Chapter e116: Drug-Induced Ophthalmic Disorders

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UPDATE SUMMARY

Update Summary

September 13, 2023

The following sections, tables, and figures were updated:

- Corrected table reference detailing strategies to prevent drug-induced ophthalmic disorders
- Updated nonpharmacologic therapeutic options to relieve dry eye
- Added consideration of perfluorohexyloctane ophthalmic solution to decrease tear film evaporation

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 9, Drug-induced Ophthalmic Disorders.

KEY CONCEPTS

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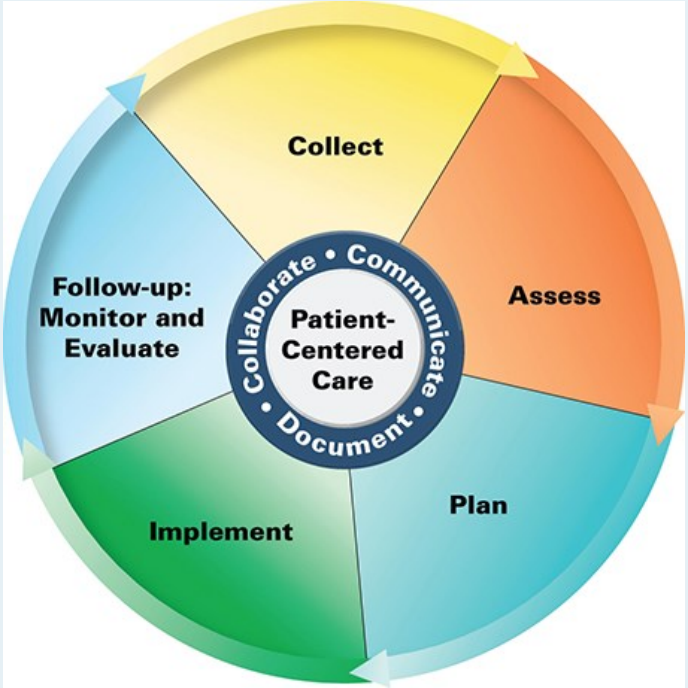
1. The eye is highly susceptible to drug toxicity due to its extensive vasculature.
2. When ophthalmic disorders occur, all medications and biologic agents, irrespective of the route of administration, are potential causes.
3. It is difficult to fully quantify the incidence of drug-induced ophthalmic disorders due to the variety of causative factors and side-effect reporting behaviors of clinicians.
4. The most common drug-induced ophthalmic disorders include dry eye, cataract, intraoperative floppy iris syndrome, optic neuropathy, and retinopathy.
5. The severity of drug-induced ophthalmic disorders varies and depends on dose, pharmacokinetics, genetic predisposition, age, extremes of body weight, and/or duration of exposure.
6. Health professionals and patients should discuss potential drug-induced ophthalmic disorders to ensure awareness, prompt identification, management, and treatment.

PATIENT CARE PROCESS

Patient Care Process for Drug-Induced Ophthalmic Disorders



Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current or recently discontinued medications including prescription, over-the-counter (OTC) aspirin/NSAID use, herbal products, dietary supplements
- Objective data (eg, drug levels)

Assess

- Appearance of ophthalmic signs or symptoms
- Presence of predisposing conditions or risk factors
- Presence of physical occlusion of the eye or eyelid
- Presence of common provoking factors (eg, recent drug use, new medications, history of allergies)
- Potential causative agent
- Appropriateness for self-care (eg, red flags that would indicate referral or higher level of care)
- Ability/willingness to administer eye drops appropriately (eg, health literacy, age of patient)

- Ability/willingness to pay for OTC options not covered by insurance
- Ability/willingness to follow-up with the provider if symptoms do not improve

Plan

- Discontinuation of the offending agent, if applicable
- Pharmacologic and nonpharmacologic treatment regimen with medication(s), dose, route, frequency, and duration of treatment (see Table e116-4)
- Monitoring parameters including efficacy (eg, resolution/improvement in symptoms); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, medication administration technique)
- Self-monitoring for resolution of symptoms
- Referral to other providers when appropriate

Implement

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up labs (eg, drug levels) and/or ophthalmic examination

Follow-Up: Monitor and Evaluate

- Resolution of eye symptoms
- Drug level results, as appropriate
- Presence of adverse effects
- Patient adherence to treatment plan and scheduled care visits
- Schedule regular ophthalmic examinations
- Reevaluate as necessary

BEYOND THE BOOK

BEYOND THE BOOK

Watch the following videos available from the US National Library of Medicine MedlinePlus for a brief overview of the anatomy and function of the eye. These videos provide the necessary foundation and will assist in understanding the mechanisms of drug-induced ophthalmic disorders.

Seeing: https://medlineplus.gov/ency/anatomyvideos/000109.htm (3:22)

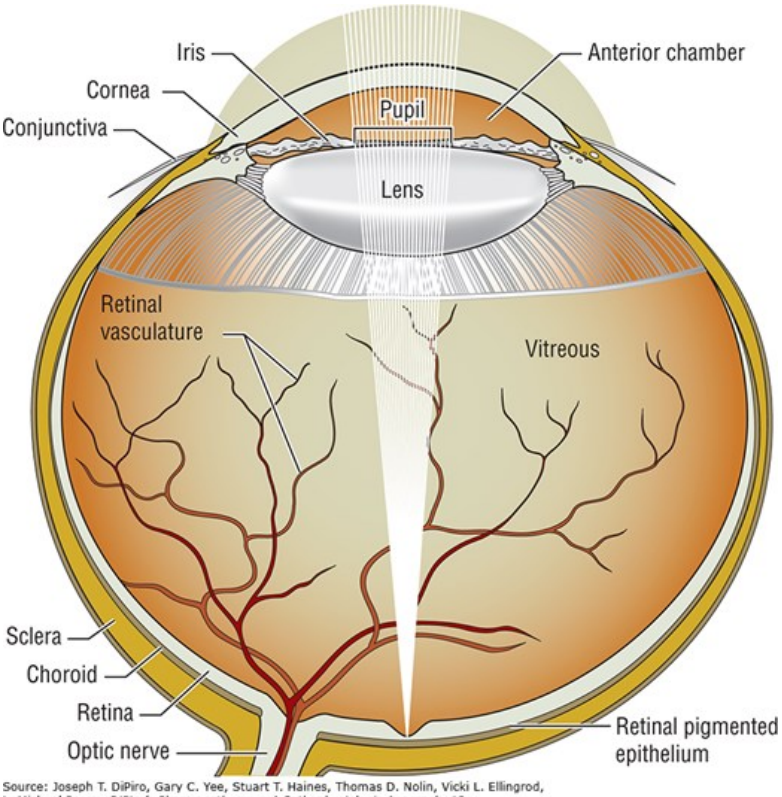
Blinking: https://medlineplus.gov/ency/anatomyvideos/000010.htm (1:01)

INTRODUCTION

The eye is an important, complex organ of the nervous system. It is composed of specialized tissues and complex structures that collectively contribute to the body's ability to visually process the environment (Fig. e116-1).[1-3] The sequence for normal, functioning eyes begins with the eyelid, which opens to allow exposure to light, bathes the eye with tear film, and helps remove waste. The eye receives light through the cornea, a clear tissue at the front of the eye. The light then proceeds through the aqueous humor and enters the pupil. The light continues through the pupil, which regulates the amount of light entering the eye to the lens. The lens changes thickness and shape to bend the received light and send it through the vitreous humor to the retina at the back of the eye.[1-3] The retina then transforms the light into electrical impulses, which travel through the optic nerve to the brain. The brain then translates these impulses into the image that is seen. The function of each structure of the eye is summarized in Table e116-1.[2,3]

FIGURE e116-1

Anatomy of the eye.



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*

TABLE e116-1

Summary of the Structures and Function of the Eye

Part of Eye	Function
Aqueous humor	Fills the anterior chamber of the eye; maintains eye pressure
Conjunctiva	Clear membrane that covers the surface of the eye
Eyelid	Protects the eye, keeps foreign bodies from contacting the eye, and keeps the eye moist by spreading tear film
Iris	Colored portion of the eye Dilates or constricts the pupil
Cornea	Clear tissue that focuses light on the retina
Lacrimal gland	Produces tears
Lens	Focuses light and changes shape to focus on objects
Macula	Functional center of the retina Responsible for fine detail, central and color vision
Meibomian gland	Produces the oil layer of the tear film
Optic nerve	Receives and transmits electrical information from the retina to the brain for processing
Pupil	Dilates or constricts to allow varying amounts of light to reach the retina
Retina	Tissue in the back of the eye that contains photoreceptors responsible for color, night, and detailed vision
Sclera	White membrane that covers the surface of the eye
Tear duct	Canal that drains tears from the eye
Tear film	Composed of three layers (mucus, aqueous, and oil) to lubricate the eye
Vitreous humor	Fills most of the eye; maintains shape of eye and holds retina in place

Data from References 2,3.

1 2 Disruption at any structure or step in the process can lead to dysfunction of the eye. This can result from many factors. Exposure to toxic substances, including medications, is one such cause of dysfunction. The combination of a rich blood supply and extensive vasculature allows for ocular exposure to systemically administered medication. The blood-aqueous and blood-retinal barriers are capable of keeping most compounds away from the eye; however, some medications are able to bypass the junctions within cells and reach the eye.[4] The eye is the second most common organ to display drug toxicities, with the liver considered most common.[5]

3 It is difficult to accurately quantify the incidence of drug-induced ophthalmic disorders overall.[4,6] All medications have the potential to induce side effects, irrespective of the mode of administration. Side effects may range from mild to severe and can affect any area of the eye. Many but not all drug-induced ophthalmic disorders are well documented in the literature; lack of clinician or patient reports is a limiting factor. Despite any potential gaps in

the literature, it is important to establish causality between an ophthalmic side effect and medication use. A popular tool used by clinicians to establish the likelihood of causality is the adverse drug reaction probability scale, commonly known as the Naranjo scale.[7] The Naranjo scale is composed of scored questions the clinician should use to assess an adverse drug reaction. Categories of definite, probable, possible, and doubtful are assigned based on the score.[7]

This chapter will discuss drug-induced ophthalmic disorders seen with commonly prescribed medications in clinical practice. A review of drug-induced glaucoma will not be covered in this chapter, as it is discussed in Chapter 114, "Glaucoma."

DRUG-INDUCED OPHTHALMIC REACTIONS

Dry Eye Disease

4 Dry eye disease (DED), also known as dry eye syndrome or keratoconjunctivitis sicca, is a common ophthalmic disorder that affects the quality of life for millions of people around the world.[6,8] In addition to the discussion of DED in this chapter, nonprescription therapies for the condition are detailed in Chapter e11, "Minor Ophthalmic Disorders (Conjunctivitis, Xerosis, Corneal Abrasions, Bacterial Keratitis)."

The prevalence of DED ranges from 5% to 50% due to a lack of a standardized definition and consistent diagnostic criteria.[6] DED accounts for $3.8 billion annually in healthcare expenditures in the United States, with quality-of-life impact on approximately $55 billion.[9]

DED is defined by the Tear Film & Ocular Surface Society International Dry Eye Workshop II (TFOS DEWS II) Definition and Classification Subcommittee as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[6]

This definition classifies DED as a condition with multiple contributing factors. The eye depends on a healthy tear film composed of mucus, aqueous, and mucin to maintain lubrication, provide nutrients, and remove waste.[2,3,10] DED can occur when any aspect of the tear film is compromised. This may be due to evaporation of the tear film, an imbalance in tear film composition, or decreased production of tears.[6,8,9] This pathophysiologic mechanism leads to patient reports of light sensitivity, pain, blurry vision, and a feeling of grittiness in the eye.[8,9]

DED is common in the older population because of polypharmacy and age-related changes. It is also common in women due to sex hormone effects on meibomian gland function and tear secretion.[6,9,10] Other risk factors for DED include anatomic disorders (floppy eyelid syndrome), autoimmune diseases (rheumatoid arthritis, Sjogren's disease), diabetes, graft versus host disease, meibomian gland dysfunction, neural dysfunction (neuropathic pain), low sex hormone levels, prolonged computer screen time, systemic lupus erythematosus, and medications.[8,9]

Numerous systemic and topical medications can cause DED. These include alpha-1 antagonists, alpha-2 agonists, anticholinergics, anticonvulsants, antihistamines, antimalarials, antineoplastics, antipsychotics, anxiolytics, beta-agonists and antagonists, bisphosphonates, cannabinoids, systemic and topical decongestants, diuretics, retinoids, oral contraceptives, and tricyclic antidepressants.[8-12] Preservatives present in topical ophthalmic products, such as benzalkonium chloride, may cause DED by disrupting tear film homeostasis and causing inflammation.[8] A thorough patient history and examination should be collected to determine the risk factors present and the likely type of tear film issue at hand.

Several strategies are used to treat DED. Interventions aim to increase liquid on the ocular surface, decrease the amount of evaporation of eye fluids, and restore balance to tear film components.[6,8,13] Many of these medications must be used chronically; their benefits are viewed as outweighing any risks of long-term therapy. Agents include topical lubricants, anti-inflammatory ophthalmic drops such as 0.05% cyclosporine, and lymphocyte function-associated antigen 1 (LFA-1) antagonists.

Additionally, discontinuation of the causative agent, if possible, or switching to preservative-free ophthalmic drops and products can help alleviate DED symptoms. Strategies to prevent drug-induced ophthalmic disorders are detailed in Table 116-2. A summary of common causative agents and treatment options is available in Table 116-4.

TABLE e116-2

Strategies to Prevent Drug-Induced Ophthalmic Disorders

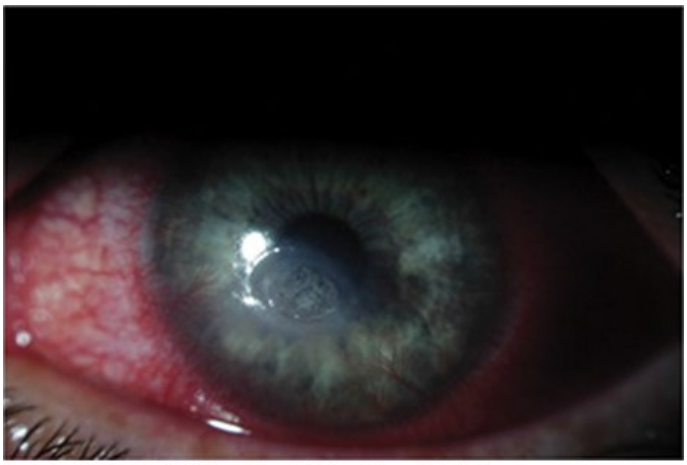
Educate patients on the signs and symptoms of common ophthalmic side effects related to prescribed medication.
Schedule regular ophthalmic examinations.
Use nonpharmacologic management when appropriate.
Prescribe prophylactic medication therapy when appropriate.
Avoid exceeding recommended daily dose, cumulative lifetime doses, or duration of therapy.
Assess for predisposing conditions or risk factors prior to use of medication.
Monitor drug levels as appropriate.
Stress importance of adherence to scheduled follow-up visits and monitoring.
Encourage communication of any new or discontinued prescription, natural medicine, or OTC products.

Data from References 4,5,14,16.

Punctal occlusion, a procedure in which the puncta—the small openings in the corner of the eye—are blocked, can benefit those with DED by decreasing tear drainage when other options have failed.[6] This provides the eye with tear availability to continually bathe the eye and decrease symptoms of DED.[6,10] If left untreated, severe DED may lead to corneal ulcers (Fig. e116-2), vascularization, and permanent vision impairment.[14]

FIGURE e116-2

Corneal ulcer caused by dry eye syndrome. (*Reproduced, with permission, from* Turno-Krecicka A, Grzybowski A, Misiuk-Hojło M, et al. Ocular changes induced by drugs commonly used in dermatology. *Clin Dermatol. 2016;34(2):129-137.*)



Cataracts

Drug-induced cataracts may occur with the use of corticosteroids, phenothiazines, alkylating agents, and statins.[5,15] Patients presenting with cloudiness in specific parts of the lens can provide clues as to the route of administration of the causative agent.[5] Table e116-3 summarizes the location of lens changes observed by route of administration for medication classes known to cause cataracts. In general, systemically administered drugs cause changes along the equator of the lens, while topically administered drugs cause central anterior lens changes. Posterior subscapular and cortical changes may also occur irrespective of the route of administration.[5]

TABLE e116-3

Location of Lens Changes Observed by Route of Administration for Common Causative Agents that Induce Cataracts

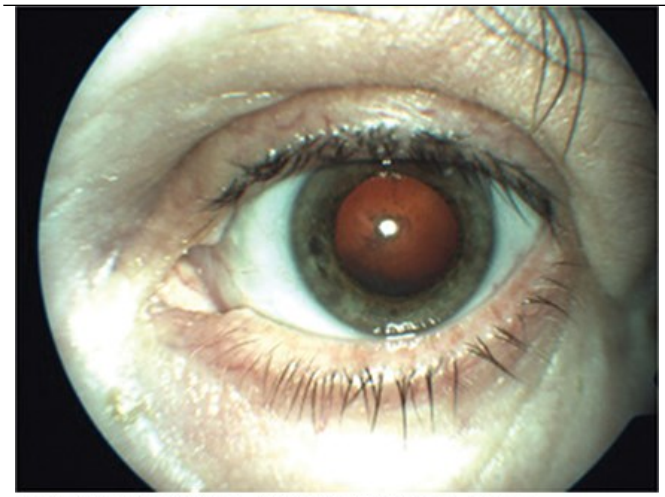
Route of Administration	Lens Change Location	Causative Medication
Systemic	Equator	Glucocorticoids
Topical	Central anterior	Phenothiazines Glucocorticoids
Mixed	Posterior subscapular	Alkylating agents (busulfan)
		Glucocorticoids
	Cortical (edges)	Statins
		Glucocorticoids

Data from References 5,14-16.

Corticosteroids may cause cataracts on any portion of the lens when used for an extended period of time (Fig. e116-3).[5,14] The incidence of cataract formation secondary to corticosteroid therapy is 22% to 58%.[14] Risk factors for adverse effects of corticosteroid therapy include young age, condition of the skin, extent of disease, location on the body, dose and duration of therapy, and use of occlusive dressings.[14] Topical application of corticosteroids to distal areas of the body, and in limited doses, has indicated minimal risk of cataract formation.[14] Discontinuation of corticosteroid therapy does not reverse the cataract.[5,14]

FIGURE e116-3

Steroid-induced cataract. (*Reproduced, with permission, from* Turno-Krecicka A, Grzybowski A, Misiuk-Hojło M, et al. Ocular changes induced by drugs commonly used in dermatology. *Clin Dermatol. 2016;34(2):129-137.*)



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*

Phenothiazines, specifically chlorpromazine and thioridazine, cause cataract formation in a dose- and duration-dependent manner.[5] Fine granules that are white to brown in color form and accumulate in the anterior cortex over time, forming a cataract. Ophthalmic side effects are rare at standard thioridazine doses less than 800 mg/day.[5,16]

Alkylating agents, such as busulfan, cause a posterior subscapular cataract by interfering with the production of nucleic acid during mitosis.[5]

Statins are associated with an increased risk of cataracts, although for quite some time statin therapy was associated with a protective effect.[15,17,18] Clinicians must weigh the benefits and risks of statins in all cases prior to initiation of therapy.

In most cases, drug-induced cataracts remain relatively stable and will not reverse once formed, irrespective of the type of causative agent exposure. Surgical removal of the lens may be necessary to restore vision.[5,14]

Intraoperative Floppy Iris Syndrome

4 Intraoperative Floppy Iris Syndrome (IFIS) occurs in approximately 0.5% to 3.7% of patients undergoing cataract surgery worldwide, with a rate of approximately 2% in the United States.[19,20] It is characterized by presentation of one or more intraoperative events: floppiness and billowing of the iris, progressive intraoperative constriction of the pupil despite pharmacologic intervention to maintain dilatation, and prolapse of the iris through the surgical wound(s).[19] IFIS complicates the surgical procedure and may lead to endophthalmitis, pupil deformity, retinal detachment, and vitreous loss.[19-22]

The use of alpha-1 antagonists (tamsulosin, silodosin, alfuzosin, doxazosin, terazosin, and prazosin) is a major risk factor for development of IFIS.[23] IFIS is most commonly seen in men; however, women prescribed alpha-1 antagonist therapy for urinary stone passage, hypertension, or chronic urinary retention have also experienced IFIS.[20] Patients taking tamsulosin are 30 times more likely to experience IFIS, with a rate of approximately 60% to 89% in those undergoing cataract surgery.[23,24] Tamsulosin is highly selective for alpha-1_A receptors located in the bladder neck, prostate, and urethra. These receptors are also present in the smooth muscle of the iris. Binding of tamsulosin to these receptors inhibits dilatation and may lead to IFIS. Discontinuing alpha-1 antagonist therapy prior to cataract surgery does not decrease the risk of IFIS.[20,24,25] Patients with a prior history of alpha-1 antagonist use are still at risk for IFIS, attributed to atrophy of the dilator muscle of the iris due to disuse.[26,27]

IFIS has also developed in patients with hypertension or those receiving therapy with other medications (finasteride, duloxetine, donepezil, quetiapine, and benzodiazepines).[23,28-33] Additional studies are needed to determine if the risk associated with hypertension is due to medication use or a disease process.[23,24] It remains unclear if the use of these medications represents an actual causative risk factor in the development of IFIS. More research is necessary to fully elucidate the iris smooth muscle relaxation activity of these agents.[23,28-31]

IFIS may be avoided by conducting a complete preoperative screening of a patient's medication regimen prior to cataract surgery. Intracameral administration of preservative-free epinephrine or phenylephrine at the beginning of surgery helps reduce IFIS and dilates the pupil.[20,28] Use of ophthalmic viscosurgical devices (OVDs), iris retractors, and pupil expanders are additional techniques that may be employed in conjunction with intracameral epinephrine or phenylephrine. Mechanical pupil stretching and partial sphincterotomy are not useful and may exacerbate IFIS.[20]

Optic Neuropathy

Drug-induced optic neuropathy (DION) is a subset of toxic optic neuropathy (TON), a disorder in which the optic nerve degenerates due to toxic exposure to medication therapy. Mitochondrial injury, blood flow disruption, and free radical exposure are possible pathophysiologic mechanisms leading to this condition.[5,34] DION is characterized by bilateral vision loss, decreased visual acuity, decreased color vision, and afferent pupillary defect.[5,34] Symptoms occur slowly over time and do not cause pain. TON is more common in developing countries due to exposure to toxins and drugs in the environment.[34] Epidemiological studies have not elucidated any age-, gender-, or race-related risk factors associated with TON or DION.[34]

DION has occurred most often with the use of amiodarone, ethambutol, linezolid, and PDE-5 inhibitors. Vision issues associated with these agents are dose and duration dependent. Discontinuation of the causative agent generally leads to reversal of symptoms.[5,14] It is critical to educate patients about this potential side effect of therapy to ensure prompt notification and discontinuation of therapy prior to development of permanent damage.

Amiodarone

Optic neuropathy is thought to occur due to accumulation of amiodarone in the axon, interfering with normal neural function and leading to vision loss.[5,16] The incidence of amiodarone-induced optic neuropathy is 1.79%.[16] Optic neuropathy occurs slowly over an average of 9 months due to the 160-day half-life of amiodarone, resulting in bilateral vision loss and optic disc edema.[4,16,34] Upon discontinuation of amiodarone, it may take months for vision loss to reverse. Ophthalmic examinations every 6 to 12 months are important, given the dose- and time-dependent nature of visual side effects related to amiodarone use.

Ethambutol

Optic neuropathy has been well documented in 6% of patients receiving ethambutol for treatment and prevention of tuberculosis.[34] The average time to development is 235 days of therapy.[5,16,34] Renal dysfunction may lead to diminished excretion of ethambutol and higher levels, lowering the time to development of optic neuropathy. Patients present with bilateral vision, loss peripheral constriction, and color vision loss.[5,16,34] Symptoms occur due to chelation of copper present in retinal cells. Chelation depletes copper available for mitochondrial activity, stunting the ability to acquire energy required for normal axonal transport.[5,16] If symptoms occur, the clinician should explore discontinuation of ethambutol as clinically appropriate.[5] Baseline eye examinations and ophthalmologic consultation is recommended to prevent vision loss and subsequent diminished quality of life.[34] Education on the risk of optic neuropathy and obtaining informed consent are also recommended as best practices for use of ethambutol.[16]

Linezolid

Linezolid-induced optic neuropathy is thought to be caused by mitochondrial injury.[5] Patients have generally experienced visual side effects after approximately 5 to 10 months of therapy, although a few cases have been reported in which loss of vision occurred after only 2 weeks of therapy.[5,34] Vision has improved after discontinuation of linezolid in most patients; some patients experience lasting visual acuity issues.[34] Patients on linezolid therapy need regular ophthalmic examinations.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE-5) inhibitors (avanafil, sildenafil, tadalafil, and vardenafil) can cause DION, which manifests as blurriness, color discrimination deficits (particularly in the blue-green and blue-purple spectrum), and light sensitivity.[34] The color-related symptoms are thought to result from drug effects on phosphodiesterase type 6 (PDE-6) receptors present on the rods and cones of the eye.[35] These symptoms are dose-

dependent and reverse upon discontinuation of the drug.[5]

Retinopathy

Retinopathies occur due to medication exposure to the retina via the vasculature of the eye. Four main classes of drugs can cause retinopathies: aminoquinolines, antiestrogen agents (tamoxifen), phenothiazines, and retinoids. In patients taking these drugs, regular ophthalmic examinations are needed to monitor for early signs of retinal disorder, as late-stage retinopathy is virtually nonreversible.[5,36]

Aminoquinolines

Chloroquine and hydroxychloroquine use is associated with retinal issues. Risk for toxicity depends on total dose and duration of therapy. Patients receiving hydroxychloroquine doses greater than 5 mg/kg/day and chloroquine doses greater than 2.3 mg/kg/day are at greatest risk for retinopathy.[4,14,37] Aminoquinoline therapy for more than 5 years also increases the risk of toxicity.[14] Advanced age, extremes of body weight, liver disease, and renal disease are also risk factors for development of retinopathy due to hydroxychloroquine or chloroquine use.[5,16]

Aminoquinolines have a high affinity for melanin within the retinal pigment epithelium, allowing accumulation and prolonged effect. This ultimately contributes to toxicity seen with this class of medications. The retinal issue associated with aminoquinoline therapy is a maculopathy, in which the macula of the retina appears as a bull's eye or ring in most patients.[5,14] Ideally, conducting regular ophthalmic screenings, as described below, should make development of this bull's eye maculopathy a rarity.[37]

Patients typically present with complaints of color vision disturbance, central visual field defect, and loss of night vision.[4,14,16] To positively attribute maculopathy to hydroxychloroquine use, the maculopathy must be bilateral. It can be detected using visual field testing and Amsler grid.[5,16]

The American Academy of Ophthalmology recommends a dilated fundus exam and visual field test at baseline. A color vision test is also recommended but optional. Clinicians must conduct ongoing monitoring and regular ophthalmic examinations, with consideration for discontinuation of therapy if medically appropriate.[14] If patients continue use of the medication beyond 5 years, follow-up examinations are recommended every 12 months.[37] Once bull's eye maculopathy occurs, reversal of vision is not possible, leading to permanent vision loss.[5,14,16]

Phenothiazines

The mechanism of toxicity for phenothiazines is similar to that of aminoquinolines, whereas drug binds to melanin in the retinal pigment epithelium, causing degeneration of the retina.[5] At high doses, chlorpromazine retinal disorder causes conjunctival lesions, pigmentation of the eyelid, while high-dose thioridazine causes a rapid, severe retinopathy with a few weeks or months of use.[5] Patients present with diminished visual field and night vision loss.

Antiestrogen Agents

Tamoxifen is known to cause retinopathy and loss of color vision. Retinopathies manifest as retinal edema, hemorrhage, swelling of the optic disc, and yellow deposits around the macula.[5] As seen with other therapies, these effects depend on dose and duration and can occur within a few weeks after initiation of therapy.

Retinal effects are generally reversible when tamoxifen is discontinued. To prevent retinopathy associated with tamoxifen use, baseline ophthalmic examination with a color vision test and slit lamp biomicroscopy are recommended to be performed, with follow-up examinations completed every 2 years thereafter.

Retinoids

Patients on high-dose isotretinoin therapy are at high risk for night vision loss, blurry vision, dry eye, and blepharoconjunctivitis. The mechanism of toxicity is thought to occur due to binding site competition between retinoid acid and retinol.[5]

PREVENTION AND MONITORING

6 Before any medication is used in the eye, there must be an appropriate indication and the patient must understand potential risks and benefits. Education on signs and symptoms of untoward ophthalmic adverse effects should accompany a discussion with the patient about the use of the medication.

In patients using ophthalmic products, clinicians should encourage patients to receive routine ophthalmic examinations and follow-up as appropriate; this is especially important during treatment with a medication with potential adverse effects on these important organs.[4] Table e116-4 provides a list of general strategies that may be used to prevent drug-induced ophthalmic disorders.

TABLE e116-4

Common Drug-Induced Ophthalmic Disorders, Causative Agents, Management, and Treatment Recommendations

Reactions	Causative Agents	Treatment and Management
Cataracts	• Alkylating agents (busulfan) • Antiestrogens (tamoxifen) • Corticosteroids • Statins	• Surgical removal of cataract

Dry eye	• Alpha-1 antagonists (alfuzosin, tamsulosin, terazosin)
	• Alpha-2 agonists (apraclonidine, brimonidine)
	• Anticholinergics (atropine, homatropine, hyoscine, ipratropium, tolterodine)
	• Anticonvulsants (valproic acid)
	• Antihistamines (cetirizine, chlorpheniramine, diphenhydramine, doxylamine)
	• Antimalarials (chloroquine, hydroxychloroquine)
	• Antineoplastics (busulfan, cyclophosphamide)
	• Antipsychotics (thioridazine)
	• Anxiolytics (lorazepam)
	• Beta-agonists (acebutolol)
	• Beta-blockers (atenolol, propranolol)
	• Benzalkonium chloride
	• Bisphosphonates
	• Cannabinoids (dronabinol)
	• Systemic decongestants (pseudoephedrine)
	• Diuretics (furosemide, indapamide, metolazone)
	• Oral contraceptives
	• Retinoids (isotretinoin)
	• Topical decongestants (naphazoline)
	• Tricyclic antidepressants (amitriptyline)
		• Nonpharmacologic therapy:
		  ◦ Warm compresses
		  ◦ Increase fluid intake
		  ◦ Use humidifier
		  ◦ Remove contact lenses
		• Increase tear volume:
		  ◦ Consider artificial tears or other topical lubricants
		  ◦ Punctal occlusion
		• Decrease inflammation:
		  ◦ 0.05% cyclosporine ophthalmic drugs
		  ◦ LFA-1 antagonist ophthalmic drops
		  ◦ Short-term ophthalmic glucocorticoids
		• Decrease tear film evaporation:
		  ◦ Consider perfluorohexyloctane ophthalmic solution
		• Medication changes:
		  ◦ Discontinue offending medication
		  ◦ Use preservative-free ophthalmic drops

Floppy iris syndrome	• Alpha-1 antagonists • Benzodiazepines • Chlorpromazine • Donepezil • Duloxetine	• Preoperative screening for previous and/or current use of causative agents • Consider cataract surgery before initiation of alpha-1 antagonist therapy • Intracameral alpha-adrenergic agonists (epinephrine,

	• Finasteride
	• Quetiapine
		phenylephrine)
		• Intraoperative devices:
		  ○ Iris retractors
		  ○ OVDs
		• Pupil expanders

Optic neuropathy	• Amiodarone • Ethambutol • Linezolid • PDE-5 inhibitors (avanafil, sildenafil, tadalafil, vardenafiil)	• Discontinuation of causative drug as medically appropriate • Regular ophthalmic examinations
Retinopathy	• Aminoquinolines (hydroxychloroquine, chloroquine) • Antiestrogens (tamoxifen) • Phenothiazines (chlorpromazine, thioridazine) • Retinoids (isotretinoin)	• Monitor via regular ophthalmic examinations, patient-reported signs and symptoms • Vision loss is irreversible

MANAGEMENT OF TOXICITY

Many cases of minor, drug-induced ophthalmic disorders resolve with dose reduction or discontinuation of the causative drug. At times, it is not possible to discontinue the offending drug, and supportive therapies may be necessary to manage symptoms until the primary agent is no longer needed. See Table 116-4 for a complete summary of common drug-induced ophthalmic disorders, causative agents, and recommendations on the appropriate management and/or treatment.

CONCLUSION

Drugs administered both systemically and/or topically have the potential to induce disorders of the eye. The severity may range from minor and temporary to severe and permanent. Clinicians must promptly examine any patient-reported side effects, establish causality with current medication therapy, discontinue medication as appropriate, and apply treatment as indicated to avoid damage to the eye.

ABBREVIATIONS

ADR	adverse drug reaction
DED	dry eye disease
DION	drug-induced optic neuropathy
IFIS	intraoperative floppy iris syndrome
LFA-1	lymphocyte function–associated antigen 1
OTC	over-the-counter
OVDs	ophthalmic viscosurgical devices
PDE-5	phosphodiesterase type-5
PDE-6	phosphodiesterase type-6
TFOS DEWS II	Tear Film & Ocular Surface Society International Dry Eye Workshop II
TON	toxic optic neuropathy

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SELF-ASSESSMENT QUESTIONS

1. Drug reaction causality is best assessed using what approach?
   A. Case reports
   B. Naranjo scale
   C. FDA bulletins
   D. Prescription records
2. Which of the following drugs is most likely to cause floppy iris syndrome?
   A. Metoprolol
   B. Dexamethasone
   C. Tamsulosin
   D. Bevacizumab
3. Which structure of the eye contains photoreceptors that control color and night vision?
   A. Retina

B. Cornea

C. Lens

D. Pupil

4. DED may occur with the use of which of the following medication classes?

A. Cholinergic agonists

B. ACE inhibitors

C. Bisphosphonates

D. Adrenergic agonists

5. Which of the following is most accurate regarding IFIS?

A. IFIS is more common in men than women.

B. Drug levels should be allowed to deplete prior to surgery to avoid IFIS.

C. Alpha-1 antagonists are the only class of medications associated with IFIS.

D. Postoperative screening should be done to assess risk for IFIS.

6. Which of the following is an acceptable treatment option for DED?

A. Topical decongestants

B. Intracameral epinephrine

C. Ophthalmic cyclosporine

D. Fluorescein drops

7. Patients suffering from DED may benefit from discontinuation of which medication from their regimen?

A. Dronabinol

B. Acetaminophen

C. Fluoxetine

D. Atorvastatin

8. Which of the following is the most appropriate strategy for prevention of drug-induced ophthalmic disorders?

A. Educate on signs and symptoms of ophthalmic side effects only if the patient asks.

B. Assess for risk factors after the patient has initiated therapy.

C. Avoid exceeding recommended daily or cumulative lifetime doses.

D. Encourage communication of only new prescription medications.

9. Which of the following is *not* an acceptable management strategy for DED?

A. Punctal occlusion

B. Dehumidifier use

C. Warm compress

D. Preservative-free ophthalmic products

10. Which best describes the mechanism of toxicity for ethambutol optic neuropathy?

A. Binds to melanin in retinal pigment epithelium

B. Competitively inhibits PDE-6 binding

C. Infiltrates vasculature creating deposit accumulation

D. Chelates copper required for mitochondria sufficiency

11. Which of the following is a risk factor for development of aminoquinoline retinopathy?

A. Family history

B. Normal body weight

C. Renal disease

D. Young age

12. What daily dose of hydroxychloroquine is associated with high risk of development of retinopathy?

A. 1 mg/kg/day

B. 3 mg/kg/day

C. 4 mg/kg/day

D. 6 mg/kg/day

13. Which of the following agents causes a posterior subscapular cataract?

A. Busulfan

B. Chlorpromazine

C. Linezolid

D. Chloroquine

14. Which medication toxicity presents as a bull's eye maculopathy?

A. Amiodarone

B. Thioridazine

C. Tamoxifen

D. Hydroxychloroquine

15. Which of the following classes does *not* cause retinopathy?

A. Phenothiazines

B. Anti-estrogenic agents

C. Retinoids

D. Beta-adrenergic antagonists

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Naranjo is the most appropriate source to establish causality between an adverse event and medication therapy.
2. **C.** Tamsulosin is an alpha-adrenergic antagonist. This class of medications is known to cause floppy iris syndrome. See section "Drug-Induced Ophthalmic Reactions" for more information.
3. **A.** Retina contains photoreceptors responsible for vision detail, color vision, and night vision.
4. **C.** Bisphosphonates are known to cause dry eye. Cholinergic agonists and adrenergic agonists increase tear production and are not associated with DED. DED is not a known adverse effect of ACE inhibitors.
5. **A.** IFIS is more common in men than women, likely due to greater use of alpha-1 antagonists. B, C, and D are not correct. IFIS development is observed in patients who have not received an alpha-1 antagonist for quite some time. Allowing depletion of alpha-1 antagonist levels will not provide decreased risk of developing IFIS. Other medication classes besides alpha-1 antagonists have been associated with the development of IFIS. Preoperative screening should be done to assess risk for IFIS.
6. **C.** Ophthalmic cyclosporine is an acceptable option to treat inflammation associated with dry eye. Topical decongestants will exacerbate DED. Intracameral epinephrine is indicated for IFIS and not DED. Fluorescein drops are not appropriate for the management of DED and are best suited for eye examination.
7. **A.** Dronabinol is a cannabinoid associated with DED.
8. **C.** Avoid exceeding recommended daily or cumulative lifetime doses, especially if specific dose thresholds have been implicated in increasing the risk of ophthalmic disorder. Risk factors should be assessed prior to initiating therapy. Education on signs and symptoms should always be done, not only upon request of the patient. Patients should report any new prescription, herbal, and OTC medications that may increase the risk of ophthalmic disorder.
9. **B.** Dehumidifiers decrease the amount of moisture in the air, which may exacerbate dry eye.
10. **D.** Ethambutol chelates copper required for mitochondrial sufficiency.
11. **C.** Renal disease is a known risk factor for development of aminoquinolines retinopathy.
12. **D.** Hydroxychloroquine doses greater than 5 mg/kg/day is associated with a high risk for development of retinopathy.
13. **A.** Busulfan has the potential to cause a posterior subscapular cataract. Chlorpromazine may induce a central anterior cataract, while linezolid and chloroquine are not known to induce cataracts.
14. **D.** A bull's eye maculopathy indicates hydroxychloroquine as the causative agent.
15. **D.** Beta-adrenergic antagonists are not known to cause retinopathy. Phenothiazines, antiestrogen agents, and retinoids do have the potential to induce retinopathy.