:III] • Tarsorrhaphy^[A:III]

Level A evidence is defined as most important. The panel also rated each recommendation on the strength of evidence in the available literature to support the recommendation made. The “ratings of strength of evidence” also are divided into 3 levels.

- Level I includes evidence obtained from at least 1 properly conducted, well-designed, randomized controlled trial. It could include meta-analyses of randomized controlled trials.
- Level II includes evidence obtained from the following: well-designed controlled trials without randomization; well-designed cohort or case-control analytic studies, preferably from more than 1 center; multiple-time series with or without the intervention.
- Level III includes evidence obtained from 1 of the following: descriptive studies; case reports; reports of expert committees/ organizations (eg, Preferred Practice Pattern [PPP] panel consensus with external peer review).

^aAmerican Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Blepharitis. San Francisco, CA: American Academy of Ophthalmology; 2011.

^bUS Food and Drug Administration, Center for Drug Evaluation and Research. Restasis cyclosporine ophthalmic emulsion) 0.05% sterile, preservative-free. NDA 50-790/S-001. 2003.

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ⁿChiang CC, Lin JM, Chen WL, Tsai YY. *Cornea*. 2007;26(7):861-863.

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prolonged computer use.^{33,34} Artificial tears may be used to treat mild dry eye. Preservative-free formulations are recommended by some physicians if frequent use is necessary (eg, >4 times a day) or if accompanying ocular surface disease is severe.³⁴ Treatment for moderate dry eye symptoms includes the same interventions for mild dry eye with the additional options of a prescription topical immunomodulator (eg, topical cyclosporine 0.05%; Restasis) or topical corticosteroids to suppress inflammation.^{33,34} Topical cyclosporine 0.05% is presently the only medication specifically approved by the FDA for the treatment of dry eye.

The efficacy and safety of topical cyclosporine was demonstrated in 2 multicenter, prospective, randomized, controlled phase 3 clinical studies in 877 patients with moderate to severe dry eye disease.³⁶ Compared with vehicle control, patients who received topical cyclosporine 0.05% had significant improve-

ments in corneal staining ($P = .008$) and Schirmer tear test values ($P < .007$) at 6 months, as well as significantly greater improvements in dry eye symptoms (eg, blurred vision, discomfort), decreased use of artificial tears, and improvement in physician’s evaluation of global response to treatment ($P \leq .05$ for each). There were no significant safety findings except for transient burning (15% of cyclosporine-treated patients vs 7% of vehicle-treated patients). More recently, in a single-arm prospective study in 158 patients with dry eye disease, cyclosporine 0.05% produced improvement in the Ocular Surface Disease Index questionnaire in 80% of patients with mild dry eye, and in 70.3% and 62.5% of patients with moderate and severe dry eye, respectively, at 3 months.³⁷

For patients with aqueous tear deficiency who are not achieving adequate relief with medical therapy, punctal occlusion may be considered.^{33,34} Silicone punctal plugs have the

■ **Table 4.** Characteristic Findings for Dry Eye Syndrome Diagnostic Testing³³

	Test	Characteristic Findings
Aqueous Tear Deficiency	Tear break-up time	Less than 10 seconds considered abnormal
	Ocular surface dye staining	Pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining typical
	Aqueous tear production and clearance (Schirmer test)	5 mm or less for Schirmer test with anesthesia considered abnormal
	Fluorescein clearance test/tear function index	Test result is compared with a standard color scale
	Lacrimal gland function	Decreased tear lactoferrin concentrations
	Tear osmolarity	Increased
Evaporative Tear Deficiency	Tear break-up time	Less than 10 seconds considered abnormal
	Ocular surface dye staining	Staining of inferior cornea and bulbar conjunctiva typical
	Tear osmolarity	Increased

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advantage of being removable if the patient develops symptoms of epiphora (ie, watering eyes), and also have a high retention rate when properly sized.³³ However, because punctal plugs may trap pro-inflammatory tear components on the ocular surface and possibly worsen dry eye symptoms, an international panel recommended treating inflammation prior to impeding tear drainage.³⁴ Results from a small prospective, open-label study indicate that using topical cyclosporine 0.05% therapy with punctal occlusion may produce an additive benefit in some patients with dry eye. While both treatments relieved dry eye symptoms in the study, combination therapy produced the greatest overall improvements and was superior to plugs alone in decreasing artificial tear use at 6 months ($P = .012$).³⁸

In June 2011, the FDA approved a new device called Lipiflow for the treatment of dry eye disease associated with meibomian gland dysfunction (MGD).³⁹ The Lipiflow device heats the inner surface of the eyelid over the meibomian glands while applying controlled pulsatile pressure to the outer eyelid to improve production of lipid-containing meibum by the glands.⁴⁰ In a clinical study, 76% of patients treated with Lipiflow had improvement in dry eye symptoms at 2 weeks versus 56% of patients treated with a warm compress in the control arm.⁴⁰ An improvement of at least 50% of dry eye symptoms was reported in 43% of patients with Lipiflow versus 11% in the control group.

Mechanically opening the meibomian gland orifice to remove obstructions (ie, meibomian gland probing) is a relatively new technique that has shown evidence of success in treating some patients with MGD.⁴¹ In a retrospective case series of 25 patients who received this procedure, all had symptom relief at 4 weeks posttreatment and most (80%) required only 1 treatment during an average follow-up of 11.5 months.⁴¹ Another newer technique that is gaining in popularity is intense pulse light therapy, which uses pulses of light to heat

the meibomian gland and improve the flow of secretions. Oral medications that stimulate the secretion of salivary and sweat glands are often prescribed to treat severe dry and dry mouth associated with Sjögren's syndrome; however, these treatments usually alleviate dry mouth to a greater degree than dry eye.³³

Conclusion

Major advances in drug therapy and surgical interventions in the past decade have vastly improved vision-related outcomes for thousands of patients with ocular diseases of aging. However, important questions remain regarding comparative effectiveness, dosing frequency, treatment combinations, tolerability, and the long-term durability of many of these newer therapies. These issues need to be addressed in ongoing and future randomized, controlled studies.

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