THE 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
  - Antibiotics
  - Steroids
  - Tamoxifen
  - Antihistamines
  - Flomax
  - Topamax
  - Viagra/Cialis

What Factors Increase the Risk – Product Specific Variables

- **Amount of Drug Administered**
  - All medications have potential for toxicity if given in excessive amounts.
  - Long term use of therapeutic doses over time increase the risk of toxicity.

- **Nature of the Drug**
  - Ease of absorption into systemic circulation.
  - Ability to penetrate the blood-brain, blood-aqueous, and blood-retinal barriers.
  - Absorption by ocular tissues such as melanin.

- **Route of Administration**
  - Highest levels of adverse effects have been seen with oral administration (over inhaled, intranasal, etc.)

What Factors Increase the Risk – Patient Specific Risks

- **Pathophysiologic Variables**
  - Liver and Kidney Function
    - **Age and Sex**
      - More common in the very young or the very old.
      - More adverse drug reactions are reported in women than in men.

- **History of Allergy to Drugs**
  - Adverse reactions are always more likely in a patient who has had a history of previous trouble.

- **Individual Idiosyncrasy**
  - Factors such as enzymatic differences, muscle mass, etc.
  - Altered tissue responsiveness to a medication is likely hereditary.

What Factors Increase the Risk?

- **Drug Interactions**
  - Incidence of ADR’s is directly related to the number of drugs administered.
  - Always important to specifically ask about social habits, supplements, etc.
Antimalarials
- hydroxychloroquine or Plaquenil
- hydroxychloroquine more common and less toxic than more effective chloroquine
- 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

Question
Which of the following depicts a retina undergoing hydroxychloroquine toxicity?
- ARMD
- Macular Hole
- OHS
- Bull’s Eye Maculopathy

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

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.

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

“Ideal” body weight versus “real weight” recommended for dosing and at <6.5 mg/kg.

2016 Recommendations

- Maximum daily HCQ use of 5.0 mg/kg real weight, which correlates better with risk than ideal weight.
- Risk of toxicity is dependent on daily dose and duration of use.
  - At recommended doses:
    - Risk of toxicity up to 5 years is under 1%
    - Up to 10 years is under 2%
    - Rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

Primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT).
- Most patients of Asian descent will show initial damage in a more peripheral extramacular distribution near the arcades (require a 24-2 as opposed to 10-2 and OCT scans need to be analyzed further out).
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

Paracentral Scotomas

Normal Retina: VF/OCT/ERG

Mild Maculopathy

Bull’s Eye Maculopathy

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PIL=PR Integrity Line

TD-OCT

SD-OCT

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Major Risk Factors

<table>
<thead>
<tr>
<th>Table 1. Major Risk Factors for Toxic Retinopathy</th>
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<tbody>
<tr>
<td>Daily dosage</td>
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<tr>
<td>Duration of use</td>
</tr>
<tr>
<td>Renal disease</td>
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<tr>
<td>Concomitant drugs</td>
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<tr>
<td>Muscle disease</td>
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CQ = chloroquine; HCQ = hydroxychloroquine.

Screening Recommendations

<table>
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<th>Table 2. Screening Frequency</th>
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<tr>
<td>Baseline Screening</td>
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<tr>
<td>Fundus examination within first year of use</td>
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<tr>
<td>Add visual fields and SD OCT if maculopathy is present</td>
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<tr>
<td>Annual Screening</td>
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<tr>
<td>Begin after 5 yrs of use</td>
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<td>SD OCT = spectral-domain optical coherence tomography</td>
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Tetracyclines

- 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)
    - In Canada: Apprilon (30 mg doxy + 10 mg slow release doxy)
- 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 patients (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
- Generally visible keratopathy develops in most patients 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 deposits
  - Will see regression in 3-7 months after discontinuation
- Other complications include:
  - Decreased visual acuity (VA)
  - Color vision defects
  - Photosensitivity
  - Dry eyes
  - Decreased corneal sensation
  - Optic neuropathy
  - 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
- Adverse SE: urinary retention, constipation, epilepsy, dry mouth, sedation, orthostatic hypotension
- Ocular SE: blurred vision, mydriasis, and increased risk of glaucoma (narrow angle, angle closure)

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 Inhibitors
- Adverse SE: Pxs 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
- Most of the side effects are transient, reversible, and cause little clinical significance.
- Most common side effects are 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.
- Increased symptoms of dry eye.

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

### 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, more common in POAG and 1st degree relatives of POAG patients, higher risk in younger children and typically presents 4-6 weeks after initiation of steroid.
- 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: 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**

- include:
  - acute angle closure glaucoma,
  - ocular pain,
  - headache,
  - hyperesthesia,
  - mydriasis,
  - uveitis,
  - visual field defects,
  - acute onset myopia, suprachoroidal effusions,
  - blepharospasm,
  - retinal hemorrhage and
  - scintis

**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.
Sildenafil citrate (Viagra) and tadalafil (Cialis)

- The other possible side effect is ischemic optic neuropathy.
- The evidence that there is a cause-and-effect relationship is tenuous.

Retinoids: Isotretinoin

- Retinoids are analogues of Vitamin A used because of their ability to damage rapidly dividing cells.
  - Isotretinoin (Sotret, Claravis, Amnesteem, Generics, Formerly known as Accutane) is the most commonly prescribed Retinoid used in the control of severe acne or various keratinizing dermatoses.
  - It was originally developed as a chemotherapy agent.
- MDA: Temporarily suppresses the sebaceous gland activity, altering the surface lipid composition on the skin, and inhibiting keratinization.

Isotretinoin

- Very frequent cause of ocular side effects.
- Complications generally begin within 4 weeks of starting the medication, and will resolve approximately 4 weeks following discontinuation.
- Symptoms are dose related.

Isotretinoin and Blepharoconjunctivitis

- Severity can vary, but may lead to corneal involvement and blurry vision.
- Nearly all patients will experience difficulty with Contact Lenses.
  - Need to reduce wearing time.
- Treatment is Artificial Tear Supplementation:
  - Which type would you recommend?

Isotretinoin

- Most commonly affects the anterior segment, but also known as a “certain” cause of nyctalopia.
  - It is believed that the drug becomes incorporated into the rod photoreceptors, thus causing dark adaptation to become reduced.
- Recommend following patients with VF testing, dark adaptometry, and ERG.
Retinoids/Isotretinoin

- Intracranial HTN (Pseudotumor Cerebri)
  - Can be caused by Vitamin A itself or the derivatives such as Isotretinoin.
  - Retinoids are one of the two main categories of drugs that result in increased intracranial pressure.
  - Second major drug class is the tetracycline derivatives, especially minocycline.
  - Risk increases if tetracyclines are used in combination with retinoids.

Ethambutol

- Bacteriostatic, antimycobacterial medication used in the treatment of tuberculosis.
- Recommended to be given in combination with first line treatment Isoniazid, Rifampin, and Pyridoxine until drug susceptibility has been determined.

Ethambutol

- Primary Ocular Manifestation: Retrobulbar Neuritis
  - Two forms resulting from toxicity:
    - Most Common: Central with loss of VA and color vision
    - Less Common: Peripherally with contraction of VF
  - Also, can have retinal findings such as ONH swelling, hemes, and macular edema = RARE.
- MOA: Damage to the amacrine and bipolar cells (Not fully understood)
- Earliest finding is often loss of contrast sensitivity, followed by color vision.
  - Isoniazid is also known to cause optic neuritis, but in much less frequent numbers.

Ethambutol

- Deterioration will continue even if ethambutol is discontinued.
- Largely affected by dosage:
  - Recommended levels should not exceed 15 mg/kg daily.
  - Can tolerate higher levels for no longer than 2 months to prevent optic nerve damage.