THE TOP 10 MEDICATIONS AND THEIR OCULAR SIDE EFFECTS

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Disclosures:

- Sun Pharmaceuticals: speakers bureau,
- Avellino: advisory board,
- Dompe: advisory board,
- RVL Pharmaceuticals: advisory board

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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
  - Topemax
  - Viagra/Cialis

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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.)

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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.

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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.

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Antimalarials

- hydroxychloroquine or Plaquenil
- hydroxychloroquine more common and less toxic than more effective chorloquine
- 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

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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.

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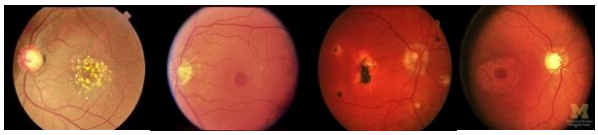
Question

Which of the following depicts a retina undergoing hydroxychloroquine toxicity?



ARMD | Macular Hole | OHS | Bull's Eye Maculopathy

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Treatment and Management: 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

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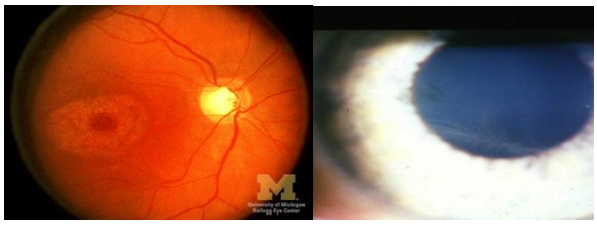
Treatment and Management: Antimalarials



Bulls Eye Maculopathy | Whorl Keratopathy

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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.

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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

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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
- "Ideal" body weight versus "real weight" recommended for dosing and at <6.5 mg/kg

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"New" New Recommendations

- **Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy** – Ophthalmology 2016; 123:1386-1394
  - Released March 2016 from American Academy of Ophthalmology
  - revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

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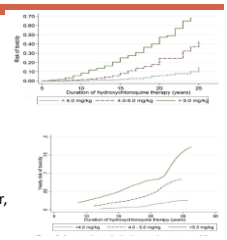
2016 Recommendations

- 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.



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2016 Recommendations

- High dose and long duration of use are the most significant risks.
  - Other major factors are concomitant renal disease, or use of tamoxifen
- A baseline fundus examination should be performed to rule out preexisting maculopathy.
- Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

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2016 Recommendations

- 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)

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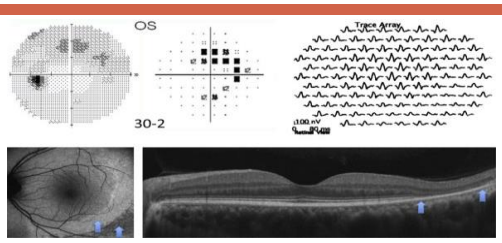

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Revised Recommendations on Screening for Retinopathy

- 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

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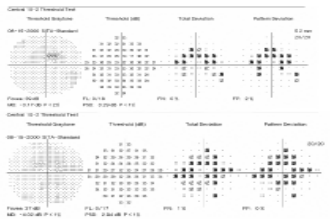
Paracentral Scotomas



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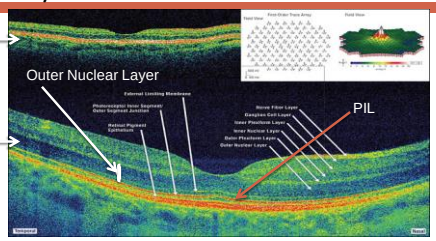
Normal Retina: VF/OCT/ERG



Rodriguez-Padilla, J. A. et al. Arch Ophthalmol 2007;125:775-780.

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PIL=PR Integrity Line

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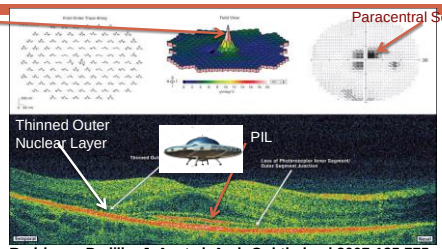
Mild Maculopathy



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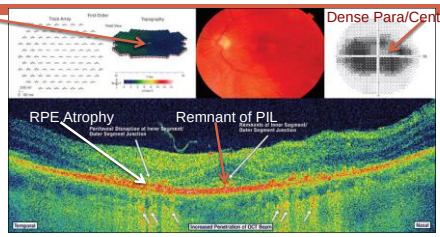
Bull's Eye Maculopathy



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Major Risk Factors

Table 1. Major Risk Factors for Toxic Retinopathy

Daily dosage	
HCQ	>5.0 mg/kg real weight
CQ	>2.3 mg/kg real weight
Duration of use	>5 Yrs, assuming no other risk factors
Renal disease	Subnormal glomerular filtration rate
Concomitant drugs	Tamoxifen use
Macular disease	May affect screening and susceptibility to HCQ/CQ

CQ = chloroquine; HCQ = hydroxychloroquine.

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Screening Recommendations

Table 2. Screening Frequency

Baseline Screening
Fundus examination within first year of use
Add visual fields and SD OCT if maculopathy is present
Annual Screening
Begin after 5 yrs of use
Sooner in the presence of major risk factors

SD OCT = spectral-domain optical coherence tomography.

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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.**

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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**

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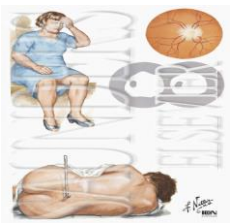
Tetracyclines: Ocular SE

- 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.



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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.

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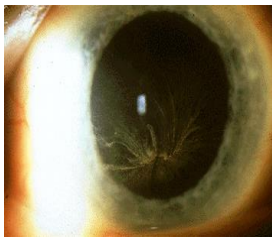
Antianginal: Amiodarone Ocular SE

- 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



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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.

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Antidepressants

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

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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
- increased symptoms of dry eye

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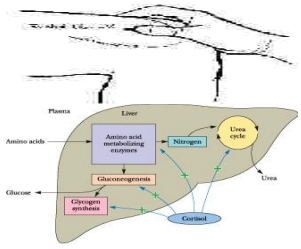
Corticosteroids (Glucocorticoids)

- 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.



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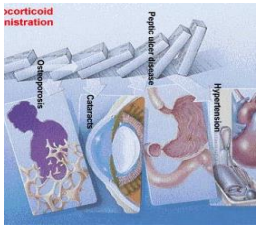
Corticosteroids- Systemic SE



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

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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

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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.

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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.

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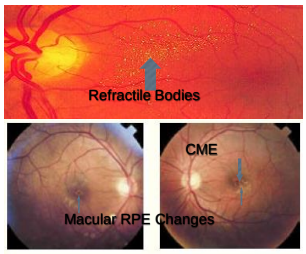
Estrogen Receptor Antagonist-Tamoxifen-Ocular SE

- 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.



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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.

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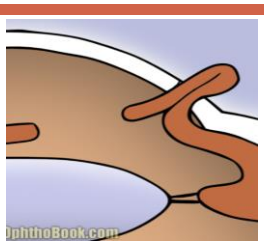
Tamsulosin (Flomax)

- 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.



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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

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Topiramate (Topamax) Ocular Side Effects

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

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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.

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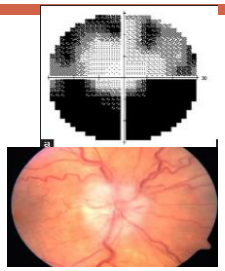
Sildenafil citrate (Viagra) and tadalafil (Cialis)

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



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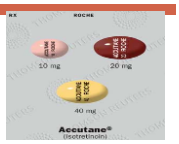
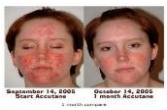
Retinoids: Isotretinoin

- 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.
- MOA: Temporarily suppresses the sebaceous gland activity, altering the surface lipid composition on the skin, and inhibiting keratinization.





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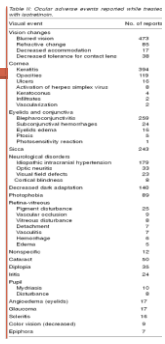
Isotretinoin

- 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.



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Isotretinoin

- Major Ocular Side Effect: Alteration of Meibomian Gland Secretions
  - Gland atrophy frequently develops which is beneficial for the treatment of acne, but harmful for the ocular surface.
  - Decreased Volume with Increased Thickness
  - Results in:
    - High levels of tear evaporation
    - Increased Tear Film Osmolarity
    - Ocular Discomfort
- Most Common Ocular Finding in 20-50%:
  - Blepharoconjunctivitis

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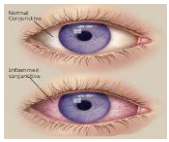
Isotretinoin and Blepharoconjunctivitis

- 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?



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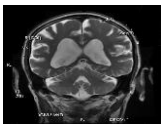
Retinoids/Isotretinoin

- 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.



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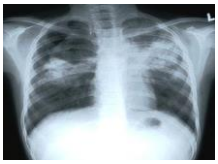
Ethambutol

- 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.



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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.

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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.

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