Ocular Side Effects of Common Systemic Medications and Systemic Side Effects of Ocular Medications

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KEYWORDS

• Ocular topical medications • Ocular side effects • Medication • Eye • Eye drops • Vision changes

KEY POINTS

- Physicians should be aware of potential ocular side effects of systemic medications when prescribing therapy.
- Ocular medications may induce systemic side effects that could affect management of various conditions; therefore, knowing patients' ophthalmologic diagnoses and therapy can be useful.
- Treatment of ocular conditions may require topical and/or systemic medications, with implications for the overall health of patients.

INTRODUCTION

We have organized this article into 2 main sections: ocular side effects of commonly prescribed drugs and systemic side effects of medications commonly prescribed by ophthalmologists. The article lists the class of drugs, their mechanism of action (MOA), known and possible ocular side effects (OSEs), and recommendations for OSEs to watch out for and/or medications that need ophthalmologic screening before or during use. For topical/ocular medications, the ocular and systemic side effects are discussed, as well as situations in which to avoid their use.

The reader is encouraged to consider these side effects when prescribing the following classes of medications and should be able to use this article as a reference when encountering a patient with visual symptoms, especially in the setting of possible ocular toxicity.

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KEY POINTS

- Hydroxychloroquine requires ongoing screening; toxicity risk increases with total lifetime (cumulative) dose, to some extent increased daily dose, and with concurrent tamoxifen use.
- Patients with current or past use of tamsulosin (and other alpha blockers) may develop floppy iris, which can complicate cataract surgery (intraoperative floppy iris syndrome).
- Corticosteroids often result in increased intraocular pressure and cataract formation, especially with prolonged use.
- Antihistamines can lead to dry eye syndrome.
- Statins may affect the ocular surface, lens, extraocular muscles, and retina.
- Isotretinoin may cause night blindness, pseudotumor cerebri.
- Various central nervous system drugs affect accommodation and near vision.
- Ethambutol can cause irreversible optic neuropathy.
- Tamoxifen deposition often presents on the cornea and the retina.
- Patients on topical beta blockers for glaucoma can have any systemic side effects of oral beta blockers.
- Anti-vascular endothelial growth factor injections are common in treatment of age-related macular degeneration, and present a small increased risk of thromboembolic events.
- Various chemotherapeutic agents can have a variety of ocular surface, retinal, and optic nerve toxicities.
- Medications instilled into the eye have the same potential side effects as when administered systemically, albeit often to a lesser degree.

OCULAR SIDE EFFECTS OF COMMONLY PRESCRIBED MEDICATIONS

Antimalarials

Indications: Antimalarial agents are also commonly prescribed to treat several rheumatic and skin conditions.

Name/MOA: Hydroxychloroquine (HCQ) and chloroquine (CQ). MOA not well-understood.

Known OSE:

- *Cornea*:
  - Diffuse punctate opacities, verticillate more with CQ than HCQ use.
  - Deposits rarely have visual sequelae and typically resolve on their own with or without discontinuation of treatment.
- *Retina*:
  - CQ and HCQ affect the outer layers of the retina, primarily the photoreceptors and retinal pigment epithelium.
  - "Bulls-eye" appearance on fundus examination; damage occurs in a ring around the fovea sparing its very center
  - At Risk: Dose and time dependent.
    - High risk: Cumulative daily dose of greater than 5 mg/kg of HCQ and greater than 2.3 mg/kg of CQ.
    - At recommended doses, risk of toxicity is less than 2% at 10 years, but rises sharply to 20% after 20 years.
    - Renal disease, tamoxifen use, and preexisting retinal or macular disease can also increase the risk of toxicity.

Possible/Rare OSE: Difficulty with accommodation and formation of cataracts.

Recommendations:
- Baseline ophthalmic examination within the first year if starting HCQ/CQ.
- Thereafter, annual ophthalmologic screenings can be deferred until 5 years of exposure if dosage is proper, or annually if high risk.
- 10 to 2 automated visual fields which focus on central vision and optical coherence tomography, which displays distinctive retinal layers should be done at all ophthalmology visits.

Antiarrhythmics

Indications: To restore sinus rhythm in patients presenting with cardiac arrhythmias, as well as to prevent recurrent arrhythmias.

Name/MOA: Amiodarone: di-iodinated benzofuran derivative.

Known OSE:
- Vortex keratopathy (cornea verticillata); corneal microdeposits occurring in 70% to 100% of patients but usually does not cause decrease in vision.
- Anterior subcapsular lens opacities.
- Multiple chalazia (styelike lesions on eyelids).
- Dry eye syndrome.
- Most serious ocular side effect is amiodarone-associated optic neuropathy, which can cause vision loss and may not resolve quickly or completely even with cessation of medication.

Name/MOA: Digoxin: Potent reversible inhibitor of cellular sodium potassium adenosine triphosphatase (Na/K ATPase), mainly in the myocardium.

Possible/rare OSE:
- Can cause optic neuropathy associated with vision loss, may not resolve quickly or completely even with cessation of medication. Potential dyschromatopsia (xanthopsia – yellow vision, cyanopsia – blue vision, chloropsia – green vision).

Name/MOA: Oxprenolol, propranolol: Beta adrenergic antagonists.

Known OSE:
- Decreased vision
- (Transient) diplopia
- Visual hallucinations
- Eyelid changes (erythema, urticaria, purpura)
- Lacrimation
- Photophobia
- Decreased intraocular pressure (IOP)

Possible/rare OSE:
- Myasthenia gravis, decreased accommodation, inflammatory intraocular pseudotumor, exfoliative dermatitis of lids

Name/MOA: Quinidine: Blocks sodium and potassium currents across cellular membranes, prolongs cellular action potential and decreases automaticity.

Known OSE:
- Visual disturbance

Possible/rare OSE:
- Color vision defect (red-green), photosensitivity, eyelid changes (urticaria, edema, lupoid syndrome), anterior granulomatous uveitis, visual hallucinations, ocular sicca (may aggravate or cause condition), myasthenia gravis, corneal deposits

Anticoagulants

Indications: prophylaxis and/or treatment of thromboembolic events such as cerebrovascular accident, pulmonary embolism, and myocardial infarction.

Name/MOA: warfarin: vitamin K epoxide reductase inhibitor.

Name/MOA: heparin: activation of antithrombin III and inactivation of thrombin.

Name/MOA: apixaban: direct inhibitor of factor Xa.

Known OSE:

- Hemorrhages
  - Within any ocular or peribulbar structures (retinal, orbital, choroidal, vitreous, retrobulbar, subretinal, hyphema).
  - Often associated with complications after recent ocular surgery.
  - One study estimated the prevalence of warfarin-associated ocular hemorrhage at approximately 3%.[1–7]
  - Novel oral anticoagulants possibly safer or equal in risk of intraocular hemorrhage.
  - Treatment: likely sufficient to temporary pause therapy, however surgical intervention may be needed.[8,9]

Recommendations:

- Complications vary from case to case and have a wide range in severity and effects on vision and ocular structures.
- Each case must be individualized depending on the location of hemorrhage and structures threatened.
- Stopping anticoagulant therapy can often lead to more devastating outcomes from systemic disease.

Antidepressants

Indications: To treat various types of clinical depression and/or anxiety disorders. May be prescribed off-label to treat other conditions not approved by the Food and Drug Administration (FDA).

Name/MOA: Amitriptyline, clomipramine, doxepin, trimipramine: Tricyclic antidepressants (tertiary amine)/serotonin-norepinephrine reuptake inhibitors.

Known OSE:

- Mydriasis
- Potential for acute glaucoma in predisposed persons
- Decreased accommodation/blurred vision
- Ocular sicca (may aggravate or cause condition)
- Decreased contact lens tolerance

Possible/rare OSE:

- Blepharospasm, oculogyric crisis, nystagmus (with toxicity)

Name/MOA: Atomoxetine, duloxetine, venlafaxine: serotonin-norepinephrine reuptake inhibitors

Known OSE:

- Mydriasis
- Decreased vision
- Potential for acute glaucoma in predisposed persons

Possible/rare OSE:

- Ocular sicca (may aggravate or cause condition), cataracts, visual hallucinations, photophobia, eyelid edema, blepharospasm

Name/MOA: Bupropion HCl: Aminoketone.

Known OSE:
- Weak mydriasis
- Decreased vision
- Visual hallucinations

Possible/rare OSE:
- Myopia, ocular sicca (may aggravate or cause condition), diplopia, eyelid edema, periorbital edema, may precipitate acute glaucoma.

Name/MOA:
Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline: selective serotonin reuptake inhibitors

Known OSE:
- Decreased vision
- Photophobia
- Ocular sicca (may aggravate or cause condition)
- Non–rapid eye movement during sleep

Possible/rare OSE:
- Oculogyric crisis, pupil changes (mydriasis, anisocoria), optic neuritis, ischemic optic neuropathy, cataracts/lens opacities

Name/MOA: Isocarboxazid, phenelzine, tranylcypromine: monoamine oxidase inhibitors (MAOIs)

Known OSE:
- Decreased vision
- Visual hallucinations (phenelzine)

Possible/rare OSE:
- Diplopia, nystagmus, strabismus, myasthenia gravis, photophobia, color vision defect (red-green)

Name/MOA: Trazodone: Triazolopyridine derivative, MOA not fully understood: serotonin reuptake inhibitor, histamine and alpha-1-adrenergic receptor blocker, affects 5-HT presynaptic receptor adrenoreceptors.

Known OSE:
- Decreased vision
- Weak mydriasis
- Potential for acute glaucoma in predisposed persons
- Visual distortions including metallic ghost images, bright shiny lights, palinopsia

Possible/rare OSE:
- Ocular sicca (may aggravate or cause condition), photosensitivity, blepharoconjunctivitis, diplopia

Antihypertensives

Indications: Reduction of blood pressure in hypertension, control of tachyarrhythmias, prevention of cardiac remodeling, and diuresis in congestive heart failure.

Name/MOA: Beta blockers: selective or nonselective inhibitors of the beta (and alpha) adrenergic receptors.

Known OSE:
- Systemic beta blockers
  - Low IOP
  - Transitory decreased vision
  - Hallucinations

- Dry eye symptoms

Name/MOA: Angiotensin-converting enzyme (ACE) inhibitors: compete for ACE to reduce levels of angiotensin II.

Known OSE:
- ACE inhibitors
  - Conjunctivitis
  - Periorbital edema
  - Facial urticaria

Name/MOA: Thiazides: inhibit sodium reabsorption of the renal distal tubules.

Known OSE:
- Thiazides
  - Decreased vision
  - Color defects
  - Acute angle closure glaucoma (AACG)
  - Band keratopathy secondary to hypercalcemia

Possible/rare OSE:
- Retinal phototoxicity, macular edema

Alpha Blockers

Indications: Benign prostatic hyperplasia, hypertension, Raynaud disease, and erectile dysfunction.

Name/MOA: Tamsulosin, Alfuzosin, Doxazosin, Prazosin, Terazosin, Silodosin: Blockage of alpha receptors leads to smooth muscle relaxation.

Known OSE

IFIS (intraoperative floppy iris syndrome)

- The iris dilator muscle, a smooth muscle with predominance of alpha-1A receptors, functions to regulate pupillary size. As the iris is anterior to the human lens, pupillary dilation is imperative for visualization to perform cataract extraction and intraocular lens insertion.
- Systemic alpha-1 receptor blockade can result in significant loss of iris tone resulting in IFIS.
- Triad of:
  - Pupillary constriction intraoperatively despite preoperative pharmacologic dilation
  - Fluttering and bellowing of iris stroma
  - Tendency of iris to prolapse toward side port incisions during surgery
- Occurrence: Within days of starting medication or even 1-time use can result in IFIS; stopping the medication before cataract surgery does not prevent IFIS, and even remote history of medication use can cause IFIS years later.

Recommendations:
- Operative strategies as well as pharmacologic and mechanical devices have helped to reduce the complications of IFIS.
- Physicians should refer patient for evaluation of cataracts (if they have not already had cataract surgery) before starting medications in this class (all alpha receptor blocking medications) whenever possible. This will allow the patient to have cataract surgery if indicated before being on the medication and therefore lessen risk of IFIS.

Antihistamines

Indication: Allergic relief, anaphylactic reactions, and drug-induced extrapyramidal symptoms.

Name/MOA: Diphenhydramine, cetirizine, loratadine: direct competitor to histamine at H1-receptor sites.

Known OSE:
- Mydriasis
- Decreased vision
- Decreased light reflex
- Decreased contact lens tolerance
- Anisocoria
- AACG[10–16]

Diuretics

Indications: To treat hypertension, chronic edema secondary to congestive heart failure, and cirrhosis. May also be used to help prevent calcium kidney stones to treat nephrogenic diabetes insipidus.

Name/MOA: Carbonic anhydrase inhibitors (CAI): Inhibition of carbonic anhydrase, which is present in the ciliary body epithelium reduces the formation of bicarbonate ions, which reduces fluid transport, thus reducing IOP. Other proposed mechanisms include vascular dilation to the optic nerve. CAIs also specifically used for altitude sickness prophylaxis and treatment of idiopathic intracranial hypertension. CAIs may have other off-label, non–FDA-approved uses.

Oral CAIs are often used either alone or in conjunction with topical glaucoma therapy to treat elevated IOP chronically. They may also be used to acutely lower IOP, commonly before/after intraocular surgery or in cases of AACG.

Known OSE:
- Inhibition of carbonic anhydrase, which is present in the ciliary body epithelium reduces the formation of bicarbonate ions, which reduces fluid transport, thus reducing IOP.
- Rarely, use of CAIs (sulfonamide derivative) can result in ciliochoroidal effusion syndrome, which causes an acute bilateral angle closure. Cessation of the CAI is the main treatment for this condition, which generally resolves after discontinuation.

Recommendations:
- As diuretics rid the body of excess fluids, they also may lead to decreased tear production regardless of class or type. Artificial tears may be beneficial in symptomatic patients.
- In sickle cell disease, metabolic acidosis due to CAI use can induce sickling. Special caution is advised if using CAIs to treat elevated IOP in patients with sickle cell disease (even patients with sickle cell trait), particularly those with a hyphema, as this can lead to anterior segment ischemia and even central retinal artery occlusion.

Name/MOA: Mineralocorticoid antagonists (MA) are potassium-sparing diuretics used to treat hypertension.

Known OSE:
- Use as diuretics has prompted investigation into therapy for several retinal diseases. Specifically, patients with central serous retinopathy have shown

resolution of subretinal fluid. There have been rare reports of eplerenone use leading to uveal effusion syndrome.

Erectile Dysfunction Drugs

Indication: Medications used to treat erectile dysfunction and (at higher doses) pulmonary hypertension.

Name/MOA: Sildenafil, tadalafil: phosphodiesterase-5 inhibition leading to buildup of cyclic guanosine monophosphate.

Known OSE:
- Color defects
- Light sensitivity
- Minimal hazy vision

Possible/rare OSE:
- Nonarteritic anterior ischemic optic neuropathy (NAION)
  - Although rare, this event may cause irreversible vision loss
  - Risk factors identified include men older than 50, hypertension, diabetes, and dyslipidemia

Recommendations:
- Return precautions for hazy vision or vision loss, especially for patients with risk factors for NAION
- Cessation of offending agent and immediate ophthalmologic evaluation in the event of sudden vision loss

Nonsteroidal Anti-inflammatory Drugs

Indications: To relieve pain and fever, reduce inflammation.

MOA: Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors.

Known OSE:
- Corneal opacities
- Macular/retinal pigmentary changes (indomethacin: long-term use, no clear relationship to dosage and retinal toxicity)
- Vortex keratopathy
- Photosensitivity
- Orbital/periorbital/eyelid edema

Possible/rare OSE:
- Ocular sicca (may aggravate or cause condition), optic or retrobulbar neuritis, papilledema secondary to pseudotumor cerebri

Proton Pump Inhibitors

Not known to cause significant OSEs.

Corticosteroids

Indication: To treat inflammatory conditions, autoimmune diseases, allergic reactions, adrenocortical insufficiency.

Name/MOA: Betamethasone, budesonide, dexamethasone, fludrocortisone, fluorometholone, beclomethasone, fluticasone, hydrocortisone, prednisone, prednisolone, triamcinolone: Effects are systemic and widespread including decreasing inflammation and immune system activity, suppressing polymorphonuclear lymphocytes migration, stabilizing leukocyte release of hydrolases, and reversing capillary permeability.

Known OSE

Systemic applications (via oral, intravenous, intramuscular, intra-articular, intranasal routes)

- Decreased vision
- Increased IOP
- Pseudotumor cerebri
- Cataract formation
- Decreased resistance to infections
- Mydriasis leading to AACG (in predisposed persons)
- Visual field defects
- Retinal edema
- Retinal hemorrhage
- Central serous retinopathy

Inhalant or topical applications

- Increased IOP
- Decreased resistance to infections
- Pseudotumor cerebri
- Cataract formation

Statins

Indications: Lipid-lowering drugs with anti-inflammatory, vascular, and immunomodulatory properties used primarily as cholesterol-lowering therapy.

*Name/MOA: P*ravastatin, atorvastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin. 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors.

Possible OSE:

- *Lens*: Interference with normal cholesterol accumulation in lens fibers and production of oxide derivatives leading to eventual cataract formation
- *Glaucoma*: Inhibition of rho-kinase and upregulation of nitric oxide leading to increased aqueous humor outflow, which lowers IOP
- *Dry eyes/Ocular inflammatory disease*: Blockage of inflammatory markers that break down the ocular surface
- *Orbital Myositis*: Extraocular muscles may be targets of the well-known statin side effects of muscle breakdown
- *Age-related Macular Degeneration (AMD)*: Reduction of inflammation, stabilization of the retinal pigment epithelium, which is the main target of macular degeneration
- *Diabetes*: Reduction of inflammatory markers and vascular endothelial growth factor (VEGF) leading to prevention of progression in diabetic retinopathy

Antidiabetic Drugs

Indication: Antidiabetic medications used to lower serum glucose levels.

Name/MOA: Sulfonylureas: stimulate pancreatic release of insulin.

Known OSE:

- Tolbutamide: color deficiencies, most commonly blue-yellow impairment
- Glyburide: decreased accommodation, color deficiencies
- Osmotic lens changes

Possible/rare OSE:

- Optic neuritis or retrobulbar neuritis

Name/MOA: Metformin: decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

- Not known to cause significant OSEs.

Recommendations:

- Drug-induced OSEs may be difficult to distinguish, as diabetes has many ocular manifestations.
- Diabetic patients should be monitored regularly with diabetic fundus examinations.

OCULAR SIDE EFFECTS OF LESS COMMONLY PRESCRIBED SYSTEMIC MEDICATIONS

Anemia Medications

Not known to cause significant OSEs.

Anti-anginal Medications

Indications: For the relief of angina caused by cerebral and peripheral ischemia, associated with arterial spasm and myocardial ischemia (possibly complicated by cardiac arrhythmias).

Name/MOA: Nitroglycerin: relaxation of vascular smooth muscle.

Possible/Rare OSE:

- Has rarely been linked to decreased vision, colored halos, variations in IOP, and pseudotumor cerebri.

Antiemetics

First-line antiemetics such as ondansetron are not known to affect ocular function. Antipsychotics with antiemetic action such as chlorpromazine and parasympathetic drugs are covered in another section.

Antiretroviral Medications

Indications: To manage and treat human immunodeficiency virus (HIV)/AIDS infection, to prevent HIV infection transfer.

Name/MOA:

Abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine: nucleoside reverse transcriptase inhibitors (NRTIs).
Delavirdine, doravirine, efavirenz, etravirine, nevirapine, rilpivirine: non-NRTIs
Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir: protease inhibitors
Enfuvirtide: fusion inhibitors
Maraviroc: CC chemokine receptor 5 antagonists
Bictegravir, dolutegravir, elvitegravir, raltegravir: integrase inhibitors
Fostemsavir: attachment inhibitors
Ibalizumab: postattachment inhibitors
Cobicistat: pharmacokinetic enhancers

Possible OSE (reported with didanosine):

- Peripheral chorioretinal degeneration, which may be progressive despite cessation of medication, immune recovery uveitis including cystoid macular edema/epiretinal membranes/optic disc neovascularization

Bisphosphonates

Indications: To treat and/or prevent osteoporosis from various causes, including postmenopausal state in women, osteoporosis in men, glucocorticoid-induced osteoporosis, Paget disease of bone.

Name/MOA: Alendronate/cholecalciferol, etidronate, zoledronic acid, risedronate, ibandronate, pamidronate, tiludronate. Inhibitors of osteoclast-mediated bone resorption.

Possible/rare OSE:
- Conjunctivitis, episcleritis, scleritis, uveitis

H2 Blockers

Indications: To treat dyspepsia, peptic ulcers, gastroesophageal reflux disease, prevention of stress ulcers (specifically ranitidine), prevention of aspiration pneumonitis during surgery (oral formulation).

Names/MOA: Ranitidine, famotidine, cimetidine, nizatidine. Reversible binding to histamine H2 receptors on gastric parietal cells; function as competitive antagonists.

Possible/rare OSE:
- Retinal vascular occlusion, optic neuropathy, retrobulbar optic neuritis.

Isotretinoin

Indications: Dermatologic conditions such as severe nodular acne and psoriasis.

Name/MOA: Isotretinoin is a synthetic vitamin A derivative that regulates epithelial proliferation and differentiation thereby inhibiting sebaceous gland function.

Known OSE:
- Night blindness (nyctalopia)
  - Slows regeneration of rhodopsin leading to retinal dysfunction
- Pseudotumor cerebri
  - May be due to alteration of lipid composition in arachnoid villi
- Blepharoconjunctivitis
  - Direct decrease of Meibomian gland function and secretion of drug via tears

Possible/rare OSE:
- Optic neuritis

Recommendations:
- Baseline dilated fundus examination could be useful before starting therapy
- Annual ophthalmologic examinations while on therapy, referral for any visual complaints while on therapy

Opioid Analgesics (Narcotics)

Indications: To provide pain relief, including anesthesia. Can also be used to reverse opioid overdose, as replacement therapy for opioid use disorder, and to suppress cough.

Name/MOA: Fentanyl: Phenylpiperidine synthetic opiate agonist.

Known OSE:
- Miosis
- Visual hallucinations
- Oculogyric crisis

Possible/rare OSE:
- Extraocular muscle abnormalities (ptosis, diplopia, abnormal eye movements), eyelid edema, periorbital edema

Name/MOA: Hydromorphone, oxymorphone: hydrogenated ketones of morphine.

Known OSE:
- Decreased vision
- Decreased accommodation
- Miosis
- Eyelid changes (urticaria, contact dermatitis)

Possible/rare OSE:
- Extraocular muscle abnormalities (nystagmus, diplopia), visual hallucinations.

Name/MOA: Meperidine: phenylpiperidine narcotic analgesic.

Known OSE:
- Miosis
- Decreased vision
- Eyelid changes (erythema, urticaria)
- Visual hallucinations

Possible/rare OSE:
- Nystagmus, ocular signs of drug-induced Parkinson disease (ptosis, diplopia, paresis/paralysis of extraocular muscles)

Name/MOA: Methadone: synthetic analgesic.

Known OSE:
- Miosis
- Talc retinopathy (with intravenous use)
- Decreased vision
- Decreased spontaneous eye movements

Possible/rare OSE:
- Eyelid changes (urticaria, edema), ocular sicca (may aggravate or cause condition), extraocular muscle abnormalities (diplopia, nystagmus, strabismus), cerebral visual impairment, reduced visual evoked potential

Name/MOA: Morphine sulfate:

Known OSE:
- Miosis
- Decreased vision
- Extraocular muscle abnormalities (diplopia, nystagmus, decreased convergence)
- Decreased accommodation
- Decreased IOP
- Visual hallucinations
- Decreased lacrimation
- Eyelid changes (urticaria, pruritis)
- Color vision defect (mainly blue-yellow, usually with chronic abuse)
- Ptosis

Possible/rare OSE:
- Myopia, ocular sicca (may aggravate or cause condition), accommodative spasm, vertical nystagmus, potential teratogenic effect of strabismus in exposed fetuses

Name/MOA: Pentazocine, Naloxone: benzomorphan narcotic analgesic.

Known OSE:
- Miosis

- Decreased vision
- Visual hallucinations

Possible/rare OSE:

- Nystagmus, diplopia, decreased accommodation, eyelid changes (erythema, edema), decreased spontaneous eye movements, oculogyric crisis

Tuberculosis Drugs

Name: Ethambutol, isoniazid, rifampicin, and streptomycin: common drugs used for treatment of mycobacterium tuberculosis (TB).

MOA:

Ethambutol: mechanism not completely understood
Isoniazid: prodrug that inhibits formation of mycobacterial cell wall
Rifampicin: inhibits bacterial RNA polymerase
Streptomycin: protein synthesis inhibitor

Known OSE:

Ethambutol-induced optic neuropathy

- Optic neuropathy be related to deficiency of copper, zinc, or vitamins E and B1.
- Symptoms: bilateral in more than 60% of patients.
  - Visual acuity loss ranging from 20/25 to no light perception
  - Visual field defects commonly involving central or cecocentral scotomas
  - Dyschromatopsia primarily affecting red/green vision and to a lesser degree blue/yellow loss
- Incidence: dose dependent: less than 1% with 15 mg/kg increasing to 18% to 33% with greater than 35 mg/kg per day
- At risk: hypertension, age older than 65, renal disease
- *Treatment*: Discontinuation of ethambutol. However, damage is often irreversible, as only 30% to 64% of patients report visual improvement.

Isoniazid:

- Can rarely cause retrobulbar optic neuritis especially in combination with ethambutol

Rifampicin:

- Staining of bodily fluids, particularly sweat and tears, to an orange-red color is common and may even be used to monitor absorption of the drug.
- Tears may permanently stain soft contact lenses but does not require medical attention.

Streptomycin:

- Can cause pseudotumor cerebri and myasthenic neuromuscular blockade. Should be avoided in patients with myasthenia gravis and anesthesia with neuromuscular blocking agents.

Recommendations: Baseline ophthalmic examination before initiation of anti-TB drugs and continued ophthalmic examinations during treatment as indicated.

Antiepileptics

Indication: Treatment of epilepsy and various headache disorders.

Name/MOA: Topiramate: Sulfonamide drug known to affect multiple targets including inhibition of voltage-gated sodium channels, enhancement of GABA-A receptors, and mild inhibition of carbonic anhydrase isoenzymes.

Known/uncommon OSE:

Ciliochoroidal effusion syndrome

- Sulfa derivatives known to cause lenticular swelling and forward displacement of iris-lens diaphragm resulting in forward rotation of ciliary body
- Presentation may mimic that of migraine headaches (headache, nausea, vomiting), but will typically include vision loss, hyperemia, corneal edema
- AACG most common and concerning adverse effect that typically occurs 7.0 to 12.8 days from administration (but can occur weeks after administration of drug)
- Acute myopia may develop within hours or weeks of starting therapy
- Treatment: cessation of offending agent, topical and systemic IOP-lowering medications to manage IOP acutely

Recommendations:

- Immediate cessation of topiramate and alternative therapy for the preexisting systemic pathology
- Prompt ophthalmologic evaluation for AACG to mitigate irreversible loss
- Acute myopia is often resolved within days but may take weeks for resolution in some cases

Pentosan Polysulfate Sodium (Elmiron)

Indications: To treat bladder pain/discomfort associated with interstitial cystitis.

MOA: Unknown; heparinlike macromolecular carbohydrate derivative resembling glycosaminoglycans.

Known OSE:

- Associated with retinal pigmentary changes (pigmentary maculopathy), cumulative dose-related so more common after more than 3 years of use. Changes may be irreversible; changes may also progress even after cessation of treatment.

Recommendations:

- Baseline retinal examination recommended within 6 months of starting therapy and periodically while continuing therapy.

OCULAR SIDE EFFECTS OF ONCOLOGIC/IMMUNOMODULATORY MEDICATIONS

Fingolimod

Indications: Oral therapy for relapsing, remitting multiple sclerosis (MS)

Name/MOA: Fingolimod: acts as an immune modulator that prevents binding of Sphingosine 1-phosphate to its receptor in lymphocytes; the primary cellular targets in MS.

Known OSE:

Fingolimod-associated macular edema (FAME)

- Interaction between fingolimod and retinal vascular endothelial cells is thought to decrease cellular adhesion and therefore increase vascular permeability resulting in macular edema.
- Symptoms: asymptomatic to decreased visual acuity and metamorphopsias
- Incidence: 0.4% in patients treated with 0.5 mg and 1% in those treated with 1.25 mg of fingolimod. All reported cases of FAME occurred within the first 4 to 6 months of starting treatment.
- At risk: History of uveitis, diabetic retinopathy, or other ocular comorbidities
- Treatment: Discontinuation of fingolimod leads to cessation of FAME in 85% of patients. Remaining patients may benefit from steroid therapy.

Possible/Rare OSE:

- Retinal hemorrhages and retinal vein occlusions

Recommendations:

- If patients have no ocular comorbidities, an initial vision should be documented by providers and baseline dilated ophthalmic examination should be done within 3 to 4 months.
- If history of previously mentioned risk factors, ophthalmic examination should precede initiation of medication to discern if patient is a good candidate for therapy.

Tamoxifen

Indications: An adjuvant treatment of patients with hormone-receptor positive breast cancer.

MOA: Tamoxifen is a selective estrogen receptor modulator.

Known OSE:

- *Cornea*: Cornea verticillate, a whorl like pattern, occurs due to the drug's resistance to enzymatic degradation once bound to lipids within the cornea. These lesions are rarely visually significant and usually do not require treatment.
- *Retina*: Crystalline deposits, macular edema and punctate pigmentary changes.
  - Symptoms: Decreased visual acuity and color vision.
  - At risk: Obesity, dyslipidemia, and dosage of medication. High doses (60–100 mg/d) may manifest as early as 1 year after initiation, whereas lower doses (10–20 mg/d) may take several years to present.
  - Incidence: 12% of patients
  - Treatment: Visual function and macular edema improve after drug cessation; however, crystal deposits do not immediately disappear. Persistent macular edema may be treated by anti-VEGF, corticosteroids, or CAIs.

Recommendations: All patients started on tamoxifen should be referred to an ophthalmologist for baseline evaluation and regular examinations while on treatment.

TOPICAL/OPHTHALMIC MEDICATIONS WITH IMPORTANT SYSTEMIC SIDE EFFECTS

Ophthalmologists prescribe medications to treat a wide variety of ocular disorders.

The volume of commercial drop dispensers (approximately 25–50 μL) is generally greater than the capacity of the conjunctival sac. When drops are instilled, only 10% of the medication is absorbed. Smaller lipophilic drugs go through the cornea, whereas larger hydrophilic drugs traverse the conjunctiva/sclera. Fifty percent or more of this absorbed dose makes its way to the systemic circulation. Although medications given topically do not reach as high a concentration in the blood, any of the eye drops can have systemic absorption with systemic side effects. Thus, what may seem as a relatively benign amount of medication may cause significant systemic toxicity. The following are common topical medications and their potential systemic side effects.

Topical Anesthetics

Indications: Used in everyday practice to numb the ocular surface before dilating drops, intravitreal injections, removal of surface corneal bodies, and much more.

Name/MOA: Tetracaine, proparacaine, lidocaine, oxybuprocaine: decrease neuronal membrane permeability to sodium ions, thus blocking initiation and conduction of nerve impulses.

- *Local side effects*: Temporary anesthesia. However, anesthetic abuse can lead to significant irreversible corneal damage and breakdown.
- *Recommendation:* Should not be prescribed to patients as an at-home medication.

Mydriatics

Indications: Induce pupillary dilation. Several diagnostic and therapeutic indications, such as obtaining refraction, dilated fundus examinations, uveitis, amblyopia penalization, and treatment of accommodative esotropia.

Name/MOA: Atropine, scopolamine, homatropine, cyclopentolate, tropicamide: paralyze the ciliary body.

- *Local side effects*: Burning, photophobia, ocular irritation, eyelid edema, hyperemia, increased IOP, conjunctivitis
- *Systemic side effects:* Dry mouth/skin, behavioral disturbances, tachycardia, disorientation, seizures, hypotension, psychosis, respiratory depression, fever
- *Avoid in:* Elderly individuals, intraocular inflammation

Name/MOA: Phenylephrine: adrenergic receptor agonist

- *Local side effects*: Burning/stinging, pigmented aqueous floaters
- *Systemic side effects:* Rare: systemic hypertension, ventricular arrhythmia, tachycardia, subarachnoid hemorrhage
- *Avoid in:* Patients taking MAOIs, tricyclic antidepressants (TCAs), antidepressants, reserpine, guanethidine, methyldopa

Intraocular Pressure–Lowering Agents

Indications: Glaucoma, lowering of IOP after intraocular surgery.

Name/MOA: Apraclonidine, Brimonidine: alpha agonists.

Alpha-1 activity: vasoconstriction, pupillary dilation, eyelid retraction.

Alpha-2 activity: Reduce aqueous production, increase aqueous outflow.

- *Local side effects*: Follicular conjunctivitis, contact dermatitis
- *Systemic side effects:* Dry mouth, allergy
- *Avoid in:* Pediatric patients due to central nervous system effects: risk of somnolence, hypotension, seizures, apnea. Patients taking MAOIs or TCAs.

Name/MOA: Timolol, betaxolol, levobunolol, metipranolol: beta blockers reduce aqueous production.

- *Local side effects*: Urticaria, alopecia, contact dermatitis, psoriasiform rashes
- *Systemic side effects:* Bradycardia, arrhythmias, syncope, hypotension, bronchoconstriction
- *Avoid in:* Patients with lung disease, patients already on oral therapy

Name/MOA: Dorzolamide, Brinzolamide: CAIs reduce aqueous production.

- *Local side effects*: Bitter aftertaste, eye burning/stinging, allergic conjunctival reaction, superficial punctate keratopathy
- *Systemic side effects:* Nausea. Of note, topical CAIs produce fewer side effects than oral treatment. Should be used with caution in patients with sickle cell disease.
- *Avoid in:* Sulfonamide allergy

Name/MOA: Pilocarpine, Carbachol: parasympathetics increase aqueous outflow by contraction of ciliary body, no longer first line for glaucoma.

- *Local side effects*: Pupillary constriction allergic dermatitis
- *Systemic side effects:* Excessive sweating, bronchospasm, vomiting, diarrhea, bradycardia, hypotension, confusion, emotional liability, agitation, concentration/behavioral disorders

- *Avoid in:* Patients with concurrent ocular inflammation.

Name/MOA: Common: Latanoprost, bimatoprost, tafluprost, travoprost, latanoprostene. Prostaglandin analogs increase aqueous outflow.

- *Local side effects*: Increased pigmentation of iris (irreversible), periorbital tissues (eyelids), and eyelashes (reversible). Elongates and thickens eyelashes. Burning, stinging, itching, increased lacrimation from irritation.
- *Systemic side effects:* Minimal. Use with caution during pregnancy (Class C: could stimulate uterine contractions leading to premature labor).
- *Avoid in:* Patients with concurrent ocular inflammation.

Nonsteroidal Anti-inflammatory Drugs/Steroids

Indications: Anti-inflammatory, anti-analgesic. Used postoperatively and for cystoid macular edema, episcleritis, and other mild ocular inflammatory disorders. Steroids can be instilled as drops, ointment, injected around the eye, or intravitreally as an implant.

Name/MOA: Common: Acular, Acuvail, bromday, bromsite, ilevro, Nevanac, ocufen, proflensa, voltaren, Xibrom. Nonsteroidal anti-inflammatory and anti-analgesic properties.

- *Local side effects*: Rare allergic contact dermatitis
- *Systemic side effects:* Rarely: Asthma, gastrointestinal effects[4,12,17–54]

Name/MOA: Fluorometholone, loteprednol, rimexolone, prednisolone, difluprednate: Steroid medications of varying potency.

- *Local side effects*: Cataract, elevated IOP. Rarely allergic reactions.
- *Systemic side effects:* Minimal.

Antibiotics

Indications: Bacterial conjunctivitis, postoperative, postinjury infection prophylaxis, corneal ulcers, intraocular infections.

Name/MOA: Moxifloxacin, ciprofloxacin, levofloxacin, ofloxacin, besifloxacin, gatifloxacin, azithromycin, gentamicin, tobramycin, erythromycin, bacitracin, polymixin B-trimethoprim, neomycin-polymyxin B-gramicidin, neomycin-polymyxin B-bacitracin, bacitracin-polymyxin B, sulfacetamide: Various MOAs: either bactericidal or bacteriostatic.

- *Local side effects*: Burning/itching, skin irritation, anaphylaxis, delayed corneal wound healing. Intravitreal vancomycin can be toxic to the retina.
- *Systemic side effects:* Minimal.
- *Avoid in:* Patients with systemic allergies to the same class(es) of antibiotics.

Ophthalmic Injections

Besides topical administration, some ocular medications are administered via injection into the subconjunctival space or vitreous cavity.

Indications: Antibiotics for infection, anti- VEGF agents for treatment of various conditions (listed in the next section), steroids for intraocular inflammation.

- *Local side effects*: Conjunctival hemorrhage, eye pain, cataract, vitreous floaters, IOP elevation, vitreous detachment, retinal detachment, endophthalmitis.
- *Avoid in:* Acute blepharitis/ocular surface infection, scleritis.

Anti-Vascular Endothelial Growth Factor Agents

Indications: To help halt growth of abnormal neovascular proliferation in the treatment of wet AMD, diabetic retinopathy, retinal vein occlusion, neovascular glaucoma, macular edema. Some of these uses are off-label for certain medications.

Name/MOA: Common: Bevacizumab, aflibercept, Lucentis, brolucizumab. Anti-VEGF agents.

- *Local side effects:* See preceding section, "Ophthalmic Injections."
- *Systemic side effects:* Arterial thromboembolic event, myocardial infarction, stroke, venous thrombotic event, transient ischemic attack, hypertension.
- *Avoid in:* Patients at increased risk of thromboembolic events.

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