COURSE TITLE:

Ocular Adverse Effects of Systemic Medications

INSTRUCTOR: Jennifer Schad, OD, FAAO
Assistant Professor, Michigan College of Optometry
Ferris State University
JenniferSchad@ferris.edu

DESCRIPTION:

Ocular structures are particularly susceptible to adverse effects of systemic medications. This course will explore these effects that may develop as the result of the agent's mechanism of action or toxic effects. The classification of and reporting protocol for adverse events will also be discussed.

LEARNING OUTCOMES:

1. Describe the difference between medication adverse events and side effects
2. Identify agencies responsible for post-market surveillance of medications
3. Define the WHO casualty assessment of adverse drug reactions
4. Describe the determinants of adverse drug reactions.
5. Discuss the adverse effects to ocular structures or their function of commonly encountered systemic medications.

COURSE OUTLINE:

Definitions and Classification of Adverse Drug Reactions

Adverse Drug Reaction: "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function."[1]

- **Adverse Event:** "any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment"[1]

- **Serious Adverse Event**: "is any event that:
  - Is fatal
  - Is life-threatening
  - Requires inpatient hospitalization or prolonging of existing hospital stay
  - Results in persistence of significant disability or incapacity"[1]

- **Unexpected Adverse Reaction:** An ADR that is "not consistent with applicable product information or characteristics of drug."[1]

- **Side effect:** "any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug"[1]

Pharmacovigilance: "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."[1]

- Who monitors ADRs?
  - WHO (World Health Organization
    - http://www.who.int/medicines/publications/druginformation/issues/DrugInformation2016_Vol30-3/en/
  - U.S. Food and Drug Administration (FDA) Medwatch
    - http://www.fda.gov/Safety/MedWatch/ucm168422.htm
  - National Drug Registry of Drug-Induced Ocular Side Effects
    - http://www.eyedrugregistry.com/
  - Canadian Adverse Drug Reaction Information System (Medeffect Canada)
    - http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
  - Canadian Ophthalmological Society's Canadian Ocular Drugs Reporting System
    - http://www.cos-sco.ca/forms/adverse-drug-reaction-form/

- Diagnosis of Adverse Drug Reactions
  - **Detailed drug history**
    - Prescription
    - OTC
    - Nutritional and Herbal Supplements
  - **Temporal relationship between drug and ocular signs**
  - **Dechallenge/Rechallenge**

- WHO Casualty Assessment of Suspected ADR
  - Certain
    - Event noted temporally to administration of a drug that **cannot** be explained otherwise by concurrent disease, other drugs or chemicals.
    - Dechallenge (withdrawal)/Rechallenge (reintroduction causes ADR recurrence) should be definitive.
  - Probable/Likely
    - Event occurs within a reasonable time to drug introduction and is **unlikely** to be attributed to concurrent disease, other drugs or chemicals.
    - Rechallenge corroboration is not available or required for this definition.
  - Possible
    - Event occurs with a reasonable time relationship to drug initiation, but **could** also be explained by concurrent disease or other drugs/chemicals.
    - Dechallenge data may be unavailable or unclear
  - Unlikely
    - Event not necessarily related, casual relationship seems improbable, and other disease states, drugs/chemicals provide plausible explanations.
  - Conditional/Unclassified
    - Reported, but requires more data to assess
  - Unable to assess/unclassifiable
    - Unverifiable report with **insufficient or contradictory** info

- Frequency of Adverse Drug Reactions
  - Very Common ≥1/10
  - Common (frequent) ≥1/100 but <1/10
  - Uncommon (infrequent) ≥ 1/1,000 but <1/100
  - Rare ≥1/10,000 but <1/1,000
  - Very Rare <1/10,000

Determinants of Adverse Drug Reactions

- **Amount administered**
  - Potency → dose required to produce specific effect
  - Efficacy → drug's capacity to produce an effect
  - Effectiveness → how well the drug works in the real world
- **Nature of Drug**
  - Pharmacologic properties and pharmacokinetics
    - Pharmacologic properties are inherent properties that determine pharmacokinetics
      - Solid, liquid, gas
      - Organic vs Inorganic
      - Drug molecular shape/weight
    - Pharmacokinetics is the movement of the drug into, through and out of the body.
      - Absorption (Bioavailability), Distribution, Metabolism, Excretion
      - Ease of passing into systemic circulation, penetrating blood-brain, blood-aqueous, blood-retinal barriers.
- **Route Administered**
  - IV vs IM vs Sub-Cutaneous vs Oral vs Inhaled vs Topical (skin) vs Ocular
- **Pathophysiologic variables**
  - Systemic conditions altering the way a drug is excreted→ example: liver/kidney disease
- **Age/Gender**
  - Very young and very old
    - Young patients have less mass and development concerns
    - Elderly have more comorbid conditions and concurrent meds
      - Also more likely to have reduced liver/kidney function
  - Women more than men
    - Hormones (including use of oral contraceptives or HRT)
    - Less mass
- **Multiple drug therapy/Potential interactions or potentiation**
  - ADRs can occur when a med is added or taken away
  - Many different sites/mechanisms can be at play, but may alter absorption, distribution, biotransformation, excretion or may alter receptor sensitivity if multiple drugs act on same receptor
- **History of drug allergies**
  - Often unpredictable
- **Individual idiosyncrasy**
  - Unexpected reaction that can occur due to variations in altered handling or abnormal tissue response (difference in enzymes)
  - Metabolites may form due to enzymes found in the ocular tissue: corneal epithelium, iris, ciliary body and RPE.

Why is the eye susceptible to ADRs?

- **Rich blood supply with small mass**
  - Uveal circulation
  - Retinal circulation
- **Lipophilic drugs** are better able to penetrate ocular structures
  - Blood-Retinal barrier
    - Tight junctions of RPE
    - Retinal capillary endothelium
- **Ocular structures act as reservoirs** and slowly release drug, enhancing toxicity
- **RPE has high metabolic activity** and is critical in drug biotransformations via cytochrome P-450 system. This can vary greatly between individuals (idiosyncrasy).

Drugs with OADR by Ocular Structure/Function

Eyelids

- Erythema multiforme: condition causing lid edema, conjunctival congestion, and inflammation of mucus membranes.
  - **Stevens-Johnson syndrome/Toxic Epidermal Necrosis,** the most severe manifestation, is a T-cell mediated cytotoxic reaction to drug metabolites
    - Erythema, edema, sloughing, blistering, ulceration and necrosis
    - Symblepharon formation
    - Corneal neovascularization
  - Common medication classes
    - Sulfonamides
      - **Sulfamethoxazole + Trimethoprim (Bactrim®, Bactrim DS®)**
      - **Carbonic Anhydrase Inhibitors**
        - **Acetazolamide (Diamox®)**
    - Anti-convulsants
      - **Phenytoin (Dilantin®)**
      - **Carbamazepine (Tegretol®)**
      - **Phenobarbital**
      - **Lamotrigine (Lamictal®)**
    - NSAIDs
      - **Cox-2 Inhibitors (Celecoxib®)**
    - HAART (Highly Active Retroviral Therapy)
- Eyelid Edema/Hyperemia
  - **Isotretinoin (Accutane®)**: retinoid that inhibits sebaceous secretion and keratinization
    - Additional effects on quality/quantity of meibum
  - **Niacin**
    - "Niacin flush" is a prostaglandin-mediated vasodilation→ Pre-treatment with aspirin ↓ flushing
  - Bisphosphonates
    - **Alendronate (Fosamax®)**
    - **Ibandronate (Boniva®)**
    - **Risedronate (Actonel®)**

- Eyelid Discoloration
  - Phenothiazines (**chlorpromazine [Thorazine®], thioridazine [Mellaril®]**: slate blue discoloration of the eyelid dermis and conjunctiva
- Ptosis
  - Atorvastatin (Lipitor®): Case report of myopathy-induced unilateral ptosis following use of Lipitor

Conjunctiva

- Conjunctival/Scleral Discoloration
  - Slate-Blue
    - **Chlorpromazine (Thorazine®)**
    - **Minocycline (Minocin®)**
  - Brown palpebral conjunctival deposits (pigmented inclusion cysts)
    - **Tetracycline**
  - Blue Sclera
    - **Sulfonamides**
- Conjunctivitis/Episcleritis/Scleritis
  - Bisphosphonates
    - **Alendronate (Fosamax®)**
    - **Ibandronate (Boniva®)**
    - **Risedronate (Actonel®)**
- Conjunctival hyperemia
  - **Niacin**
- Subconjunctival hemorrhage
  - **NSAIDs:** inhibition of prostacyclin (inhibitor of platelet aggregation) increases risk of bleeding
    - Irreversible COX inhibitor
      - **Aspirin**
    - Reversible COX inhibitor
      - Non-selective cox inhibitors: **ibuprofen and naproxen (Aleve®)**
      - Selective cox-2 inhibitors: **celecoxib (Celebrex®)**
  - Erectile Dysfunction Agents: inhibit phosphodiesterase-5 which increases cGMP causing vasodilation
    - **Sildenafil (Viagra®)**
    - **Tadalafil (Cialis®)**
    - **Vardenafil (Levitra®)**

Tear Film

- **Decrease production** through <u>direct anticholinergic</u> effects
  - Anti-Muscarinics
    - Muscarinic receptors in the conjunctival goblet cells contribute basal tear secretion
    - Muscarinic antagonists block these receptors, <u>decreasing tear production</u>.
    - Agents
      - **Atropine** + diphenoxylate **(Lomotil®), scopolamine (Transderm Scop®)**
      - Overactive bladder medications: **oxybutynin (Ditropan®), tolterodine (Detrol®)**, fesoterodine (Toviaz®)
      - **Benzotropine (Cogentin®)**
        - Anti-Parkinson's agent (also used to managed extrapyramidal symptoms associated with anti-psychotics

- **Decrease Production** through indirect anticholinergic effects:
  - H1 anti-histamines
    - 1st generation H1-antihistamines have greater affinity for muscarinic receptors than 2nd generation (moderate/high level of anticholinergic effects)
      - **Diphenhydramine (Benadryl®)**
      - **Dimenhydrinate (Dramamine®)**
      - **Chlorpheniramine (Chlor-Trimeton®)**
      - **Hydroxyzine (Atarax®, Vistiril®)**
    - 2nd generation (low level of anticholinergic effects)
      - **Loratadine (Claritin®), desloratadine (Clarinex®)**
      - **Cetirizine (Zyrtec®)**
      - **Fexofenadine (Allegra®)**
  - Anti-Psychotic medications
    - 1st generation (typical) inhibit peripheral muscarinic receptors causing "atropine-like" effects (moderate/high level of anti-cholinergic effects)
      - Phenothiazines
        - **Thioridazine (Mellaril®),**
        - **Chlorpromazine (Thorazine®)**
      - **Haloperidol (Haldol®)**
    - 2nd generation (atypical, low level of anti-cholinergic effects)
      - **Quetiapine (Seroquel®)**
      - **Risperidone (Risperdal®)**
      - **Aripiprazole (Abilify®)**
  - Anti-Anxiety agents
    - Benzodiazepines (low level of anti-cholinergic effects)
      - **Diazepam (Valium®)**
      - **Lorazepam (Ativan®)**
      - **Alprazolam (Xanax®),**
      - **Clonazepam (Klonopin®)**
  - Anti-Depressants
    - TCAs (Tricyclic Anti-depressant, block reuptake of norepinephrine and serotonin, moderate/high level of anti-cholinergic effects)
      - TCAs also block histamine and cholinergic receptors
        - **Amitriptyline (Elavil®)**
        - **Imapramine (Tofranil®)**
    - SSRIs and SSNRIs have less blocking activity on cholinergic receptors than TCAs (low level of anticholinergic effects
      - SSRIs (Selective Serotonin Reuptake Inhibitors)
        - **Fluoxetine (Prozac®)**
        - **Citalopram (Celexa®)**
        - **Escitalopram (Lexapro®)**
        - **Sertraline (Zoloft®)**
      - SSNRIs (Selective Serotonin-Norepinephrine Reuptake Inhibitors)
        - **Venlafaxine (Effexor®)**
        - **Duloxetine (Cymbalta®)**
        - **Desvenlafaxine (Pristiq®)**

- Anticonvulsants
  - **Carbamazepine (Tegretol®)** (moderate/high level of anticholinergic activity)
  - **Oxcarbazepine (Trileptal®)** (moderate/high level of anticholinergic activity)
  - **Valproic acid (Depakene®), divalproex (Depakote®)** (low level of anticholinergic activity)
- Anti-Parkinson's agents
  - **Carbidopa/Levodopa (Sinemet®):** (low level of anticholinergic activity)
  - **Pramipexole (Mirapex®):** (low level of anti-cholinergic activity)
    - Anti-Parkinson's and restless leg syndrome
- Skeletal muscle relaxants (moderate/high level of anticholingeric activity)
  - **Methocarbamol (Robaxin®)**
  - **Tizandine (Zanaflex®)**
  - **Cyclobenzaprine (Flexeril®)**
  - **Baclofen (Gablofen®)**

- **Decrease production** through adrenergic activity
  - **Beta-(Adrenergic) Blockers** → Reduce adrenergic effects on tear secretion (accessory lacrimal glands) or may also lead to blood vessel constriction and reduced blood flow through lacrimal gland (proposed mechanisms)
    - **Propranolol (Inderal®)**
    - **Atenolol (Tenormin®)**
    - **Metoprolol (Lopressor® and Toprol XL®)**
  - **Decongestants** (α selective agonists)→ Reduce blood flow to lacrimal gland through vasoconstriction, reducing tear production
    - **Pseudoephedrine (Sudafed®)**
    - **Phenylephrine (Sudafed PE®)**
- **Decrease production** through hormonal activity
  - **Oral Contraceptives/hormone replacement therapy**
    - Lacrimal gland and meibomian glands appear to be androgen target organs, meaning their function may be impacted by the amount of circulating sex hormones

- **Decrease production** miscellaneous
  - Diuretics
    - **Furosemide (Lasix®)**
    - **Hydrochlorothiazide (Microzide®)**
    - **Spironolactone (Aldactone®)**
    - **Triamterene (Dyrenium®)**
  - Vitamin A Analogs
    - **Isotretinoin (Accutane®)**
      - Reduction in meibum secretion → evaporation, destabilizing the tear film
      - Reduction in aqueous secretion is also implicated
  - Vitamins/Herbal
    - Niacin
    - Echinacea
    - Kava

- **Increase production** through cholinergic activity
  - Cholinergic agonists
    - **Pilocarpine (Salagen®)** used in treatment of Sjögren's syndrome
  - Cholinesterase inhibitor
    - **Donepezil (Aricept®)** for the treatment of dementia
    - **Neostigmine (Prostigmine®)** used in treatment of Myasthenia Gravis

- **Increase production** through adrenergic activity
  - Non-selective adrenergic agonists (α and ß receptor agonists) increase blood flow through lacrimal gland and stimulatory effects on accessory lacrimal glands
    - **Ephedrine**
    - **Epinephrine**

- **Increase production** miscellaneous
  - **Hydralazine (Apresoline®)** causes release of nitric oxide leading to vasodilation

Cornea

- Whorl-like Deposits
  - **Amiodarone (Cordarone®)**
    - Drug characteristics
      - Lipid soluble
      - Deposits in the cornea, lens, retina and optic nerve
    - Amiodarone keratopathy
      - Found in 69-100% of patients
      - Symptoms are blurred vision or colored rings around lights
      - May occur as early as 6 days after initiation of treatment, but more commonly after 1-4 months
      - Deposits are located in the epithelium/basal epithelium/stroma
      - Generally, lower dosages (100-200mg daily) will remain clear or show only mild keratopathy
      - Higher dosages (400-1400mg daily) will have advanced keratopathy until dosage is reduced or discontinued
      - Keratopathy resolves slowly over 3-20 months after discontinuing
  - Other agents causing whorl-like opacities
    - **Chlorquine (Aralen®)/ hydroxychloroquine (Plaquenil®)**
    - **Indomethacin (Indocin®)**
    - Atovaquone (Mepron®)
- Other agents causing corneal deposits
  - **Phenothiazines**: Deposits on endothelium or Decemet's membrane usually present with concomitant lens deposits
    - **Chlorpromazine (Thorazine®)**
    - **Thioridazine (Mellaril®)**
  - **Isotretinoin (Accutane®)**: opacities, punctate keratitis
- Delayed corneal wound healing
  - **Corticosteroids**
- Ulceration, epithelial defects, reduced corneal sensitivity
  - Crack-cocaine

Lens

- Lenticular Deposits
  - Phenothiazines: **Chlorpromazine (Thorazine®), thioridazine (Mellaril®)**
    - Anterior subcapsular
    - Stellate-shaped
    - Rarely evident when total dosage <500g
    - 90% with lenticular deposits when total exceeds 2,500g
    - Typical daily dosage 800+mg so lenticular pigment can appear by 14-20 months
    - 2,000mg daily as soon as 6 months
  - **Amiodarone (Cordarone®)**
    - Anterior subcapsular
    - Fine anterior subcapsular opacities in ~50% of patients taking mod-high dosages (600-800mg daily) after 6-18 months. They begin as golden brown or white-yellow punctate opacities.
    - Opposite to chlorpromazine, lenticular changes develop in the presence of marked keratopathy.
- Cataract formation
  - **Corticosteroids**
    - Most commonly posterior subcapsular

Pupils

- Agents causing **mydriasis** through anticholinergic activity
  - **Anticholinergics** (muscarinic antagonists)
    - Primary anticholinergic activity
      - **Atropine** diphenoxylate **(Lomotil®)**
      - **Scopolamine (Transderm Scop®)**
      - **Overactive bladder agents**
      - **Ipratropium (Atrovent®)**→ inhaled anticholinergic agent that has been linked to mydriasis and angle closure when aerosolized in nebulizer treatments
    - Secondary anticholinergic activity
      - **Anti-psychotics**
      - **Anti-anxiety agents**
        - Benzodiazepines
      - **Antidepressants**
        - TCAs
        - SSRIs (Selective Serotonin Reuptake Inhibitors)
        - SSNRIs (Selective Serotonin-Norepinephrine Reuptake Inhibitors)
      - **Anticonvulsants**
      - **Anti-Parkinson's** agents
      - **Skeletal muscle relaxants**
- Agents causing **mydriasis** through adrenergic activity
  - CNS stimulants (Adrenergic agonist/sympathomimetic)
    - Act on the brainstem→ decreases reuptake of dopamine and norepinephrine
      - Amphetamines
        - **Amphetamine/dextroamphetamine (Adderall®)**
      - **Methylphenidate (Ritalin®),** dexmethylphenidate (Focalin®), lisdexmethylphenidate (Vyvanse®)

        - **Cocaine**
            - Negative pressure generated by sniffing cocaine may allow retrograde ocular delivery via the nasolacrimal duct.
            - Absorbed systemically via the nasal mucosa
- Agents causing **miosis** through cholinergic activity
    - Cholinergic agonists
        - **Pilocarpine (Salagen®)** used in treatment of Sjögren's syndrome
    - Cholinesterase inhibitor
        - **Donepezil (Aricept®)** for the treatment of dementia
        - **Neostigmine (Prostigmine®)** used in treatment of Myasthenia Gravis
    - Opiates
        - Stimulate the oculomotor nucleus and the pre-ganglionic parasympathetic fibers that travel within the oculomotor nerve to the ciliary ganglion
            - **Heroin**
            - **Hydrocodone**
            - **Codeine**
            - **Morphine**
            - **Fentanyl**

Uvea

- **Intra-operative floppy iris syndrome** secondary to Alpha-1 antagonists
    - Alpha-1 adrenergic antagonists block action of norepinephrine on the target tissue resulting smooth muscle relaxation (vascular, but also bladder and prostate).
    - High affinity for alpha 1-a which are the dominant alpha-1 receptors in the prostate and iris dilator
    - Structural changes (namely atrophy) with long term use in the iris dilator and receptor antagonistic effects both contribute
    - Iris may billow; cause insufficient dilation with progressive operative miosis; a tendency to catch the phaco/irrigation tips or prolapse toward the corneal incisions.
    - Complications include: poor visibility, iris damage with surgical instruments, rupture of the posterior capsule and loss of lens material into vitreous.
        - Benign Prostate Hyperplasia (BPH)
            - **Tamsulosin (Flomax®)**
        - Hypertension and BPH
            - **Toxasin (Cardura®)**
            - **Terazosin (Hytrin®)**
        - Hypertension
            - **Prazosin (Minipress®)**
- Uveitis
    - Bisphosphonates
        - Remember lid edema, non-specific conjunctivitis, episcleritis/scleritis
        - **Alendronate (Fosamax®)**
        - **Ibandronate (Boniva®)**
        - **Risedronate (Actonel®)**
    - **Sulfonamides** → Uveitis (Possible)
        - Remember erythema multiforme, conjunctivitis

- **Etanercept (Enbrel®)**, Tumor necrosis factor blocker → Uveitis (Possible)
  - Case reports with temporal association and dechallenge/rechallenge
  - However, some in this category are used on and off label to treat recalcitrant uveitis, especially
    - **Adalimumab (Humira®)** FDA approved
    - **Infliximab (Remicade®)** Off-label use
- **Rifabutin (Mycobutin®)** → Uveitis (Certain)
  - Used to treat Mycobacterium Avium
- **Vistide® (cidofovir)** → Uveitis vs immune-recovery uveitis (Probable)
  - Used to treat CMV in AIDS

Uvea

- Agents causing **increased IOP**
  - Acute or Sub-Acute/Chronic Angle Closure
    - Adrenergic Agonists
    - Anticholinergics
      - Primary → Muscarinic antagonists
      - Secondary
        - Antihistamines
        - TCAs/SSRIs/SNRIs/Antipsychotics
    - Sulfonamides or Sulfa based drugs
      - **Topiramate (Topamax®)**
        - Oral sulfamate that resembles the sulfonamide part of acetazolamide → Hypersensitivity response causes choroidal effusion/inflammation places pressure on the vitreous body and compresses the iris/lens diaphragm, causing anterior displacement and closure of the angle.
        - Myopic shift in conjunction with angle closure due to anterior displacement of lens and congestion of the ciliary body→ zonules become lax with resultant lens thickening
        - This will **usually occur very early in the treatment**, sometimes after the initial treatment, but generally by 1 month. Of the cases reported with angle closure **85% occur within the 1st 2 weeks**.
      - Watch out for ACG in **Thiazide diuretics and CAIs** (contraindicated in sulfa allergies)
  - Open Angle
    - **Corticosteroids**
      - In steroid responders, there is a **60% greater increase in IOP with oral steroids** vs topical. Due to greater concentration in the AC with systemic steroids
      - Multiple contributors to decrease aqueous outflow:
        - Increased accumulation of fibronectin, glycosaminoglycans and elastin
        - Inhibition of phagocytosis causing reduced ability to remove TM debris
        - Physical obstruction with crystalline steroid particles.

- Agents causing **decreased IOP**
  - Beta-Blockers (systemic)
    - Decreased aqueous production due to antagonism of ß-2 receptors on the non-pigmented ciliary epithelium
    - Usually receptor blockade is complete from systemic beta-blocker such that addition of topical often produces little additional IOP lowering with concomitant use.

- Cardiac Glycosides
  - **Digoxin (Lanoxin®)**
  - Aqueous formation can be reduced as much as 45% after several days of digoxin therapy.
  - Suspected to inhibit sodium pump which is needed to produce aqueous
- Cannabinoids
  - 25-30% IOP lowering reported, but maximum hypotensive effect within 60-90 minutes, lasting only approximately 4 hours
  - Possible mechanism is not CNS related, but due to cannabinoid receptors that influence both uveoscleral outflow and aqueous production.
- Ethanol
  - Short-acting hyperosmotic agent
  - Remember hyperosmotics may be used in angle closure attacks (glycerin and mannitol)

Refractive Effects

- Acute myopia
  - Choroidal effusion → anterior displacement of lens and CB congestion relaxing zonules
    - Sulfonamides or Sulfa containing medications
      - **Bactrim®** (sulfamethoxazole/trimethoprim)
      - **Topiramate (Topamax®)**
      - Carbonic anhydrase inhibitors → **acetazolamide (Diamox®)**
      - Diuretics → **furosemide (Lasix®), bumetanide (Bumex®)**
    - **Aripiprazole (Abilify®)**: several case reports involving transient myopia
      - Mechanisms postulated include: choroidal effusion (including CB), ciliary spasm, or ocular serotonergic effects
  - **Isotretinoin (Accutane®)**
    - Published case reports of transient myopia
- Cycloplegia
  - **Chloroquine (Aralen®)**: previously used in treatment of nocturnal leg cramps, "muscle relaxant" effect
  - Agents with anticholinergic effects
    - Phenothiazines, antihistamines, anti-anxiety, antidepressants

Retina (Structure and Function)

- Pigmentary changes
  - **Chloroquine (Aralen®), hydroxychloroquine (Plaquenil®)**
    - Mechanism is poorly understood, but initially changes are detected in the cytoplasm of ganglion cells and photoreceptors with later involvement of the RPE as molecules bind melanin and disrupt normal metabolism.
    - Manifestations:
      - "Bulls-Eye" maculopathy (later stages)
      - Central visual field defects
      - Acquired color deficiency

        - American Academy of Ophthalmology Screening Guidelines (2016)
            - Thorough ocular examination, documenting any pre-existing conditions, and
            - Humphrey central 10-2 white on white, and
            - One of the following:
                - Fundus autofluorescence
                - Multifocal electroretinogram (mfERG)
                - Spectral domain OCT
            - Until 5 years of treatment, annual funduscopic examinations are needed, but ancillary tests are not required unless high risk for toxicity or abnormalities are noted on baseline exam
            - Annual examination including ancillary tests after 5 years of treatment
    - **Phenothiazines→ chlorpromazine (Thorazine®), thioridazine (Mellaril®)**
        - Retinal pigmentary changes that begin as non-descript macular pigment change, followed by salt 'n pepper pigmentary loss which may coalesce into broader areas of atrophy of the RPE and choriocapillaris
        - VF defects, disturbance of dark adaptation
    - **Ezogabine (Potiga®)**
        - Damage to photoreceptors with resultant vision loss.
        - Monitor every 6 months
    - **Indomethacin (Indocin®)**→ pigmentary changes and color vision loss found in case reports
    - Carmustine (IV anti-neoplastic agent)→ macular pigment changes and vascular occlusion
- Vascular attenuation
    - **Quinine**
        - Anti-malarial used for benign nocturnal muscle cramps
        - Symptoms of acute toxicity→ "headache, nausea, vomiting, tremor, hypotension, and loss of consciousness and is associated with profound vision loss, which may be irreversible"
        - Mild retinal edema and venous dilation in the acute phase
        - Arteriolar attenuation and optic atrophy develop over several weeks
        - With treatment, central vision may recover, but peripheral remains constricted
- Impaired function (dark adaptation, visual field)
    - **Phenothiazines** → Pigmentary changes, disturbance of dark adaptation and VF loss
    - **Quinine** → Vascular attenuation, impairment of dark adaptation and VF defects
    - **Ivabradine (Corlanor®**, heart failure medication) → impaired dark adaptation
    - **Isotretinoin (Accutane®)** → Impairment of dark adaptation
    - **Vigabatrin (Sabril®)** → Visual field constriction
        - Visual field constriction in <u>at least 30% of patients</u>, causing <u>constriction up to central 10°</u>
        - Vision management plan ages 10+ years
            - Evaluation period of 3 months.
            - Should be monitored every 3 months during maintenance phase
            - Monitoring continues every 3-6 months after discontinuing
        - Vision management plan ages 1 month – 2 years
            - Evaluation period of 2-4 weeks
            - Should be monitored every 3 months during maintenance phase
            - Monitoring continues every 3-6 months after discontinuing

- **Topiramate (Topamax®)**
  - Homonymous VF defects are reported that are not found in other gamma-aminobutyric acid-ergic drugs.
  - Defects are independent of acute glaucoma.
  - Mechanism is not understood, but case reports suggest a depression in retinal function
  - Defects tend to develop after two to three months of usage
  - Partially or completely reversible after discontinuation.
- **NSAIDs**
  - Published reports of VF defects with COX-2 inhibitors: **Celebrex® (celecoxib)** and Vioxx® (rofecoxib withdrawn from market).
  - Few case reports of ibuprofen related VF defects.
  - Retinal hemorrhage is an additional retinal adverse effect

- Retinal hemorrhage and vascular occlusions
  - **Oral contraceptives** → retinal hemorrhage/occlusion/thrombosis
  - Interferon → retinal hemorrhage or macular edema
  - Carmustine (anti-neoplastic agent) → retinal hemorrhage/occlusion, macular pigment changes
- Macular edema
  - **Sildenafil (Viagra®)/ vardenafil (Levitra®)/ tadalafil (Cialis®)** → Central serous chorioretinopathy
  - **Niacin** → "pseudo" cystoid macular edema
  - **Tamoxifen** → Macular edema and crystalline retinopathy posterior pole
    - Refractile intraretinal deposits, concentrated in the perifoveal macula
    - Macular edema may be present
    - Crystals may remain after ME resolves
  - **Pioglitazone (Actos®)/Rosiglitazone (Avandia®)** →worsening DME possibly due thiazolidinediones causing increased fluid retention (additional risk for heart failure)
  - **Fingolimod (Gilenya®)**
    - Used in the treatment of relapsing forms of multiple sclerosis
    - Shown to have secondary effects on vascular endothelial barrier → compromising the blood-retina barrier
    - Recommendation is for baseline exam then at 3-4 months when ME would most likely manifest; followed by 6 months then 1 year if no ME detected.
  - Interferon
- Color vision disturbances
  - Cardiac Glycosides: **digoxin (Lanoxin®)**
    - Visual disturbances are often the earliest indications of toxicity, but may include GI or cardiac symptoms as well
    - Xanthopsia (yellow halos in vision)
    - Visual snow
    - Photopsia
    - Reduction in VA or VF defects
  - PDE-5 inhibitors: **Sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®)**
    - Cyanopsia-blue vision
    - Shimmering around objects
    - Central serous chorioretinopathy
    - NAION

Optic Nerve

- Non-Arteritic Ischemic Optic Neuropathy
  - PDE-5 inhibitors: **Sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®)**
    - Postulated that hypotensive effects or vasodilation effects of nitrous oxide on ONH blood supply → reduced ONH perfusion→ Ischemia
  - **Amiodarone (Cordarone®)**
    - Amiodarone-induced ION is more common in males, where classic NAION has equal sex predilection
    - Classic NAION presents unilaterally, where amiodarone-induced may present bilateral and simultaneous
    - Vision loss is more insidious with amiodarone-induced, where classic NAION is more sudden
    - Classic NAION resolves in the matter of weeks, amiodarone within months
  - **Sumatriptan (Imitrex®)**
    - Case reports of NAION
    - Agent causes cerebral vessel constriction and elevation in BP
- Increased intracranial pressure
  - **Oral contraceptives/Hormone replacement therapy**
  - **Tetracyclines** (Doxycycline, Minocycline)
  - **Corticosteroids**
  - Tamoxifen
  - Macrobid® (nitrofurantoin)
  - NegGram (nalidixic acid)-early quinolone antibiotic, not commonly prescribed
  - Vitamin A (retinoids, isotretinoin)
  - NSAIDs (uncommon, but reported; more likely with indomethacin)
- Other optic neuropathies including optic neuritis/papillitis
  - **Ethambutol (Myambutol®)**→ retrobulbar neuritis
  - **Isoniazid (Nydraziad®)** → optic neuritis (rare)
  - **Adalimumab (Humira®), infliximab (Remicade®), etanercept (Enbrel®)**→ optic neuritis (suspected that TNF-α antagonists may exacerbate demyelinating disease)
  - **Methotrexate**
    - Optic neuropathy, likely secondary to folate deficiency
  - **Oral contraceptives** → optic neuritis vs increased intracranial pressure vs ION due to thrombosis
  - Chloramphenicol → optic neuritis/retrobulbar neuritis
  - NSAIDs → papillitis, optic neuritis
  - Linezolid (Zyvox®)
    - Used in treatment of MRSA
    - Peripheral and optic neuropathy
    - Found in prolonged dosing schedules—FDA approval is based on 28-day studies

Eye Movements

- Decreased saccadic velocity and impaired smooth pursuits
    - **Benzodiazepines/Barbiturates**→ positive modulator of GABA-receptor, reduces excitability of neurons
    - **Gabapentin (Neurontin®)**→ mechanism not fully understood, but reduces release of glutamate (a stimulatory neurotransmitter)
    - **Anticonvulsants** (multiple mechanisms reduce neuronal transmission)
    - **Antipsychotics**→ dopamine antagonists slow initiation of movement
        - 1st generation
        - Atypical
    - **Amphetamines**
        - Damages dopaminergic nerve endings
    - **Opioids**→ affects GABA receptors in the cerebellum or through inhibiting neurotransmitter release
    - **Alcohol**
    - **Skeletal muscle relaxants**
- Internuclear Ophthalmoplegia→ lesion in MLF blocks signals from horizontal gaze center to CNIII; affected side cannot adduct (or is very weak) in horizontal gaze, but can adduct in convergence, with nystagmus of the contralateral eye
    - **TCAs**
    - **Barbiturates**
    - **Phenothiazines**
    - **Lithium**→ reduces dopamine and glutamate, enhances GABA
    - **Beta-blockers**
    - **Opioids**
- Gaze palsy
    - **TCAs**
    - **Anticonvulsants**
    - **Barbiturates**
    - **Lithium**
    - **Skeletal muscle relaxants**
- Opsoclonus→ involuntary conjugate saccadic movements that may be horizontal, vertical or torsional and do not follow a rhythmic pattern (saccadomania)
    - **TCAs**
    - **Anticonvulsants**
    - **Lithium**
    - **Diphenhydramine (Benadryl®)**
- Nystagmus
    - **Anticonvulsants**
    - **Lithium**
- Convergence spasm
    - **Phenytoin (Dilantin®)**
- Oculogyric Crisis→ bilateral dystonic elevation of gaze lasting minutes to hours
    - **Cetirizine (Zyrtec®)**→ has ability to block dopamine receptors
    - **Anticonvulsants**→ including **carbamazepine (Tegretol®), lamotrigine (Lamictal®)**
    - **Anti-psychotics**→ including **phenothiazines, aripiprazole (Abilify®)**
    - **Lithium**
    - Cefixime (Suprax®)
    - Metoclopramide (Reglan®)→ anti-emetic that is a dopaminergic (D2) antagonist

Herbal/Supplements with OADRs

- Canthaxanthine
  - Crystalline Retinopathy (Certain)
- Chamomile
  - Allergic conjunctivitis (Certain)
- Datura
  - Mydriasis (Certain)
- Echinacea Purpurea
  - Conjunctivitis (Probable)
- Ginko Biloba
  - Spontaneous hyphema, retinal hemorrhage (Possible)
- Liquorice
  - Vasospasm, visual loss associate with migraine-like symptoms (Possible)
- Vitamin A
  - Intracranial hypertension (large doses, Certain)