Top 10 Medications and Their Ocular Side Effects
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Agenda
• Review of the most common systemic medications and their uses and associated ocular side effects:
  – Hydroxychloroquine (Plaquenil)
  – Tetracyclines
  – Amiodarone
  – Antidepressants
  – Steroids
  – Tamoxifen
  – Anti-histamines
  – Flomax
  – Topumax
  – Viagra/Cialis

Antimalarials
• hydroxychloroquine or Plaquenil
• Common medication used by patient’s who are suffering from rheumatoid arthritis
• usual dose is 200-400 mg/d @night with onset of action after a period of 2-4 months
• Primarily used to help manage pain and increase mobility, has a mild affect on slowing down joint destruction
Antimalarial Ocular Complications

- affinity for pigmented structures such as iris, choroid and RPE
- Toxic affect on the RPE and photoreceptors leading to rod and cone loss.
- slow excretion rate out of body with toxicity and functional loss continuing to occur despite drug discontinuation.

Question

Which of the following depicts a retina undergoing hydroxychloroquine toxicity?

ARMD Macular Hole OHS Bull’s Eye Maculopathy

Antimalarial Ocular Complications

- Toxicity can lead to whorl keratopathy, “bulls eye” maculopathy, retinal vessel attenuation, and optic disc pallor.
- Early stages of maculopathy are seen as mild stippling or mottling and reversible loss of foveal light reflex
- “Classic” maculopathy is in form of a “bulls eye” and is seen in later stages of toxicity – this is an irreversible damage to the retina despite discontinuation of medication
Antimalarials

![Bulls Eye Maculopathy and Whori Keratopathy](image)

Fabry Disease

- alpha-galactosidase-A deficiency.
  - insufficient breakdown of lipids, which build up to harmful levels in the eyes, kidneys, autonomic nervous system, and cardiovascular system.
- Fabry disease is one of several lipid storage disorders and the only X-linked lipid storage disease.
- Lipid storage may lead to impaired arterial circulation and increased risk of heart attack or stroke.
  - The heart may also become enlarged and the kidneys may become progressively involved.
- Other signs include decreased sweating, fever, and gastrointestinal difficulties.

Revised Recommendations on Screening for Retinopathy

- 2002 recommendations for screening were published by Ophthalmology
- Revised recommendations on screening published in Ophthalmology 2011;118:415-42
  - Significant changes in light of new data on the prevalence of retinal toxicity and sensitivity of new diagnostic techniques
  - Risk of toxicity after years of use is higher than previously believed
    - Risk of toxicity approaches 1% for patients who exceed 5 years of exposure
Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- Screening Tests: **Newer objective tests, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields.** It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for evaluation by objective testing. Because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull's-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage.

Revised Recommendations on Screening for Retinopathy

- Amsler grid testing removed as an acceptable screening technique
  - NOT equivalent to threshold VF testing
- Strongly advised that 10-2 VF screening be supplemented with sensitive objective tests such as:
  - Multifocal ERG
  - Spectral domain OCT
  - Fundus autofluorescence

Revised Recommendations on Screening for Retinopathy

- Parafoveal loss of visual sensitivity may appear before changes are seen on fundus evaluation
  - Many instances where retinopathy was unrecognized for years as field changes were dismissed as "non-specific" until the damage was severe
  - 10-2 VF should always be repeated promptly when central or parafoveal changes are observed to determine if they are repeatable
  - Advanced toxicity shows well-developed paracentral scotoma
Bull’s Eye Maculopathy

![Diagnosis](image)


Revised Recommendations on Screening for Retinopathy

<table>
<thead>
<tr>
<th>Factors Increasing Risk of Retinopathy</th>
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<tbody>
<tr>
<td>Duration of use</td>
<td>&gt; 5 years</td>
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<tr>
<td>Cumulative Dose</td>
<td>&gt; 1000g (total)</td>
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<tr>
<td>Daily Dose</td>
<td>&gt; 400 mg/day</td>
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<tr>
<td>Age</td>
<td>Elderly</td>
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<tr>
<td>Systemic Disease</td>
<td>Kidney or liver dysfunction</td>
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<tr>
<td>Ocular Disease</td>
<td>Retinal disease or maculopathy</td>
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Tetracyclines

- Nonresistant strains concentrate this antibiotic intracellularly resulting in inhibition of protein synthesis.
- Broad spectrum, bacteriostatic,
  - effective against gram (+) and (-) bacteria and against non-bacterial organisms
  - widespread resistance has limited their use.
- Drug of choice for Rocky Mountain Spotted Fever, Cholera, Lyme disease, mycoplasma pneumonia, and chlamydial infections.
- Side effects include gastric discomfort, effects on calcified tissues, vestibular problems.
- Should not be used in children under the age of 8 due to discoloration of teeth.
Tetracyclines

- This group includes:
  - Tetracycline (250mg - 500 mg cap BID-QID) needs to be taken 1 hour before or 2 hours after a meal.
  - Minocycline (100 mg cap BID)
  - Doxycycline (20mg - 100 mg cap or tab BID)

- Rules of Thumb with Doxy:
  - Do not take before lying down (>2 hours before)
  - Do not take with calcium and avoid antacids
  - Do not take with dairy
  - Do take with food

Tetracyclines: Ocular SE

- Systemic use of this group rarely causes serious SE.
- The most commonly reported SE is pseudotumor cerebri associated primarily with tetracycline and minocycline. Increased intracranial pressure is not dose dependent and may occur as early as 4 hours after first taking the drug or after many years of drug use.
- All tetracycline agents are photosensitizers.

Antianginal: Amiodarone

- Brand names: Cordarone, Pacerone
- Antiarrhythmic agent used in the treatment of atrial and ventricular tachcardias.
- Systemic adverse SE include: interstitial pulmonary fibrosis, GI intolerance, tremor, ataxia, dizziness, liver toxicity, photosensitivity, muscle weakness etc.
- After long-term use, more than 50% of Px have to discontinue use due to toxic responses.
Antianginal: Amiodarone Ocular SE

- corneal microdeposits occur in nearly all Px who are using the drug long-term
  - epithelial whorl-like pattern similar as seen in chloroquine treatment
  - horizontal, irregular branching line near the junction of the mid to outer 1/3rd of cornea

Antianginal: Amiodarone Ocular SE

- generally visible keratopathy develops in most Px within 6 weeks after drug initiation and reach peak within 3-6 months
- minimal deposition in Px on a dose of 100-200 mg/day though 400 mg or more will have all Px show deposit
- will see regression in 3-7 months after discontinuation
- other complications include:
  - decreased VA,
  - color vision defects,
  - photosensitivity,
  - dry eyes,
  - decreased corneal sensation,
  - optic neuropathy and pseudotumor.

Antidepressants

- Includes:
  - Tricyclic antidepressant (TCA): amitriptyline, nortriptyline (Elavil, Levate) (inexpensive medication)
  - Selective serotonin re-uptake inhibitors (SSRI): fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft) (all of these are very expensive medications!)
  - monoamine oxidase (MAO): isocarboxazid (Marplan)
Antidepressants - TCA’s

- TCA’s block both norepinephrine and serotonin re-uptake thus increasing the levels in the synaptic cleft
- Results in increased mood, improved mental alertness, increased physical activity and decreased morbid preoccupation

Antidepressants - TCA’s

- Adverse SE’s: urinary retention, constipation, epilepsy, dry mouth, sedation, orthostatic hypotension
- Ocular SE’s: blurred vision, mydriasis, and increased risk of glaucoma (narrow angle, angle closure)

Antidepressants - SSRI

- SSRI: specifically inhibit serotonin re-uptake with little muscarinic, alpha-adrenergic or H1 blocking
- Relatively safe so preferred for prevention of overdose
- 2-3 weeks to improve mood and function
Antidepressants-SSRI

- Adverse SE: GI upset, weakness, sexual dysfunction, sleep disturbances, and potential drug interactions
- Ocular SE: mydriasis, decreased accommodation (blurred vision), and infrequently conjunctivitis, photophobia, diplopia, eye pain

Antidepressants-MAO

- MAO is a mitochondrial enzyme that inactivates any excess neurotransmitter molecules. MAO inhibitors increase the amount of nt in the synaptic cleft.
- Use of MAO inhibitors is limited due to complicated dietary restrictions.

Antidepressants-MAO Inhibitors

- Adverse SE: Px receiving MAO inhibitors are unable to degrade tyramine found in aged cheeses, chicken etc resulting in HA, tachycardia, nausea, HTN, stroke.
- Ocular SE: mydriasis, decreased accommodation (blurred vision), and infrequently conjunctivitis, photophobia, diplopia, eye pain
Antidepressants: Summary of Ocular Side Effects

- decreased or blurred vision
- decreased or paralysis of accommodation
- mydriasis which may precipitate narrow angle glaucoma
- decreased or absent reaction to light
- increased symptoms of dry eye

Antidepressants: Summary of Ocular Side Effects

- most of the side effects are transient, reversible, and cause little clinical significance
- most common side effects is blurring of vision which is generally mild and transient (improves with sustained use of medication)
- mydriasis can be a concern in patients with NAG or narrow angles
- diplopia and nystagmus have been reported though generally in patients who are currently using other agents such as lithium or diazepam

Corticosteroids (Glucocorticoids)

- Glucocorticoids promote normal metabolism (e.g. glucogenesis, protein catabolism), increase resistance to stress, alter blood cell levels (e.g. decrease eosinophils, basophils, monocytes and lymphocytes), and have anti-inflammatory action.
Corticosteroids (Glucocorticoids)

- Systemically corticosteroids are effective in:
  - replacement therapy
  - treatment of inflammatory and allergic disorders.
  - topically used to relieve inflammatory and pruritic dermatoses.

Corticosteroids (Glucocorticoids)

- Corticosteroids include: cortisone, dexamethasone, fluorometholone, hydrocortisone, medrysone, prednisolone, prednisone.
- Brand names include Beconase, Beclovent, Decadron, Dexasone, Solu-Medrol, Kenalog, etc.
- Ophthalmic solutions include AK-Dex, Decadron, Maxidex, Flarex, FML, AK-Pred, Econopred, Inflamase Forte/Mild, Pred Forte/Mild, etc.

Corticosteroids- Systemic SE

- Systemic administrations can result in:
  - Osteoporosis
  - Increased appetite
  - Emotional disturbances
  - Hypertension
  - Edema
  - Peptic ulcers
  - Increased risk of infection
Corticosteroids - Ocular SE

- Systemic use can result in:
  - PSC cataracts
  - Increased IOP
  - Delayed wound healing
  - Decreased resistance to infection
  - Visual hallucinations
  - Subconjunctival/retinal hemes and edema
  - Papilledema

Corticosteroids: Ocular SE

- Ocular SE due to systemic or ocular administration are common and have significant clinical importance.
- The idea of "safe" steroids is questionable as there has been shown no significant correlation between Px taking oral steroids and PSC cataracts based on total dosage. However, PSC cataracts do result from steroid use in those susceptible Px, though don’t know who is a susceptible Px! Even excessive use of nasal inhalation steroids can result in PSC formation.

Corticosteroids: Ocular SE

- Race is important as steroid induced glaucoma is more frequent in whites than blacks, and depigmentation from SC injection is more frequent in blacks.
- Steroid IOP responders tend to have more field loss than non-responders.
- Steroids affect all ocular structures resulting in development of steroid induced glaucoma, PSC cataracts, enhanced HSK infections, decreased wound healing, band keratopathy, etc.
Estrogen Receptor Antagonist-Tamoxifen

- Tamoxifen is used in the treatment of breast cancer (normal breast tissue stimulated to grow by estrogens, so estrogen antagonists can result in tumor regression)
- The most common adverse affects include: hot flashes, nausea, and vomiting. Menstrual irregularities and vaginal bleeding can also occur.

Estrogen Receptor Antagonist-Tamoxifen- Ocular SE

- Significant visual loss can occur with tamoxifen. Stopping Tx usually prevents further deterioration but may not result in visual recovery.
- Tamoxifen retinopathy characterized by presence of refractile bodies (due to axonal death).
- Additional findings may include CME, macular and peripheral retinal RPE changes, parafoveal hemes and subepithelial corneal deposits.

Antihistamines

- Antazoline, pyrilamine, tripelemamine (available in multiple ophthalmic drops)
- Azatadine, cyproheptadine (Optimine, Periactin)
- Chlorpheniramine, dimethindene, pheniramine (Chlor-Tripolon, Contac Allergy, PediaCare Allergy)
- Carbonoxamine, clemastine, diphenhydramine (Allerdryl, Benadryl, Insomnal, Sleep-Eze D)
- Used in the symptomatic relief of allergic or vasomotor rhinitis, allergic conjunctivitis and allergic skin problems
Antihistamines: Ocular SE

- Systemic use of the medications have a weak atropine action that accounts for the pupillary changes. With chronic use, anisocoria, decreased accommodation, and blurred vision can also occur.
- There has also been evidence to demonstrate a decrease in tear production making Px symptomatic for dry eyes and CL intolerance.

Tamsulosin (Flomax)

- Used to treat prostate enlargement and improve urinary flow in men (urologists are treating women with this drug).
- The well-known syndrome, intraoperative floppy iris syndrome, used to occur only in men but now has to be a concern for women who may also be taking the medication.
- Even if the drug is discontinued, the patient is at a lifetime risk of more complicated cataract surgery.

Topiramate (Topamax)

- Used for the treatment of:
  - seizures,
  - epilepsy,
  - migraine prophylaxis,
  - bipolar and post-traumatic stress disorders, and neuralgias.
- used off-label to control binging and purging, and to promote weight loss in people with eating disorders.
Topiramate (Topamax) Ocular Side Effects

- acute angle closure glaucoma,
- ocular pain,
- headache,
- hyperemia,
- mydriasis,
- iritis,
- visual field defects,
- acute onset myopia, suprachoroidal effusions,
- blepharospasm,
- retinal hemorrhage and
- scleritis

Sildenafil citrate (Viagra) and tadalafil (Cialis)

- Prescribed for men with erectile dysfunction. These drugs divert blood flow away from the head.
- They cause two problems:
  - can cause blue vision, because they interfere with neurotransmission within the retina. That is fortunately not a permanent side effect.
  - The other possible side effect is ischemic optic neuropathy.
- The evidence that there is a cause-and-effect relationship is tenuous.