

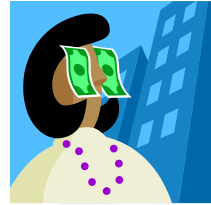
Ocular Side-Effects from Systemic Medications: Case Studies

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Disclaimer:

Dr. Yudcovitch does not hold proprietary financial interest in any of the products or companies mentioned in this presentation.

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Goals

1. Review the most common systemic drugs that can cause ocular complications
2. Recognize key potential ocular side-effects from systemic drugs
3. Reinforce pertinent tests in managing patients taking at-risk systemic drugs

Definitions

Toxic

- Pertaining to, resembling, or caused by poison

Toxicology

- Science concerned with toxic substances, detecting them, their chemistry/pharmacologic actions, antidotes/treatments, and preventing or controlling exposure to them or their harmful effects

ADR

- Adverse Drug Reaction

AODR

- Adverse Ocular Drug Reaction

“At Risk” Patients on Orals

- Polypharmacy
- Seeing multiple providers
- Geriatric/pediatric
- DM
- CHF
- Liver disease
- GI disease
- Kidney disease
- Lung disease
- Smokers
- Alcoholism
- Depression



Oral Meds for Geriatrics

- Metabolism is significantly reduced
- Reduced renal clearance as well
- Reduced muscle mass affects distribution
- Know the other drugs your patient takes
- Watch vitamin supplement effects
- Start with smaller dosage ranges



Dosing Based on Weight

- Need to treat a child's eye infection
- You decide to prescribe erythromycin antibiotic suspension
- Suspension made as 125mg/5ml concentration in a 200ml bottle
- Appropriate pediatric dosage is 20mg/kg/day
- You weigh the child at 50 lb
- We know 1lb = 0.45 kg
- How much mg erythromycin needed per day?



Dosing Based on Weight

$$\frac{50\text{lb}}{X\text{kg}} = \frac{1\text{lb}}{0.45\text{kg}}$$

$$X = 22.5 \text{ kg}$$

$$22.5\text{kg} \times 20\text{mg/kg} = 450\text{mg per day needed}$$

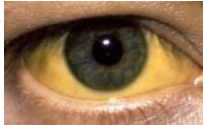
$$5\text{mL}/125\text{mg} \times 450\text{mg} = \underline{18\text{mL}} \text{ per day}$$

(Just for your info, 1mL is 0.2 tsp (teaspoon)
Therefore, 18mL is 3.6 tsp)



Toxicity to the Eyes

- In some cases eye involvement may be minor...but signals development of significant systemic toxicity
- Example: orange-yellow conjunctival discoloration in liver toxicity induced by acetaminophen (Tylenol)



Why is the EYE so often involved in toxic reactions to systemic drugs?

- It is richly vascularized
 - Blood
 - Lymph
- It's tissues associated with functions patients quite 'aware' of
 - Acuity, colour vision, metamorphopsia, diplopia, ptosis, periorbital edema, etc.
- It's structures and functions are prominent and easy to view, largely through non-invasive means



Commonly-Affected Ocular Areas

- Periocular skin, Lids, and Conjunctiva
- Tearfilm and Tear Quality
- Pupil Size and Function
- EOMs/Ocular Stability and Mobility
- Ciliary Body/Accommodation
- Cornea and Crystalline Lens
- Intraocular Pressure (IOP)
- Retina
- Optic Nerve



Systemic Medication Access to the Eye

- Uveal vasculature
- Retinal vasculature
- Drug depots – cornea, lens, retina
- Cholinergic and adrenergic stimuli
- Individual Idiosyncrasy – unexpected reactions



Top 10 Common Ocular Adverse Reaction 'Warnings':

1. "Visual disturbance"
2. "Blur/decreased vision"
3. "Dry eyes/irritation/pain"
4. "Redness"
5. "Pupil dilation/glaucoma"
6. "Focusing difficulty"
7. "Light sensitivity"
8. "Hallucinations"
9. "Double vision"
10. "Color disturbances"

Drug Facts	
Active ingredient (in each tablet)	Purpose
Chloramphenicol ophthalmic drug	Antibiotic
Uses Temporarily relieves these symptoms due to hay fever or other upper respiratory conditions: <ul style="list-style-type: none"> • sneezing • runny nose • itchy, watery eyes • red, itchy eyes 	
Warnings <ul style="list-style-type: none"> • Ask a doctor before use if you have: <ul style="list-style-type: none"> • eye infections • eye conditions such as conjunctivitis or chronic bronchitis. • Avoid contact with eye if eye gets irritated. • Ask a doctor or pharmacist before use if you are taking barbiturates or sedatives. 	
Directions <ul style="list-style-type: none"> • Adults and children 12 years and over: Use 2 tablets every 4 to 6 hours, not more than 12 tablets in 24 hours. • Children 6 years to under 12 years: Use 1 tablet every 4 to 6 hours, not more than 8 tablets in 24 hours. • Children under 6 years: Ask a doctor. 	

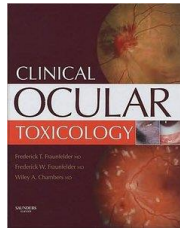
Drug Facts (continued)	
Other information	Keep this and all other medicines out of the reach of children.
Other information Store at 20-25°C (68-77°F). <ul style="list-style-type: none"> • protect from excessive moisture. 	Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. <ul style="list-style-type: none"> • Keep out of reach of children.
Inactive ingredients: Cellulose, No. 10, croscarmellose sodium, hydroxypropyl methylcellulose, polyethylene glycol. <ul style="list-style-type: none"> • Contains parabens. 	

This Course's Med List:

acetaminophen	flunisolide	oxytocone
acetylsalicylic acid	fluorinated quinolones	oxamteronate disodium
aletrinate	fluoxetine	Penicillin
amidofarone	fluticasone propionate	pentosan polysulfate sodium
Atenolol	Ginkgo biloba	phenylephrine
atropine	glucosamine	placipol
auriothioglucose	haloperidol	prilocam
beclomethasone	heiron	prednisone
Carthaxanthine	hydrochlorothiazide	propionic acid
carmustine	hydrocortisone	pseudoephedrine
celecoxib	hydroxychloroquine	quinine
cephalosporins	ibuprofen	ribavirin
certizine	indomethacin	Rifampin
chloramphenicol	interferon alfa-2b	omeprazole
chloroquine	isoniazide	oxitropium
chloropheniramine	isonicotinic acid hydrazide	risdroneate
chlorpromazine	isoretronin	rofecoxib
citalopram	ketorolac	scopolamine
codeine	licorice root	sertaline
cyclosporine	lisinopril	sildenafil
datura (Jimson Weed)	lithium	sirocobin
desloratadine	lorazidone	sulfamethoxazole
dichlorophenamide	lumiracocib	tadalafil
diclofenac sodium	macrolides	talc
digoxin	methamphetamine	tamoxifen
digoxin	methanol	tamsulosin
dipyrone	methotrexate	thioridazine
dofetilone	methylprednisone	trifluoperazine
ethambutol	minocycline	triamcinolone
ethanol	morphine	tetracycline
etidronate	naproxen	tobacco
etidolac	niacin	topiramate
fenofibrate	Nimesulide	valdecoxib
fenofibrate	omega-3	varidenafil
fenofibrate	pegasertan	warfarin

Some Drug Resources:

- *Clinical Ocular Toxicology* (Fraunfelder et al) 8th Ed.
- Up to Date
 - <http://www.uptodate.com>
- Micromedex
 - <http://www.micromedex.com>
- Medscape
 - <http://www.medscape.com/>
- MedlinePlus:
 - <http://medlineplus.gov/>
- Drugs@FDA



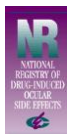
The WHO Causality Assessment Guide of Suspected Adverse Reactions:



- **Unassessable/Unclassifiable**
 - Information insufficient or contradictory; unverifiable
- **Conditional/Unclassified**
 - More data needed for proper assessment
- **Unlikely**
 - Causal relationship improbable; other drugs, chemicals or disease may explain
- **Possible**
 - Drug use timing to reaction linked, but could be explained by disease or other drugs or chemicals
- **Certain**
 - Response to withdrawal of drug (dechallenge) linked
 - Reaction definitive pharmacologically or phenomenologically
- **Probable/Likely**
 - Reaction follows drug use; improvement on dechallenge

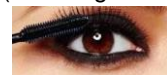
Adverse Drug Side-Effect Reporting Organizations

- World Health Organization (WHO)
 - <http://www.who.int/medicines/publications/drug-information/>
- Food and Drug Administration (FDA)
 - <http://www.fda.gov/medwatch>
- National Registry of Drug-Induced Ocular Side-Effects
 - <http://www.eyedrugregistry.com/>



Covered Under Reporting

- Prescription or OTC meds
- Hospital/outpatient meds (i.e. infusions)
- Biologics (blood/plasma/allergenic elements, human cells/tissue, cell/tissue-based products)
- Medical devices (including in vitro diagnostics) Combination products
- Nutritionals (diet supplements/infant formulas)
- Foods/drinks (including serious allergic rxns)
- Cosmetics



NOT Covered Under Reporting

- Vaccines
- Investigational Devices
- Dietary Supplements
- Investigational (study) drugs
- Veterinary Medicine Products

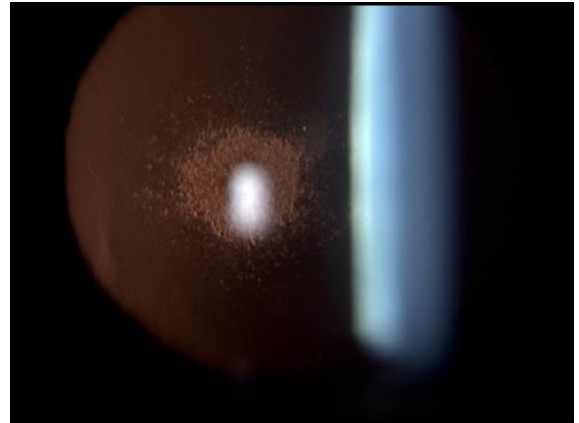


Medicolegally...

- It is advisable to take a conservative approach in dealing with situations
- If the agent might be harming the patient's eye, vision, or body, take the possible correlation seriously
- Check references and resources to see a connection between the symptom(s), sign(s) and the drug have been documented

Practice Pearl

- Monitor patients closely, from a vantage point of suspicion and vigilance
- Seek to maintain awareness of those drugs associated with toxicity
- Seek to contribute your insights to the professional knowledge base
- Report the instances that you see arise to:
 - Patients
 - Prescribing practitioner, colleagues
 - Reporting agencies if warranted

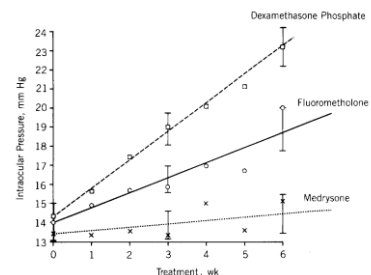


Corticosteroids

- prednisone (Orasone, Deltasone)
- methylprednisone (Medrol)
- hydrocortisone (Cortef)
- triamcinolone (Azmacort)
- *Noted ocular side-effects:* increased IOP, cataract formation
- These side-effects can occur with any route of administration (topical ophthalmic, oral, inhalation, intravenous, cutaneous, nasal aerosols – i.e. fluticasone = Flovent)



Corticosteroids



Joel S. Mindel, MD, PhD; Henry O. Tavitan, MD; Harry Smith, Jr, PhD; Ethel C. Walker, LPN Comparative Ocular Pressure Elevation by Medrysone, Fluorometholone, and Dexamethasone Phosphate *Arch Ophthalmol.* 1980;98(9):1577-1578.

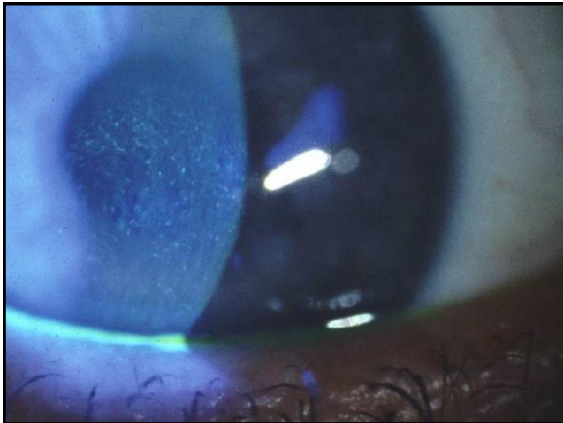
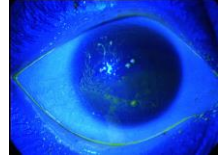
Corticosteroids

- **Cataract:**
 - Steroid enters lens fiber cell → interacts with lens crystalline amino acids → exposes sulfhydryl groups to form disulfide bonds → protein aggregation complexes → opacity
- **IOP Increase:**
 - glycosaminoglycans (GAG) or trabecular meshwork-inducible glucocorticoid response (TIGR) protein accumulation, obstructing outflow
 - cytoskeletal changes inhibiting pinocytosis of aqueous or clearing of GAG, obstructing outflow



Corticosteroids

- Children can develop higher IOPs and PSC cataract formation sooner than adults
- Other potential ocular side-effects:
 - Retardation of corneal epithelial healing
 - Secondary ocular infection
 - Scleral thinning/melting
 - Uveitis
 - Mydriasis
 - Ptosis
- *Pertinent tests:* tonometry, dilated biomicroscopy, optic nerve/RNFL evaluation



Antihistamines

- **Several:**
 - fexofendaine (Allegra)
 - loratidine (Claritin)
 - cetirizine (Zyrtec)
 - desloratidine (Clarinex)
- *Noted ocular side-effects:* reduced lacrimal and mucin secretion, mydriasis
- *Pertinent tests:* tear meniscus/break-up time, Schirmer/phenol, staining, pupils



Antihistamines

- H1-receptor antagonist
- Some atropine (anticholinergic) effect
 - Mydriasis, decreased accommodation
- Reduces lacrimal gland secretion
 - Decreased aqueous production
- Possible secretion of mucin
 - Decreased tear film stability




Ousler, George W.; Wilcox, Katrina A.; Gupta, Gaurav; Abelson, Mark B. An evaluation of the ocular drying effects of 2 systemic antihistamines: loratadine and cetirizine hydrochloride. *Annals of Allergy, Asthma and Immunology*. Volume 93, Number 5, November 2004 pp. 460-464(5)

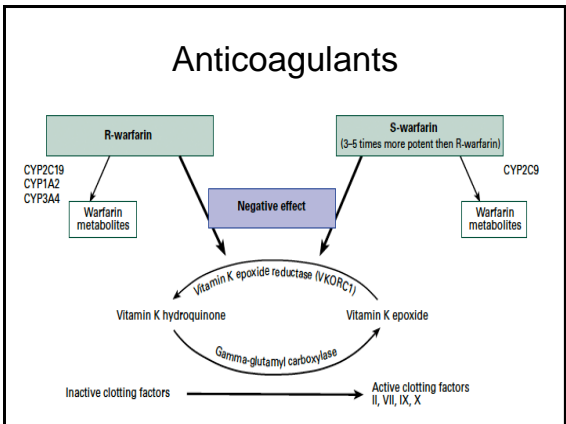
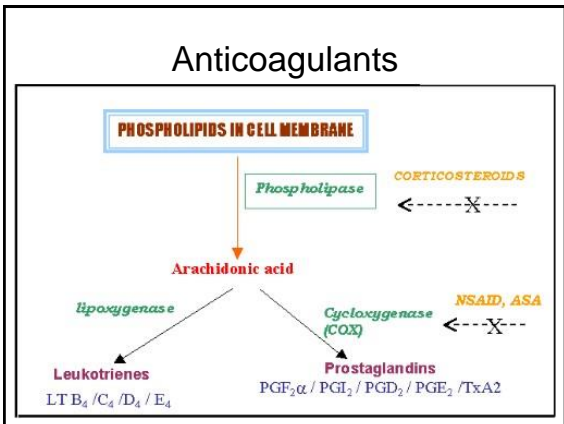


Anticoagulants

- acetylsalicylic acid (Aspirin)
- warfarin (Coumadin)
- *Noted ocular side-effects:* subconjunctival hemorrhage
- *Less common side-effects:* retinal hemorrhages



H. Lewis, S. H. Sloan, R. Y. Foe: Massive intraocular hemorrhage associated with anticoagulation and age-related macular degeneration Graefes Archive for Clinical and Experimental Ophthalmology Volume 226, Number 1 / January, 1988 pp. 59-64.
 C. Nischler, W. Hitzl/S.F. Egger: Risk of hemorrhage after photodynamic therapy in patients with anticoagulant medication Spektrum der Augenheilkunde Volume 23, Number 1 / March, 2009 pp. 36-8.
 Yu-Yen Chen, Ying-Ying Chen, Shwu-Juan Sheu: Spontaneous Suprachoroidal Hemorrhage Associated with Age-related Macular Degeneration and Anticoagulation Therapy. Journal of the Chinese Medical Association Volume 72, Issue 7, July 2009, Pages 385-387



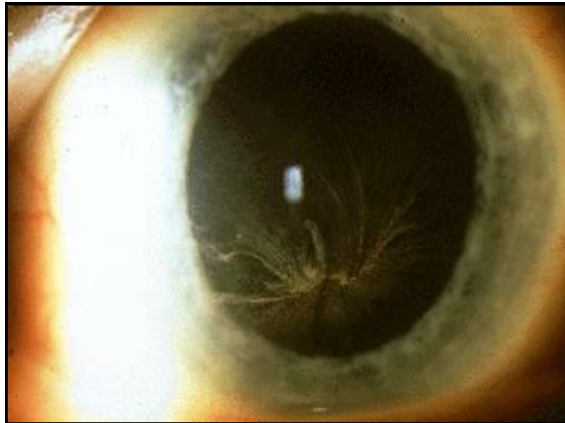
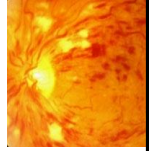
Anticoagulants

- Hemorrhagic retinopathy – rare
- Report adverse side effects to PCP
- Avoid ASA immediately following surgery, blunt trauma, and/or hyphema
- May be contraindicated if known G-I disorders or bleeding abnormalities exist
- Vitamin E also implicated in bleeds
- *Pertinent tests:* anterior biomicroscopy, fundus examination, photos



Side note: Estrogens

- Retinal vasospasm/vascular occlusive disease
- Increased blood viscosity
- Oral contraceptives
- Estrogen replacement therapy (ERT)
 - associated with menopause management
- Greater thrombus risk in women > 35 years old
- Greater risk with “clot-predisposing” conditions:
 - lupus, diabetes
- Discontinue drugs pending “clotting profile” lab study, if optic disc/retinal hemorrhages noted



Amiodarone

- Trade names: Coradone, Pacerone
- *Noted ocular side-effects:* whorl-like keratopathy, lens opacities, conjunctival deposits, 2% optic neuropathy (NAION)
- Intercellular deposition of drug crystals
 - Primarily corneal epithelial basal cells
 - As soon as 2 months after treatment start
- Haloes, photophobia, glare symptoms



Uçakhan, Ömür Ö. M.D.; Kanpolat, Ayfer M.D.; Yılmaz, Nurgül M.D.; Özkan, Muhip Ph.D. Amiodarone Keratopathy: An In Vivo Confocal Microscopy Study Eye & Contact Lens: Science & Clinical Practice, July 2005 31(4) pp. 148-15

Amiodarone

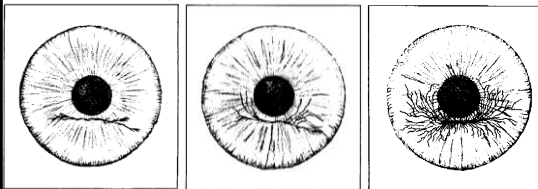


Fig 1—Stage 1.

Fig 2—Stage 2.

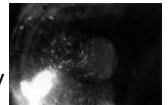
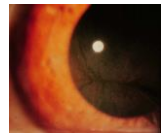
Fig 3—Stage 3.

Kaplan L.J, Cappaert WE. Amiodarone keratopathy: corrections to dosage and duration. Archives of Ophthalmology, April 1982, pp. 601-2.

Amiodarone

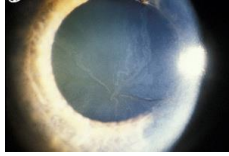
Corneal whorl differentials:

- Fabry's disease
 - Lack alpha-galactosidase A
 - galsidase beta (Fabrazyme) IV for life current treatment
- Hudson-stahl lines
- quinines, chlorpromazine, indomethacin
- Hurricane/blizzard keratopathy



Amiodarone

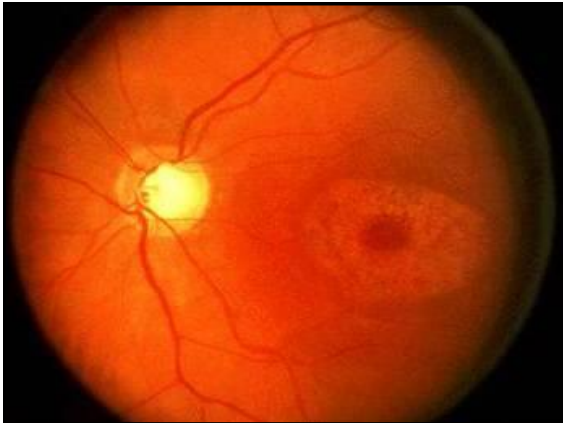
- Whorl-like keratopathy can resolve within months after drug discontinuation
- Optic neuropathy (disc edema) occurs in 1.8% of individuals taking drug
 - Can cause reversible VF defects as result
 - This indicates drug should be discontinued
- *Pertinent tests:* anterior biomicroscopy, fundus examination, photos, Amsler, VF, OCT



Damien C Macaluso, William T Shuts, Friedrich T Fraunfelder Features of amiodarone-induced optic neuropathy American Journal of Ophthalmology, May 1999 127(5), Pages 610-612

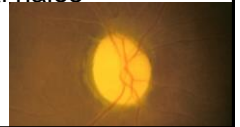
Case 5

- 56-year-old female
- Gradual blur x 1 year OU; dry eyes x 15 yr
- Rheumatoid arthritis x 12 years
- Taking Plaquenil and Motrin daily x 8 years, prednisone for acute flare-ups
- BCVAs 20/30-2 OD, 20/40-3 OS
- IOPs 15 OD, OS @ 3:20 PM; PERRLA-MG
- Ishihara: 8/14 plates correct OD, OS
- Amsler: central 8 degree scotoma OD, OS



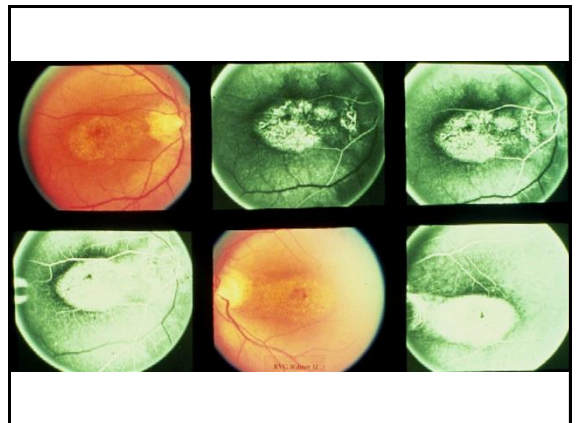
Antimalarials

- hydroxychloroquine (Plaquenil)
- chloroquine (Aralen)
- quinine (Qualaquin)
- *Noted ocular side-effects:* whorl-like keratopathy, bulls-eye maculopathy, dyschromatopsia, visual halos
- *Quinine:* optic atrophy, vessel attenuation



Antimalarials

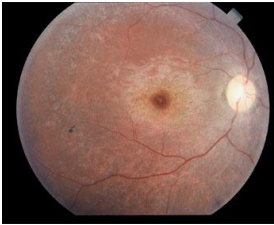
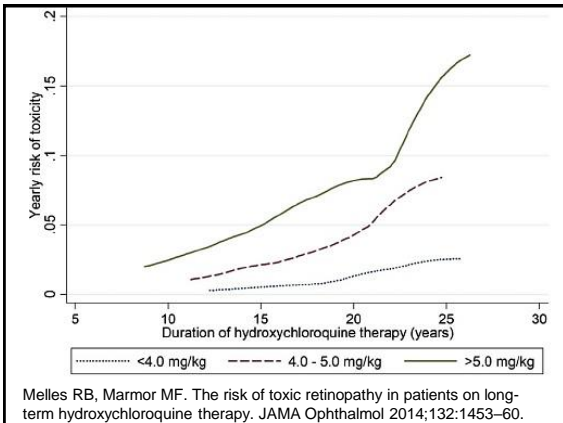
- hydroxychloroquine and chloroquine bind to melanin
- Pigmented tissue in eye holds drug for long time – even after discontinuance of drug
- RPE degeneration occurs
- Migration of pigmented cells of the RPE to the outer plexiform and outer nuclear layers
- Foveal cones often spared
- Classic 'bull's eye' appearance





Antimalarials

- Differential: retinitis pigmentosa (chloroquine toxicity can mimick this)
- *Pertinent tests:* color vision, pupils, Amsler grid, threshold VF, biomicroscopy, fundus photos, baseline info.
- 2011 Am. Acad. Ophthalmology Guidelines:
 - 1) DFE
 - 2) 10-2 VF
 - 3) SD-OCT or AF or mfERG

Major Risk Factors for Toxic Chloroquine/Hydroxychloroquine 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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Clinical Education / Guidelines / Clinical Statements

About Clinical Statements

MAR 2016 ; REVISED MAR 2016

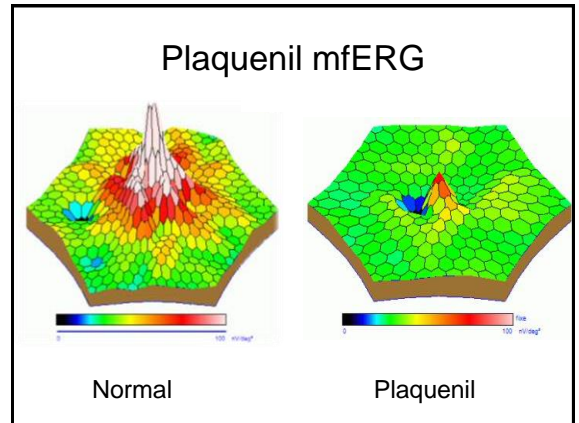
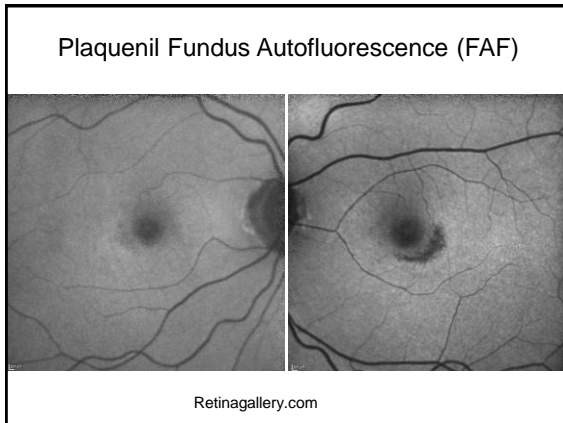
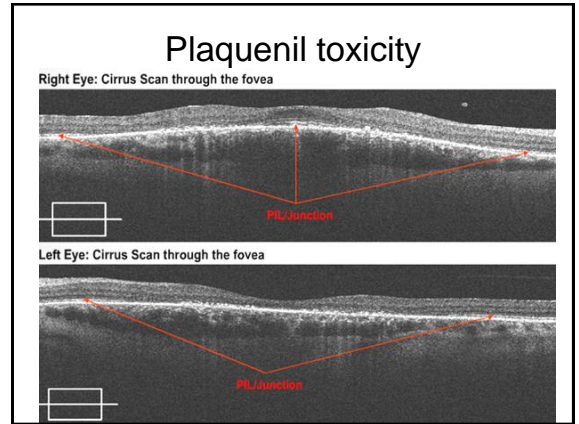
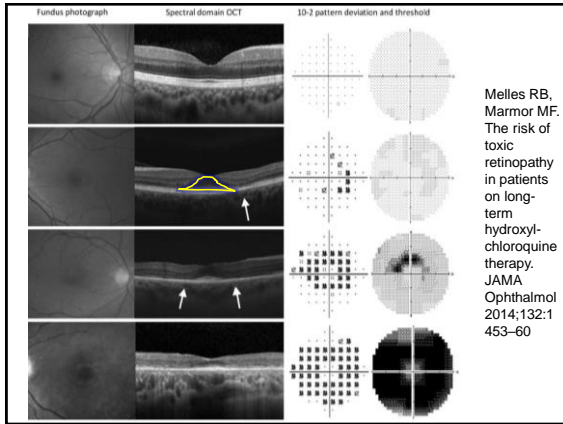
Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy - 2016

AAO Quality of Care Secretariat, Hoskins Center for Quality Eye Care

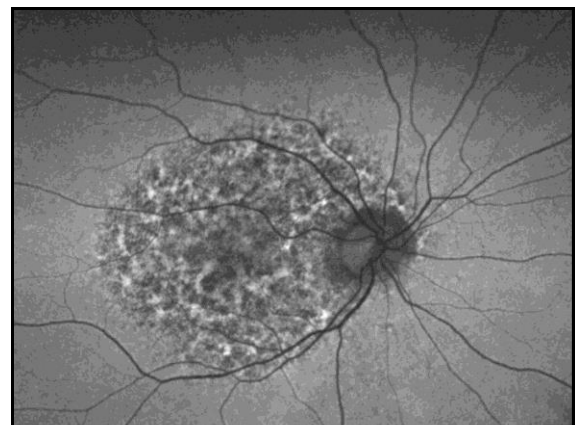
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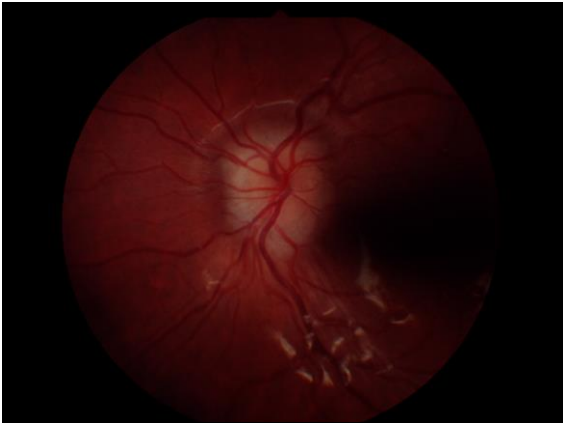
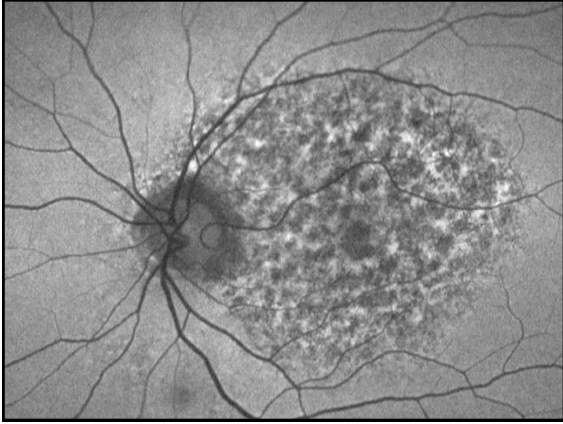
American Academy of Ophthalmology 2016 Plaquenil Guidelines

- Baseline DFE; 2nd DFE within 1yr of drug start
- Annual screenings can begin 5 years after initial drug start, if dose acceptable + no risk factors
- 24-2 or 30-2 threshold fields for Asian patients
- 10-2 threshold field for other patients
- Recommended tests: threshold VF, SD OCT
- Option mfERG and/or fundus autofluorescence
- Microperimetry, adaptive optics retinal imaging may be future tests



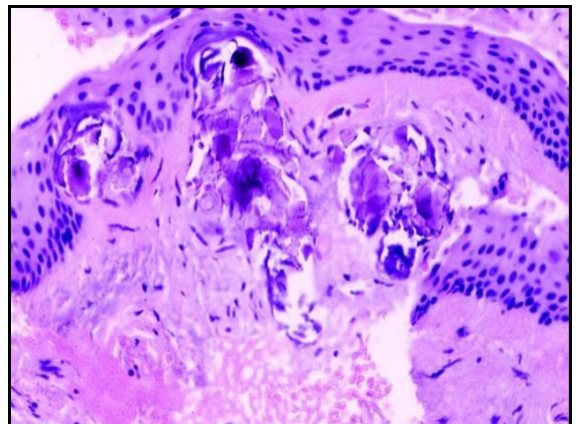
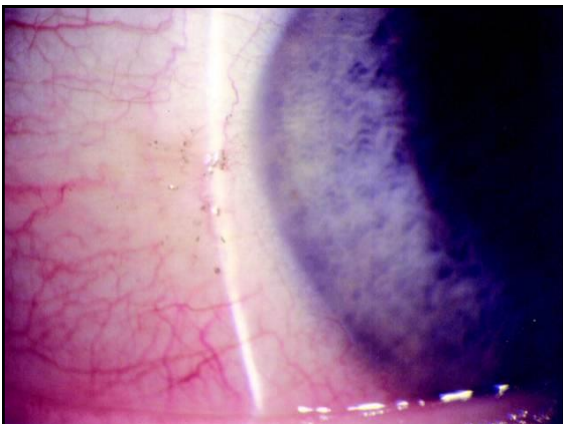
- ### Sidenote: Elmiron
- pentosan polysulfate sodium
 - Janssen Pharmaceuticals, Inc.
 - 100mg PO TID
 - Treats pain/discomfort from a certain bladder disorder (interstitial cystitis)
 - Side-effect: pigmentary maculopathy
 - This side-effect was not listed on the label until recently





Tetracyclines

- tetracycline (Terramycin, Symycin)
- doxycycline (Vibramycin)
- minocycline (Mincon)
 - Lipophilic
 - Penetrates blood-brain barrier more readily
 - Attains higher cerebrospinal fluid (CSF) levels
- *Noted ocular side-effects:* papilledema from pseudotumor cerebri, deposits



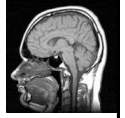
Adrenochrome deposits

- Tetracyclines
- Epinephrine
- Gold
- Antipsychotics



Tetracyclines

- Exact ICH mechanism unknown:
 - excessive CSF and extracellular edema
 - Increased venous sinus pressure
 - defective CSF absorption
- Condition resolves over a few weeks upon discontinuance of the tetracycline
 - Carbonic anhydrase inhibitor, K+ to treat



Debra E. Weese-Mayer, Renee J. Yang, Jonathan R. Mayer, Zibute Zaparackas. Minocycline and Pseudotumor cerebri: The Well-Known but Well-Kept Secret. Pediatrics Vol. 108 No. 2 August 2001, pp. 519-520

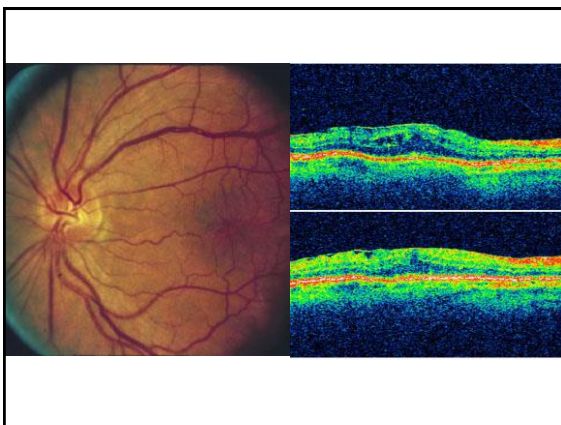
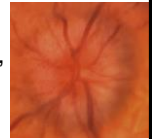
Side note: chloramphenicol

- Trade name: Chloromycetin
- Ophthalmic ointment: aplastic anemia
- Systemic: optic neuritis, retrobulbar neuritis
 - Can occur as soon as 10 days into therapy
 - Bilateral severe vision reduction and VF defects
 - ONH atrophy; may not resolve after d/c drug
- *Pertinent tests*: color vision, threshold VF, pupils, dilated fundus exam, OCT, photos



isotretinoin

- Trade names: Accutane, Claravis, Sotret, Amnesteem
- 13-*cis*-retinoic acid
- *Noted ocular side-effects*: CL intolerance, nyctalopia, papilledema, optic neuritis (9%)
- May compete with transport molecules or retinol binding sites on retinal receptor cells
- *Pertinent tests*: color vision, threshold VF, pupils, dilated fundus exam, photos
- Referral for EOG/ERG/dark adaptometry



Nicotinic Acid

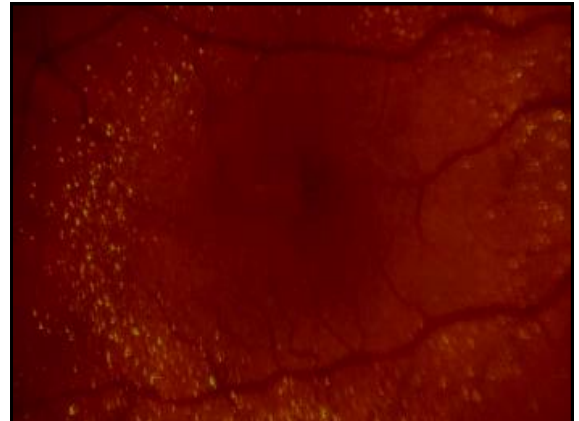
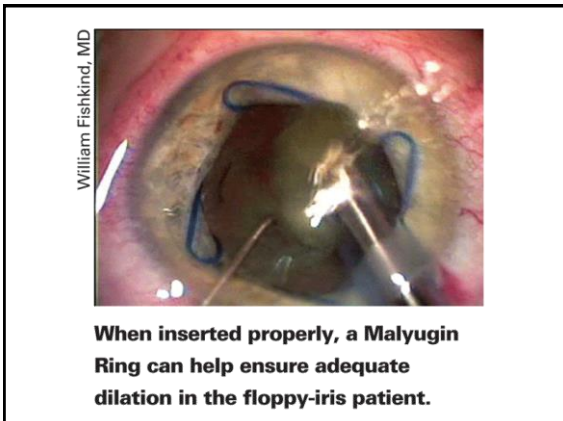
- Trade name: niacin (vitamin B-3)
- *Noted ocular side-effects*: 'pseudo'-cystoid macular edema, toxic amblyopia
 - Intracellular fluid (rather than extracellular)
 - Lacks angiographic leakage
- *Minor side-effect*: face/eyelid flushing
 - This can be alleviated with aspirin
- Gilenya (fingolidmod) for MS; similar ADR
- *Pertinent tests*: color vision, threshold VF, pupils, dilated fundus exam, photos, OCT





tamsulosin

- Trade name: Flomax
- Benign prostate hyperplasia Tx
- Newer drug: Rapaflo (silodosin)
- Alpha 1A receptor antagonist
- *Noted ocular side-effects:* intraoperative floppy iris syndrome (IFIS) - <2%
 1. Flaccid iris that billows with irrigation
 2. Progressive miosis even with dilation drugs
 3. Potential iris prolapse to phaco incision
- *Pertinent tests:* pupils, slit lamp, photos



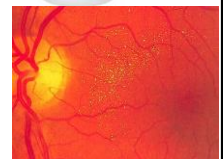
Antineoplastics

- tamoxifen (Nolvadex)
- *Noted ocular side-effects:* whorl-like keratopathy, crystalline retinopathy, optic neuritis
- White or yellow refractile bodies in macula/paramacular area; NFL, IPL
 - Refractile bodies: axon degenerative products
- Normal tamoxifen dose: 20mg BID
- 90g cumulative dose tamoxifen required:
 - 80-120mg BID for 1-2 years



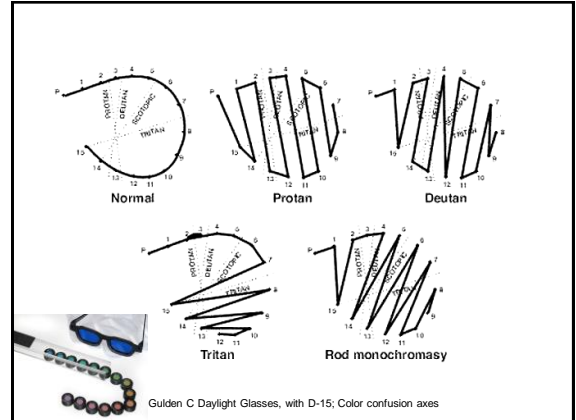
Side note: Canthaxanthin

- Oral agent that enhances suntanning
- Prolonged used over time can cause maculopathy in donut-shaped ring around both maculae
- These deposits in superficial retina
- Generally benign



Antineoplastics

- carmustine (BCNU)
- Chemotherapy IV
 - carotid artery infusion drug
- Retinal infarction, periphlebitis, retinal artery occlusion, macular edema - toxic
 - 65% 2-14 weeks post-treatment; VA loss
 - Infusing beyond ophthalmic artery helps
- *Pertinent tests*: color vision, pupils, Amsler grid, threshold VF, biomicroscopy, dilated fundus exam, photos, OCT



Cardiac Glycosides

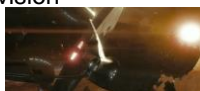
- digoxin (Lanoxin)
- digitoxin
- *Noted ocular side-effects*: xanthopsia, retrobulbar optic neuritis, diplopia, mydriasis, corneal edema
- High concentrations accumulate in choroid and retina → inhibits Na/K-ATPase → cone receptor function reduced



Cardiac Glycosides

Visual Symptoms

1. Dyschromatopsia
2. Flickering or flashes of light
3. Colored spots surrounded by coronas
4. Snowy, hazy, or blurred vision
5. Dimming of vision
6. Glare sensitivity



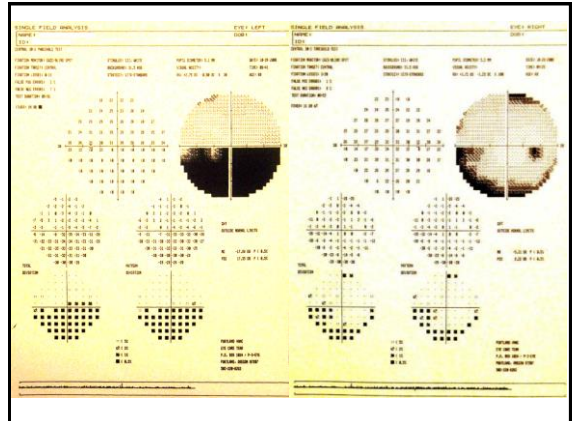
Robertson DM, Hollerhorst RW, Callahan JA. Ocular manifestations of digitalis toxicity. Discussion and report of three cases of central scotomas. Arch Ophthalmol 1966; 76:640-645

Welleber RG, Shalts WT. Digoxin retinal toxicity. Clinical and electrophysiologic evaluation of a cone dysfunction syndrome. Arch ophthalmol 1981; 99:1568-1572

Cardiac Glycosides

- Digoxin affects color vision more than digitoxin
- Symptoms may appear as soon as 1 day post-treatment; more often 2 weeks post.
 - Some may not have effects till years later
- Symptoms improve within weeks post-discontinuance of drug
- NOTE: Dilantin (phenytoin) – seizure Tx, can also cause xanthopsia (and nystagmus, diplopia, ophthalmoplegia)





Erectile Dysfunction Drugs

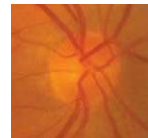
- sildenafil (Viagra)
- tadalafil (Cialis)
- vardenafil (Levitra)
- *Noted ocular side-effects:* blue vision, AION (ischemic optic neuropathy), possible CSME
- Selectively inhibits phosphodiesterase types 5 (PDE5) & 6 that breaks down cGMP (which normally maintains vascular tone) → reduced vascular perfusion to eye/ONH



Erectile Dysfunction Drugs

“Disc-at-risk”:

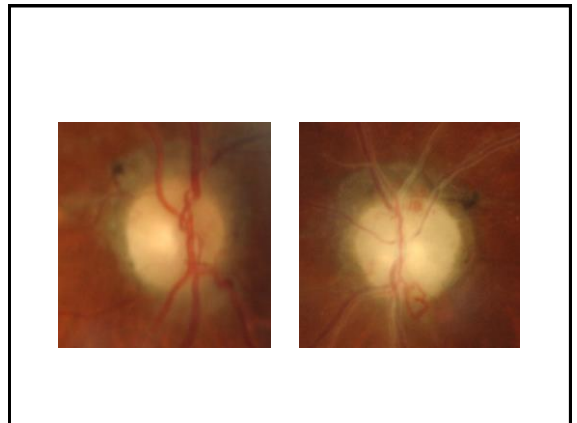
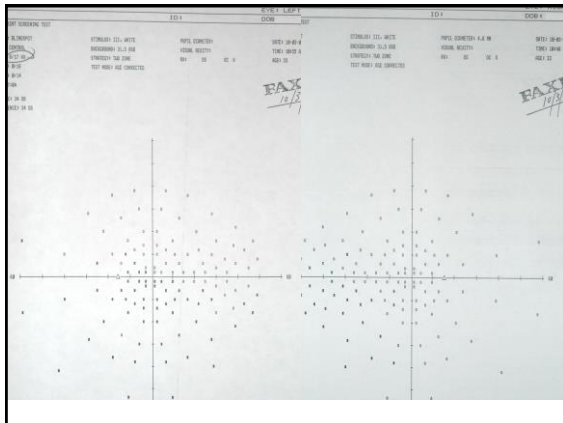
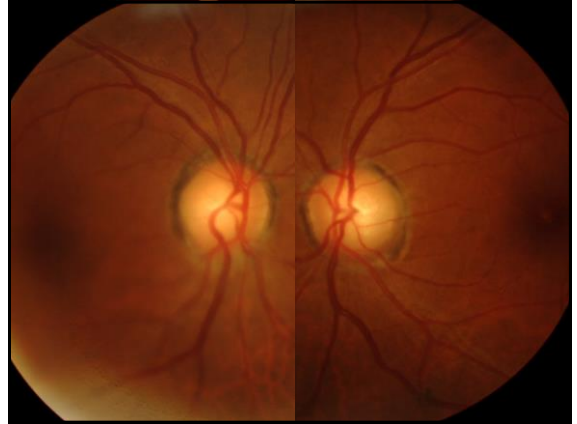
1. Small ONH with small or absent cup
 2. Abnormal central vessel branching
 3. NFL bundles obscures disc margin
- *Pertinent tests:* color vision, pupils, threshold VF, biomicroscopy, dilated fundus exam, photos, OCT



Burde RM. Optic disk risk factors for nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1993; 116:759-64.

Erectile Dysfunction Drugs

- Association between sildenafil and NAION is 'possible' according to WHO criteria
- There is no well researched explanation as to how it could cause NAION
- Over 27 million men have used these meds
 - most are vasculopathic and fall into age group in which they are already at risk for NAION
- Santaella & Fraunfelder: patients who should not take PDE5 inhibitors are those who have previously had NAION in one eye



Tuberculosis Drugs

- isoniazid (Nydrazid)
- rifampin (rifampicin, Rifadin)
- ethambutol (Myambutol)
- *Noted ocular side-effects:*
 - optic neuropathy
 - retrobulbar neuropathy
 - red-green color defects
 - visual field loss
 - uveitis (rifampin)




ethambutol

- Retrobulbar neuritis
 - weeks to months use
- Color vision changes
 - may precede neuritis
- Numerous visual field defects, acuity loss
- Doses above 15mg/kg/day pose more risk
- May affect amacrine and bipolar cells
- May chelate copper in ONH mitochondria
- Possible toxic glutamate pathway cause



Ethambutol Optic Neuropathy:

- May occur 2-8 months after starting therapy
- Can progress 1-2 months after drug discontinued
- Early symptoms: decr. VA/color, central scotomas
 - Bitemporal VF defects (optic chiasm affinity) 
- Usually reversible; irreversible blindness described
- Related to dose and duration of therapy
 - 1% at <15mg/kg/day
 - 5-6% at 25 mg/kg/day
 - 50% of patients taking 60-100mg/kg/day
- hydroxocobalamin (vitamin B12) may be 'antidote'

Ethambutol Toxicity:


- AOA: monthly or "as-needed" depending on findings
- US PDR: monthly eye exams if dose > 15mg/kg/day
- Santaella & Fraunfelder: recommend informed consent prior to examining patients taking ethambutol
 - Explain neuropathy can occur at any dose despite regular eye exams
 - Explain that vision loss can be severe and irreversible
- Report ADRs (including VA drop of 2 lines or more) to infectious disease specialist, pulmonary specialist, or PCP to review and consider treatment change
 - consider discontinuing after **any** VA/color vision loss, or visual field defect

Other Tuberculosis Drugs

- isoniazid
 - Optic neuritis and atrophy
- rifampin
 - Rare cases of uveitis
 - Yellow (jaundiced) discoloration of conj/lids
 - can change tears, sweat, saliva, urine, feces and contact lenses a red-orange color
- *Pertinent tests:* color vision, pupils, ON/RNFL OCT, threshold VF, biomicroscopy, dilated fundus exam, photos; VEP possibility



NSAIDS

- ibuprofen (Advil, Motrin, Nuprin)
- indomethacin (Indocin) 
- naproxen (Naprosyn, Anaprox, Naprelan)
- *Noted ocular side-effects:* photosensitivity, macular edema/hemes, pseudotumor cerebri, optic neuritis, vortex keratopathy; cataracts (ibuprofen)
- May have direct or indirect retinotoxic effect on RPE (evidenced by ERG/EOG)

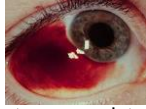
indomethacin

- Discrete perifoveal pigmentation
 - Sometimes more peripheral posterior pole
 - Usually irreversible
- Whorl-like keratopathy
 - Similar to amiodarone
- Retinal hemorrhages
 - More with long-term use
- Diplopia



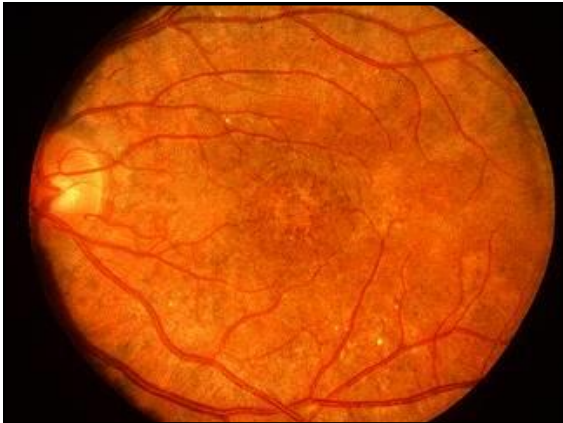
NSAIDs

- Color vision changes, blur not uncommon
- Watch for subconjunctival hemes as well
- Vertigo (rare)
 - Neuro/neuro-ophth/ENT if symptoms persist
- Stevens-Johnson syndrome (very rare)
 - Prompt referral to PCP or dermatologist
- *Pertinent tests:* color, pupils, threshold VF, biomicroscopy, dilated fundus exam, photos
- Note: COX-2 inhibitors have few ocular ADRs



Opiates

- codeine (Tylenol #1-4)
- oxycodone (OxyContin)
- morphine
- heroin
- *Noted ocular side-effects:* miosis, accommodative dysfunction, dry eyes
- Miosis due to CNS action of drug
 - Possibly visceral nucleus of oculomotor nuclear complex
- *Pertinent tests:* pupils, biomicroscopy



Neuroleptics

- phenothiazines:
 - chlorpromazine (Thorazine, Largactil)
 - thioridazine (Mellaril)
- Lithium (Eskalith, Lithobid)
- *Noted ocular side-effects:*
 - lens and corneal deposits (chlorpromazine)
 - “salt and pepper” retinopathy (thioridazine)
 - nystagmus/diplopia (lithium)

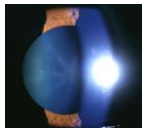
Largactil
Chlorpromazine Hydrochloride

Mellaril
Thioridazine

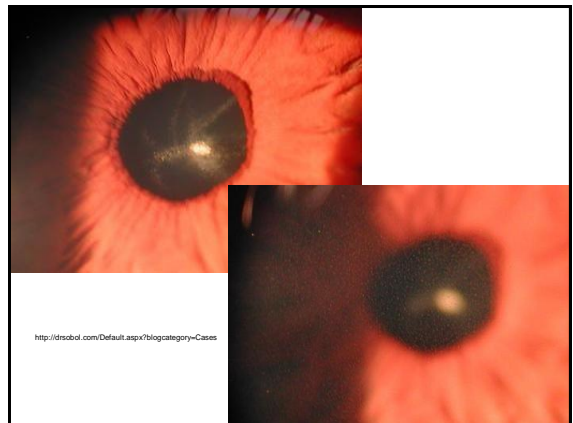
LITHOBID
Lithium Carbonate, USP

chlorpromazine

- ‘Oculo-skin syndrome’
 - Blue coloration, scleral icterus, pigmentary deposits by limbus
- Anterior lens opacification:
 - Stellate pattern
 - 5 stages
- Corneal pigmentation: usually endothelial
 - White, yellow, brown, or black
- facial movement/tics
 - 2’ to tardive dyskinesia



Haldol
Haloperidol
5mg 10mg Tablet



<http://drrsobel.com/Default.aspx?blogcategory=Cases>

thioridazine



- Strong binding affinity to melanin
- Fine “peppery” pigmentation with “salt”-like plaque-like lesions and hypopigmentation/atrophy → VA reduction and VF loss
- Retinal toxicity if greater than 500mg/day
 - RPE clumping/atrophy from periphery inwards
 - Progressive retinopathy and onset can occur even up to 10 years after therapy discontinued
- trifluoperazine (Stelazine): similar effects

lithium



- Beating nystagmus
 - Lateral gaze and downgaze
- Saccades are normal
- Usually normal therapeutic levels
- Nystagmus may persist 6 months or years after discontinuance of lithium
 - Rule-out other causes of nystagmus
- *Pertinent tests:* biomicroscopy, threshold VF, fundus exam, photos, color, Amsler, OCT

Antidepressants

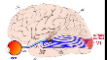


- fluoxetine (Prozac)
- sertraline (Zoloft)
- SSRIs
- Sympathetic-like effect on body
- *Noted ocular side-effects:* reduced accommodation, mydriasis, blur, EOMs
- *Pertinent tests:* pupils, binocular testing, motility testing, accommodative testing
- NOTE: Zoloft bullseye maculopathy cases

Immunosuppressive Agents

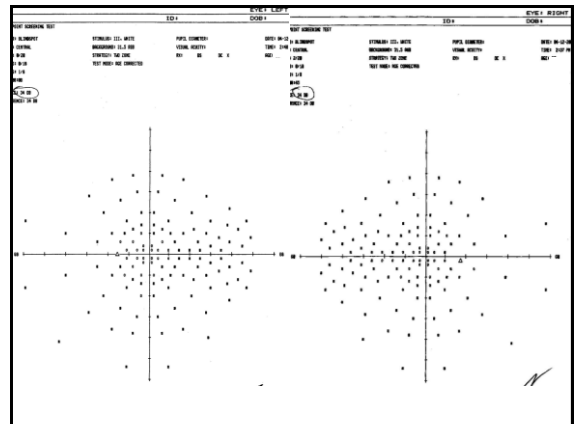
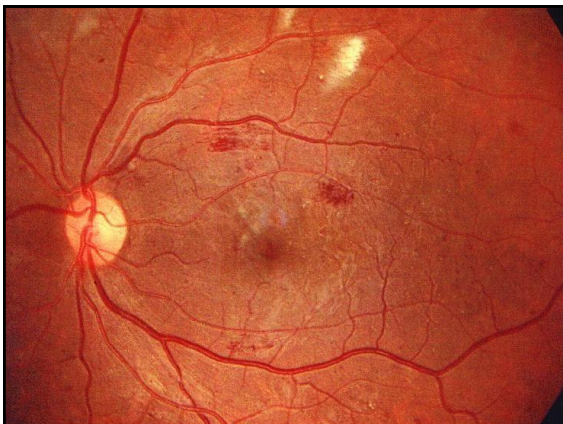
cyclosporine (Sanimmune):

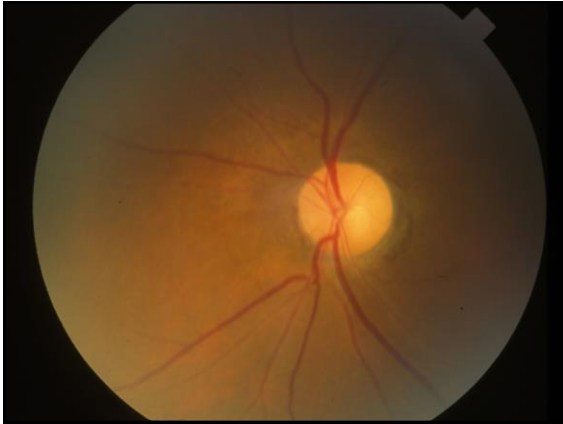
- Primary use for colon cancer treatment
- *Noted ocular side-effects:* reversible cortical blindness, optic disc edema



interferon (with or without ribavirin):

- Primary use for hepatitis C treatment
- *Noted ocular side-effects:* retinopathy
- *Pertinent tests:* color vision, pupils, threshold VF, biomicroscopy, dilated fundus exam, photos, Amsler grid



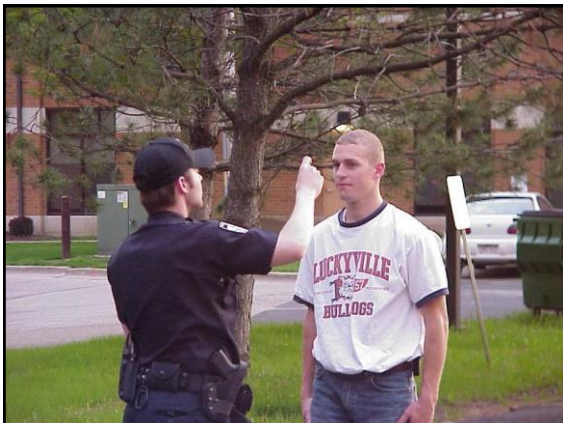


Alcohols

- *Noted ocular side-effects:* poor EOMs, nystagmus, diplopia, toxic neuropathy
- Impairment of mitochondrial oxidative phosphorylation, thiamine depletion
- Gradual accumulation of formic acid
- Poor Vitamin B12 absorption; CNS effects
- *Pertinent tests:* binocular testing, motility testing, color vision, pupils, threshold VF, biomicroscopy, dilated fundus exam, photos



Thomas Paparrigopoulos, Elias Tzavellas, Dimitris Karaiskos, Ioannis Liappas. Alcoholic Optic Neuropathy: Another Complication of Alcohol Abuse J Neuropsychiatry Clin Neurosci 20:368-a-369, August 2008



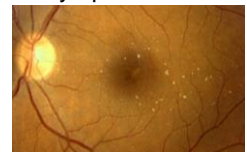
Talc Maculopathy

- talc is inert filler material for tablets
 - Comprised of magnesium silicate
- IV, sub-Q, IM routes of administration
- talc particles enter and embolize
 - Most parts of bloodstream including the retina
- *Noted ocular side-effects:* retinal deposits, retinal vascular emboli
- *Pertinent tests:* pupils, threshold VF, dilated fundus exam, photos



Talc Maculopathy

- Extent of talc corresponds with amount and duration of drug abuse
 - Routinely found if injected over 12,000 tablets
- Most patients have no visual symptoms
- VAs usually normal
- However, blur/blind spots in VFs can occur
- 'Microtalc retinopathy' variant – finer deposits:
 - NFL defects, glaucoma-like VF loss



Talc Maculopathy

- Drug abuse counseling
- Pulmonary consultation may be needed
 - Ocular talc indicates excess lung involvement
 - Lung function may be compromised
- Annual retinal evaluation
- Annual fundus photography
- Annual threshold VF testing
 - If glaucoma risk factors with VF loss, ocular hypotensive medications may be indicated



Biphosphonates

- Inhibits bone resorption
 - binds to hydroxyapatite crystals, preventing breakdown
- IV: pamidronate disodium (Aredia)
- Oral: alendronate, risedronate, etidronate
- *Infrequent ocular side-effects:*
 - **Conjunctivitis, uveitis, scleritis**
- *Rare ocular side-effects:*
 - **Papilledema, CN palsy** (pamidronate)
- Eye exam within *first week* recommended
 - Average ADR onset : 48 hrs to 2 wks
 - Clinical report: biphosphonate had to be discontinued for scleritis to resolve, even on full medical therapy



F.W. Fraunfelder and F.T. Fraunfelder, *Biphosphonates and ocular inflammation* [letter]. N Engl J Med 348 (2003), pp. 1187-1188.

topiramate (Topamax)

- Antiepileptic; treats migraine, pain and depression
- WHO Ocular ADR List:
 - Certain: **Acute glaucoma (usu. bilateral)**, anterior chamber shallowing, mydriasis, suprachoroidal effusions
 - Probable: Blepharospasm, oculogyric crisis, hemes, uveitis
 - Possible: Scleritis, teratogenic ocular malformations
- Up-to-Date Ocular ADR List:
 - **Nystagmus** (10 -11%), abnormal vision (<1-13%)
 - Conjunctivitis (1%), diplopia (2% to 10%), myopia (1%)
 - **Acute myopia** up to 8.75 D may occur within hrs of starting topiramate; may take wks to fully resolve, on or off med
- Presents as acute angle closure glaucoma attack. Usually occurs in first 2 weeks of treatment but has also been reported within hours after doubling dose



Side Note: Herbal Medications

- ~40% do NOT disclose this info to their doctor
- Chamomile (*M. chamomilla*; tea)
 - Contact can cause severe allergic conjunctivitis
- *Datura* (dried leaves):
 - Contains scopolamine; pupillary dilation
- *Echinacea purpurea*:
 - Allergic conjunctivitis, possible autoimmune response
- *Ginkgo biloba*:
 - Spontaneous hyphema and retinal hemes
- licorice (*Glycyrrhiza glabra*)
 - Ocular migraine-like symptoms; vasospasm effects



Summary/Important Points

1. Educate patients
2. Keep drug info updated
3. Note dosages/duration
4. Stay with same pharmacy
5. Take complaints/findings seriously
6. Perform appropriate baseline/progression tests
7. Determine if timing of findings and drug use match
8. Communicate with patient's PCP and specialists
9. Be aware of contraindications to various drugs
10. Document all pertinent information



THANK YOU!

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