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Disclosures

- Aerie Pharmaceuticals
- Alcon
- Biotissue
- DiopsysMacuLogix
- Ivantis
- Nidek
- Nova Oculus
- Optovue
- Quantel
- Reichert
- RevolutionEHR Shire
- Shire

Why is the Eye at Risk?

- Rich blood supply.
 - Systemic Drugs can reach the eye via the uveal and retinal blood vessels.
- Relatively small mass.
- Ocular tissues can act as drug reservoirs, enhancing the potential for toxicity.

Why is the Eye at Risk?

- Ocular Adverse Drug Reactions (OADR's) are more commonly noticed than the mild reactions that occur elsewhere in the body.
 - Tissues are associated with functions that patients are aware of.
 Ex) Change of Acuity, Ptosis, Diplopia,
 - Ex) Change of Acuity, Ptosis, Diplopia, Color Vision Changes, etc.
 - Structures are prominent and easy to view without highly invasive procedures.



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 Gender
- 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.



The Major Pharmaceutical Offenders

- Corticosteroids
- Tetracyclines
- Plaquenil
- Amiodarone
- Topamax (Topiramate)
- Viagra/Levitra/Cialis
- Flomax
- Isotretinoin

- Fosamax
 - Ethambutol • Anticoagulants
 - Interferons
 - Beta-Blockers
 - Antihistamines
 - Sulfonamides
- Many, many more....
- Tamoxifen

Plaquenil Toxicity

- Antimalerials:
 - Chloroquine
- Hydroxychloroquine (Plaquenil)
- Now used for RA, SLE, Sjogren's, etc.
- Toxicity risk is low, but....
- Lots of different screening recommendations have been proposed

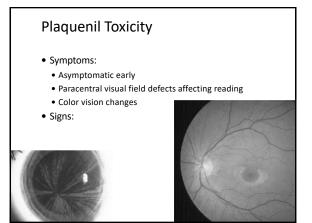
Plaquenil Toxicity

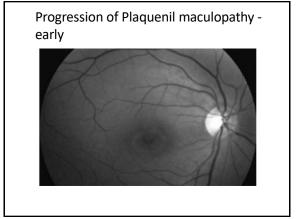
- Risk Factors:
- Cumulative dose**
- 1000 gram cumulative dose for Plaquenil
- 6.85 years to reach that
- Daily dose
- Age
- Liver or kidney dysfunction
- Pre-existing retinal disease or maculopathy

Risk Factors

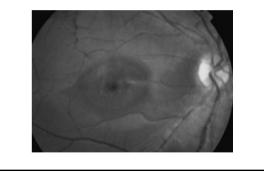
- Max safe dose = 5 mg/kg/day • 80 kg weight = 400 mg/day
 - 175 lbs
 - Typical dose = 200 mg bid



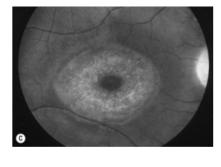




Progression of Plaquenil maculopathy - moderate



Progression of Plaquenil maculopathy - advanced



Plaquenil Toxicity

- Recommended Screening Guidelines:
 - 1. Baseline exam within the first year of starting Plaquenil
 - Biomicroscopy exam, 10-2 VF, Fundus photos
 - After 5 years, annual screening exams
 - SD-OCT or
 - mfERG or
 - Fundus autofluorescence

When is your Next exam?

• 5 years later!

• Unless in a high risk group - annual (or more) exams

What's high risk?

- Exceeds max dose based on weight
- Kidney disease
- Tamoxifen use (5x retinopathy risk)
 Concurrent macular disease (AMD, etc)



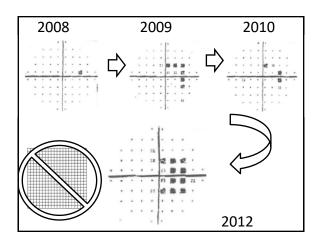
• Liver disease and age no longer considered risk factors

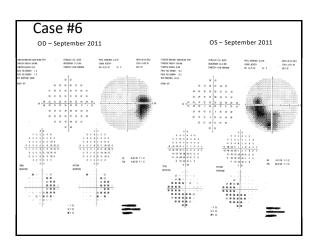
When is your Next exam?

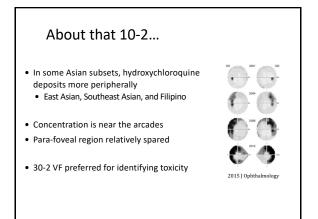
5 years later!

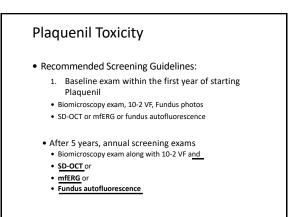
- Unless in a high risk group annual (or more) exams
- Maculopathy < 1% in low risk
- 2% at 10 years
- 20% at 20 years with + 4% for every additional year

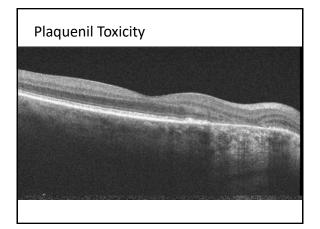
Plaquenil Toxicity Recommended Screening Guidelines: Baseline exam within the first year of starting Plaquenil Biomicroscopy exam, 10-2 VF, Fundus photos After 5 years, annual screening exams 10-2 VF and SD-OCT or mfERG or Fundus autofluorescence

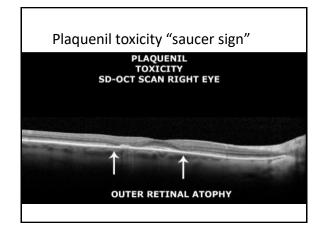


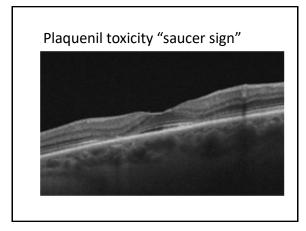


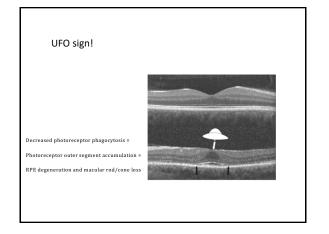


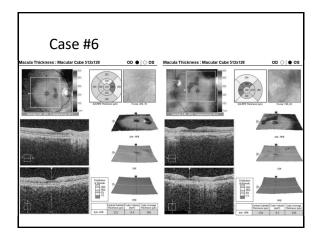


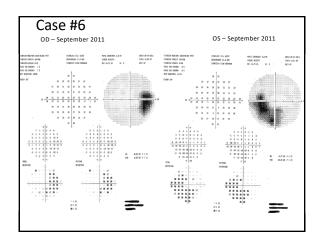












Fundus Autofluorescence & mfERG

Animal Weight Constrained State of State Announces of State Annou

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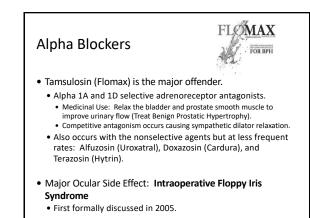


Plaquenil Toxicity

- Tests not recommended for screening
- Fundus photography
- Time-domain OCT
- FA
- Full-field ERG
- EOG
- Color vision testing
- Amsler grid

Plaquenil Toxicity

- Treatment:
 - No medical therapy is available to treat/cure the toxicity
 - D/C the med if possible
 - Work with the PCP



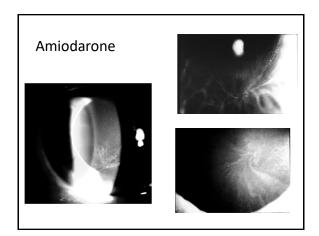
Tamsulosin (Flomax)



- Mechanism of Miosis = blockage of the iris dilator muscle causing diffuse atrophy of the smooth muscle.
 - Thus effects may continue even after d/c of the medication.
- Results in Significant Problems during Cataract Surgery:
 Flaccid iris stroma that billows on irrigation
 - Fraccia iris stroma that billows on irrigation
 Tendency of the iris to prolapse toward the side port incisions and
 - phaco tip
 - Progressive intraoperative miosis despite pharmacological dilation.
- Must screen all of your pre-operative patients.

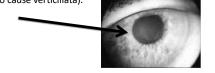
Amiodarone (Cordarone or Pacerone)

- Amiodarone is an antiarrhythmic used to treat cardiac arrhythmias by relaxing overactive heart muscles.
- Major ocular side effect: Whorl Keratopathy (Corneal Verticillata or Vortex Keratopathy)
 - Corneal changes occur in 69 100% of patients
 - Epithelial changes usually present within 1-4 months of drug usage.
 - Severity of keratopathy has direct relation to total drug dosage.
 - Findings are bilateral, but often asymmetric.
 - Resolves 3 -20 months after D/C med.
 - Usually pts are asymptomatic, but if severe can get reduced VA, glare, and halos.



Amiodarone

- MOA: Amiodarone binds to polar lipids and accumulates within lysosomes. These complex lipid complexes deposit in the cornea mimicking a lipid storage disease.
- Big DDx: Fabry's Disease, chloroquine, indomethacin (all can also cause verticillata).



Additional SE's of Amiodarone

• Lens:

- 50% of patients receiving moderate to high dosages (600 to 800 mg daily) will have fine anterior subcapsular lens deposits.
 - Deposits develop at the same time as the corneal changes.
- Possibly linked to light exposure Amiodarone is a photosensitizer and the lens changes are often limited to within the pupil boundaries. · Generally cause no visual symptoms.

Optic Nerve Head:

- Estimated levels are approximately 2% of patients. Cause of NAION (non-arteritic ischemic optic neuropathy), but unlike the typical vascular causes of NAION this has an insidious onset, slow progression, and bilateral vision loss.
- ONH swelling is long-standing and will stabilize within months of d/c medication.

Sildenafil (Viagra)



- Phosphodiesterase 5 (PDE 5) inhibitors used for the management of Erectile dysfunction and pulmonary hypertension:
- Viagra is the most commonly prescribed and studied, but Tadalafil (Cialis) and Vardenafil (Levitra) are also known to cause these adverse reactions.
- Enzyme PDE-5 plays a role in the degradation of cyclic GMP. Inhibiting the enzyme allows for relaxation of the smooth muscles in the blood vessels that supply the penis and lungs.
- Inhibits PDE-5 with 10X more affinity, but also show some effect on PDE-6, which is found in the retina and acts on retinal phototransduction.
 - Likely, results in some of the visual side effects.

Sildenafil (Viagra): **Accepted Side Effects**



- Confirmed Ocular side effects are dose dependent: • Those taking 200mg of Viagra have a 50% chance of ocular side
 - effects. • Those taking 50 mg (normal dose), less than 5% chance.
 - "Confirmed" ocular side effects occur in ~10% of patients taking 100
 - mg.
 - Known Findings Include:
 - Mild color vision defects
 - · Bluish-tinge to vision
 - Also have reports of pink or yellow tinge.
 Blurred vision, flashing lights, increased photosensitivity.
- Most of these visual symptoms last several minutes to a few hours.

Sildenafil (Viagra): Possible Side Effect

- Non-arteritic anterior ischemic optic neuropathy (NAION)
 - This was not reported during clinical trials, but has been a big concern in recent years.
 - At the current time, the WHO does not believe the correlation is strong enough to discourage use of the medications.
 - Frequency of NAION does not appear to be related to dosage and they have been unable to find the mechanism for the damage to occur.

Sildenafil (Viagra)

- Ocular SE's may be linked to the blood pressure lowering capabilities of this medication and the activity level following use of the medication, more so than the medication itself.
 - If a pt has a "disc at risk" and/or low BP may need to consider D/C patient off of Viagra due to NAION risk.
- Viagra has also been linked to vascular events in the retina and subconjunctival hemorrhages.

Topiramate (Topamax)

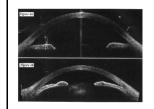
- Antiepileptic medication used off label for the treatment of migraine headaches and bipolar disorder.
- Also a component of the weight loss drug Qsymia.



Topiramate (Topamax and Qsymia)

- Major ocular side effect:
 - Uveal Effusion syndrome
 - Swelling and anterior rotation of the CB which causes the lens-iris diaphragm to move forward and the anterior chamber to shallow = acute angle closure glaucoma.
 - Topiramate is a sulfa-based derivative, and much like the sulfa antibiotics this can cause a myopic shift (6-8 diopters).
 - Sulfa Derivative (likely MOA behind ocular SE's involves hypersensitivity reaction).
- Topiramate has also been linked to choroidal effusion and detachments.

Topiramate (Topamax)



- Almost always bilateral***
- 85% occur within first 2 weeks of treatment initiation.
- Etiology -> possible inflammatory mechanism.
 LPI is not an effective treatment.
- Responds poorly to ocular hypotensives.

Antineoplastic Agents: Tamoxifen



- Tamoxifen citrate (Nolvadex) is a nonsteroidal antiestrogen used in the treatment of metastatic breast cancer.
- Adverse ocular drug reactions have been seen in 6.3% of patients prescribed.

Antineoplastic Agents: Tamoxifen

- Tamoxifen Retinopathy: Yellow, white refractile opacities mainly of the macular and perimacular area.
 - May be found with or w/out macular edema.
- High dose tamoxifen therapy has been proposed to cause axonal degeneration in all the levels of the sensory retina and the refractile opacities are the by-products.





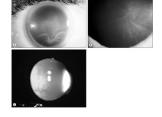
Antineoplastic Agents: Tamoxifen

- Retinopathy is rare at low dosages (0.9% if 20 mg daily).
- Often the level of retinopathy is asymptomatic.
- Low dosages also show greater reversibility.
- High dose levels (90-120 mg BID) often result in toxicity within 1-2 years of use once levels have reached 90 grams.



Antineoplastic Agents: Tamoxifen

• Rarely and at high doses, Tamoxifen is also capable of producing corneal findings similar to that of amiodarone or hydroxychloroquine.



Pseudotumor Cerebri

- AKA
 - Idiopathic intracranial hypertension
- Elevated intracranial pressure
 - Not caused by tumor, infection, or obstruction of the ventricular system
 - Increased production vs. decreased absorption
- Etiology:
 - Idiopathic (young, obese females)
 - Medications
 - · ???
 - Trauma

Pseudotumor Cerebri

AKA

- Idiopathic intracranial hypertension
- Elevated intracranial pressure
 - Not caused by tumor, infection, or obstruction of the ventricular system
 - Increased production vs. decreased absorption
- Etiology:
 - Idiopathic (young, obese females)
 - Medications
 - Oral contraceptives, Tetracyclines, too much vitamin A
 - Trauma

Pseudotumor Cerebri

■ Symptoms:

- HA's (90-98%)
- Visual disturbances (72%)
- Transient visual obscurations (TVO's)
- Tinnitus (20-60%)
- N&V (30-40%)
- Diplopia (20-30%)
- Blurred vision
- Abnormal color vision rare

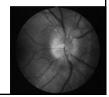
Pseudotumor Cerebri

Signs

- Papilledema hallmark sign of PTC Increased intracranial pressure -> slowing axonal transport -> accumulation of axonal contents in the NFL -> elevated ONH's
- Bilateral disc edema
- Blurred disc margins
- Obscuration of blood vessels*
- Hyperemia of the disc
- Venous dilation
- Peripapillary hemorrhages & CWS
- Paton's lines

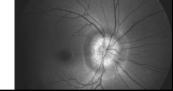
Pseudotumor Cerebri

- Other signs
 - Enlarged blind spot
 - 6th nerve palsy
 - Tends to subside as treatment is effective



Pseudotumor Cerebri

- Differential Diagnosis:
 - Intracranial tumor/mass
 - Intracranial bleed
 - Hydrocephalus
 - Venous sinus thrombosis
 - IIH



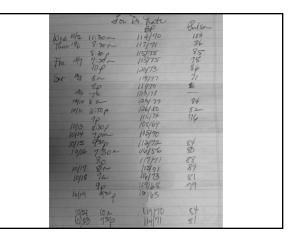
Pseudotumor Cerebri Pseudotumor Cerebri Diagnosis: Treatment: Clean MRI/MRV Weight Loss* Lumbar puncture Papilledema resolution with weight loss of 6% of total Elevated ICP > 250mmH₂0 in an obese pt body weight > 200mmH₂0 in a non-obese pt • Normal CSF composition Diamox (acetazolamide) • 500 mg Sequels BID-QID Taper as the sx's stabilize No other neurological findings Exception -> 6th nerve palsy Lumbar-peritoneal shunt (CSF shunting) SVP Optic nerve sheath fenestration/decompression • Yes -> not Pseudotumor • No -> ?????

Non-arteritic Ischemic Optic Neuropathy (NAION)

- Lack of perfusion to the ONH or embolic disease that affects the arteries/arterioles that supply the ONH
- Mean age of onset = 61-66 years old

Associated risk factors:

 HTN, atherosclerosis, DM, nocturnal hypotension, sleep apnea



Non-arteritic Ischemic Optic Neuropathy (NAION)

• SYMPTOMS:

- Sudden, unilateral, painless loss of vision
- "I woke up and I can't see out of this one eye"

Non-arteritic Ischemic Optic Neuropathy (NAION) □ <u>SIGNS</u>: Diffuse or segmental disc edema Peripapillary flame-shaped hemes Retinal arterial attentuation

- (+) APD
- VF defect often inferior altitudinal
- What does the other eye look like? • Small nerve?

 - Small cup?

Non-arteritic Ischemic Optic Neuropathy (NAION)

DIAGNOSIS:

- Normal ESR & CRP • (-) symptoms of GCA
- DIFFERENTIAL DIAGNOSIS:
 - AAION
 - Papilledema
 - Brain tumor do a VF



- unilateral.....
- guarded.....but it depends on many factors

Non-arteritic Ischemic Optic Neuropathy (NAION)

<u>TREATMENT:</u>

- No proven effective treatment
- Options?
- Aspirin
- Lower IOP??
- Intraocular VEGF treatment

Prognosis:

- unilateral.....
- guarded.....but it depends on many factors

Giant Cell Arteritis

- Chronic inflammatory disorder affecting the medium-large sized cranial blood vessels
- Inflammatory mediators cause:
- proliferation, thickening, and fibrosis of vessel walls -> inflammatory occlusion
- Risk factors:
 - Age
 - Females
 - Scandinavian
- Accounts for 6% of ischemic optic neuropathy cases

Giant Cell Arteritis

- Symptoms:
 - New onset HA
 - Jaw claudication
 - Scalp tenderness/pain
 - Flu-like sx's/weight loss
 - Pain and stiffness in the shoulders, hips, torso Polymyalgia Rheumatica (PMR)
 - Sudden, severe, painless vision loss
 - Usually unilateral
 - Diplopia

Giant Cell Arteritis

- Signs:
 - Sudden, severe, painless vision loss
 - (+) APD
 - Pale, swollen optic disc Flame shaped hemes
 - CWS's
 - CRAO
 - Ocular ischemic syndrome
- EOM problems

Giant Cell Arteritis

Diagnosis:

Clinical symptoms



- Prominent temporal artery Lack of temporal artery pulsation
- CBC with differential & platelets
- ESR males = age/2 females = (age+10)/2
- CRP
- Platelets
- Temporal artery biopsy

Giant Cell Arteritis

- Treatment:
 - Refer
 - IV and/or oral steroids • IV 250 mg i.v. q6h (1g/day) for 3 days and/or
 - Oral 1-2mg/kg/day
 - Baby aspirin
- Prognosis:
 - Extremely poor

Giant Cell Arteritis Tx

- Actemra (tocilizumab) FDA approved for moderate-severe RA
- Sub-Q injection
- Double-blind placebo controlled trial

 - Actemra + standard prednisolone regimens vs. placebo + standard prednisolone regimens vs.
 Primary endpoint proportion of patients achieving sustained remission from week 12 through week 52
 A greater portion of the Actemra + steroid group achieved sustained remission
 The cumulative prednisolone does was lower in trated patients with
 - The cumulative prednisolone dose was lower in treated patients with Actemra compared to placebo
- Boxed warning for serious infections

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.





with lootnetinoin.	
Visual event	No. of report
Isotretinoin Constant Sector Constant Sector	473 85 17 38 394
Very frequent cause of ocular side	119 16 8 4 2 2
effects.	259 24 16 5 1
 Complications generally begin within 4 weeks of starting the medication, and 	243 179 33 23 8 140
will resolve approximately 4 weeks following discontinuation.	89 25 9 8 7 6 5
• Symptoms are dose related.	12 50 35 24 10 8

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 CAUSES BIRTH DEFECTS • Increased Tear Film Osmolarity Ocular Discomfort • Most Common Ocular Finding in 20-50%: Blepharoconjunctivitis

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.





Oral Contraceptives

- Hormonal preparations that may contain combinations of estrogen and progestin or progestin alone to prevent pregnancy.
- Estrogen increases the levels of clotting factors, thereby increasing the risk of blood clots, which is one of the main side effects of their use.



Oral Contraceptives

- Vascular Lesions of the Retina
- Can Include: Retinal Vascular Abnormalities, Occlusions, venous thrombosis, or retinal hemorrhages.



- The UK did a large study of 63,000 women and found a notable increase in risk of retinal vascular lesions for patients on oral contraceptives.
 - Risk further increases with patients who are smokers.

Oral Contraceptives

- Additional Ocular Concerns:
 - Reduced Tear Production
 - Lacks well-documented studies, but a common clinical finding.
 - Estrogenic and androgenic receptors exist on the conjunctival and corneal surfaces.
 - Imbalance leads to symptoms of ocular surface dryness.
- Pseudotumor Cerebri



Tetracyclines

- Conjunctival Deposits or Discoloration is a Common Adverse Reaction from Tetracyclines:
 - Dark brown to black granules in the palpebral conjunctiva.
 Very similar in appearance as the granules formed with topical epinephrine.
 - Likely the result of chelation calcium also occurs in the cysts.



Tetracyclines

- Biggest Ocular Concern: Intracranial HTN
- May begin within hours of starting treatment, but often takes months.
- Occurs most commonly with minocycline, and least commonly with doxycycline.
- Minocycline is more lipophilic = better crossing of the blood-brain barrier.
- MOA: Reduce cerebrospinal fluid absorption due to the effect on cyclic adenosine monophosphate of the arachnoid villi.

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.
 - Isoniazid is also known to cause optic neuritis, but in much less frequent numbers.



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.

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.



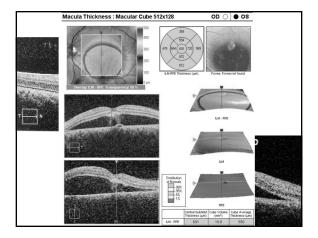
Sabril (vigabatrin)



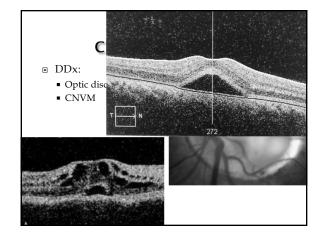
- Medication used in the treatment of seizure disorders.
 Exact mechanism is unknown, but it irreversibly inhibits GABA metabolism.
 - Only used as adjunctive treatment and if success is not noticed must be discontinued.
- Black Box Warning: Causes Irreversible Progressive and Permanent Vision Loss
 - >30% of adults will experience bilateral concentric VF constriction that may lead to decreased visual acuity.
 - Risk increases with total dose and duration of use, but not known to have any safe levels. Loss will continue to occur after discontinuing.

Central Serous Chorioretinopathy (CSR)

- Demographics
 - 25-50 year old men, stressed/Type A personalities
- Symptoms
 - Unilateral, blurred vision
 - VA -> usually 20/20 20/80
 - Metamorphopsia
- Signs
 - Localized serous detachment of the neurosensory retina in the macula







Central Serous Chorioretinopathy

Med associations:

- Steroids
 - Nasal sprays, steroid creams, oral, injectable

Ephedra

• Ephedrine & pseudoephedrine

Treatment:

- Observation/lifestyle change
- D/C steroid if possible
- Possible laser therapy

Questions? Thank You!