Complications of Pharmaceuticals Every Optometrist Should Know!

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Delaware Optometric Association
Winter Thaw Seminar
February 2, 20/20

Disclosure Statement (next slide)

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Disclosures- Greg Caldwell, OD, FAAO

- Will mention many products, instruments and companies during our discussion
  - I don't have any financial interest in any of these products, instruments or companies
- Pennsylvania Optometric Association –President 2010
  - POA Board of Directors 2006-2011
- American Optometric Association, Trustee 2013-2016
- I never used or will use my volunteer positions to further my lecturing career
- Lectured for: Aerie, Alcon, Allergan, BioTissue, Optovue
- Advisory Board: Allergan, Maculogix, Sight Sciences, Sun, Takeda
- Envolve: PA Medical Director, Credential Committee
- OCT Connect – Facebook page co-administrator with Dr. Julie Rodman
- Optometric Education Consultants- Scottsdale, St. Paul, Quebec City, and Nashville, and OCT meeting in Orlando/Disney; Owner

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Course Description

- Optometrists use topical and oral (systemic) pharmaceuticals for the treatment of a variety of ocular conditions in patient care
- Comparably, systemic medicines are used to treat numerous conditions by various practitioners in the healthcare system
- These treatments or pharmaceutical agents have the potential to produce ocular adverse side effects and systemic complications
- This course will discuss the complications and adverse events that every optometrist should know
- This presentation will immediately aid in everyday patient care

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Antibiotics

- Fluoroquinolones
  - Levaquin™ (levofloxacin)
  - Cipro™ (ciprofloxacin)
    - Retinal detachment
      - 1 in 2,500 will experience (compared to 1 in 1,000 who will experience tendinitis)

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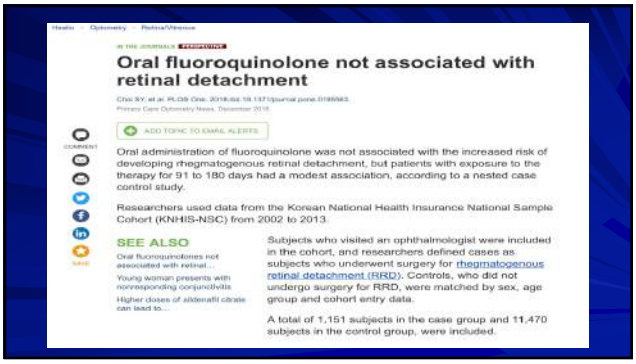

Oral fluoroquinolone not associated with retinal detachment

Oral administration of fluoroquinolone was not associated with the increased risk of developing rhegmatogenous retinal detachment, but patients with exposure to the therapy for 91 to 180 days had a modest association, according to a nested case control study.

Researchers used data from the Korean National Health Insurance National Sample Cohort (KNHIS-NSC) from 2002 to 2013.

SEE ALSO

Subjects who visited an ophthalmologist were included in the cohort, and researchers defined cases as subjects who underwent surgery for rhegmatogenous retinal detachment (RRD). Controls, who did not undergo surgery for RRD, were matched by sex, age group and cohort entry data.

A total of 1,151 subjects in the case group and 11,470 subjects in the control group, were included.

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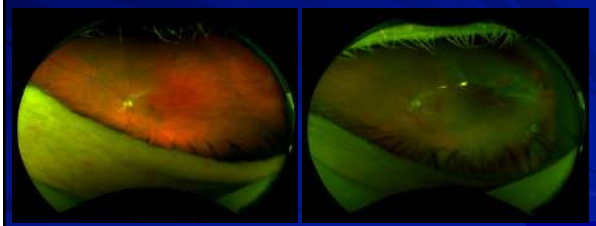
Antibiotic Fluoroquinolones
Dropless Cataract Surgery with Moxi and Kenalog



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Antibiotic Fluoroquinolones
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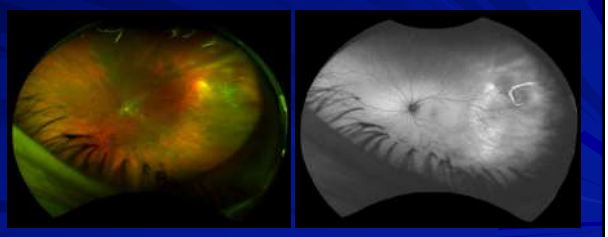

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Antibiotics (anti-inflammatory)
Adverse Drug Reactions

- Tetracycline analogs
  - Doxycycline
  - Minocycline
- Enhanced photosensitivity
- Avoid in children and pregnancy (Category D), and in breastfeeding women
  - Stained teeth
  - Small incisors
- Enhances the effects of
  - Coumadin
    - Comment on antibiotic drug interactions...
  - Digoxin
- Idiopathic intracranial hypertension
  - Pseudotumor cerebri
- Hyperpigmentation

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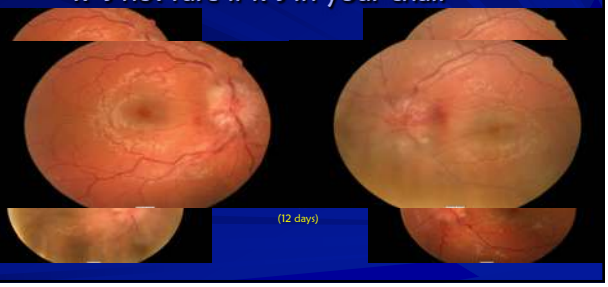
Benign intracranial hypertension
"It's not rare if it's in your chair"



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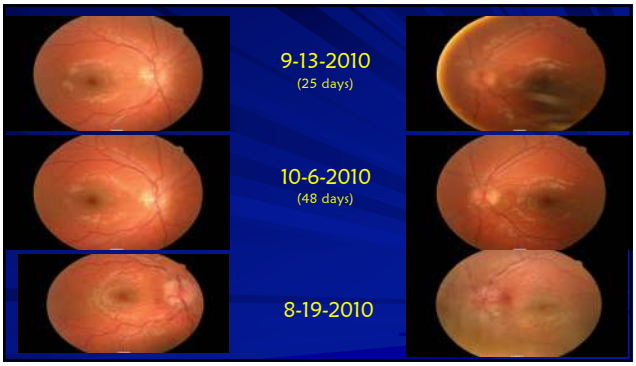

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OMG

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6 Months Later

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1 Year Later

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Alpha 1 Blockers

- Floppy iris syndrome!
- Treatment of enlarged prostate:
  - Uroxatrol™ (Alfuzosin)
  - Flomax™ (Tamsulosin)
    - These two agents LIKELY have the highest incidence of causing floppy iris syndrome, as they are selective for alpha 1a receptors, which also predominate in the eye
- Treatment of CHF and/or hypertension
  - Coreg™ (Carvedilol)
    - Alpha1/beta 2 blocker
- Treatment of refractory hypertension:
  - Hytrin™ (Terazosin)
    - Alpha 1 blocker

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Alpha 1 Blockers

- Floppy iris syndrome and miosis!
- After 4 rounds of phenylephrine, tropicamide, and cyclopentolate, if poor dilation
  - Iris hooks
- What happens at the time of making the incision?
  - Tricks with different viscoelastic agents
- Post op day 1, IOP 43
  - What's the caution?

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Anti-arrhythmics

- Treatment of cardiac arrhythmia
  - Cordarone™ (amiodarone)
    - Corneal deposits
    - Optic neuritis

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65 year old woman

- Patient reports decreasing vision over past 6-9 months. Especially at near
- Vision 20/50 OU

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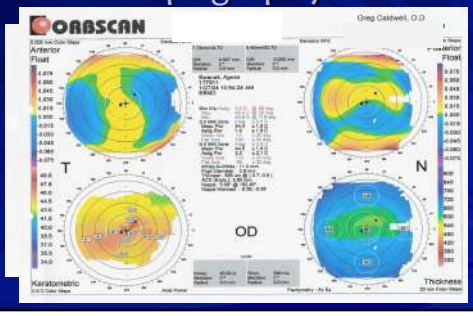
Topography



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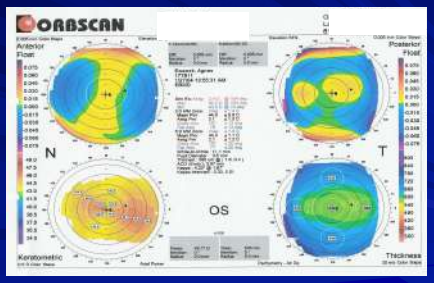
Topography



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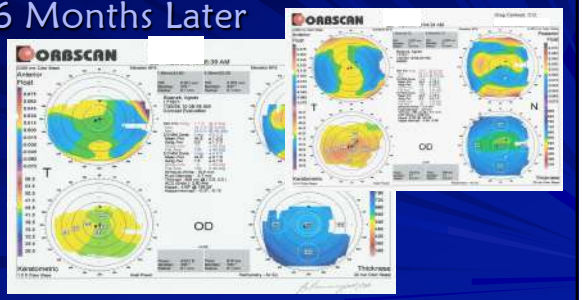
6 Months Later



20/25 BVA

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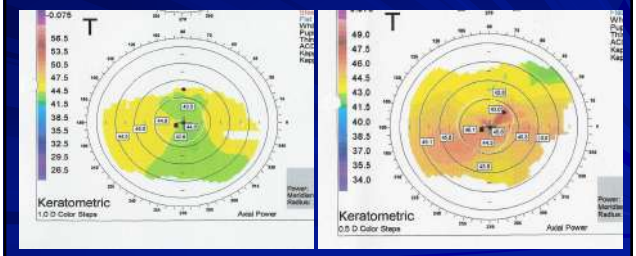
OD



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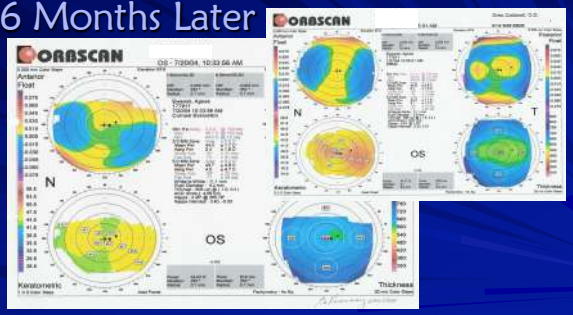
6 Months Later



20/25 BVA

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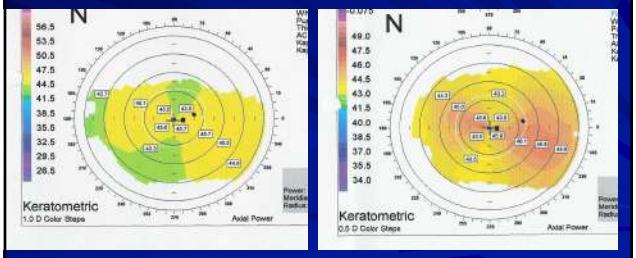
OS



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67 year old man complains of vision slowly deteriorating over the past 8 months

- History of NA-ION 10 months ago OD
- Patient sees family physician for physical due to recent NA-ION
  - Patient has not been to PCP for 35 years
  - Patient started Cardarone™
  - VA 20/80 OD 20/25 OS (9 months ago)
- VA 20/400 OD 20/200 OS (today)
- CF: severe constriction OU
- SLE: vortex corneal whorls OU

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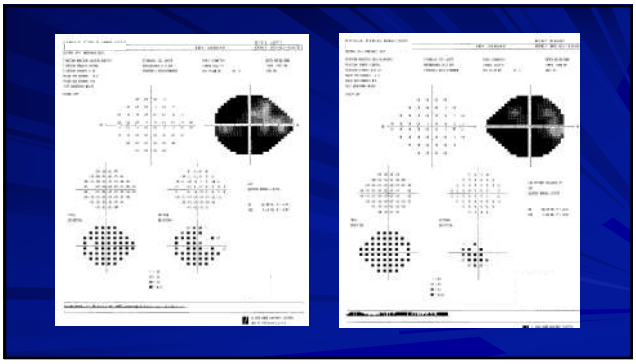

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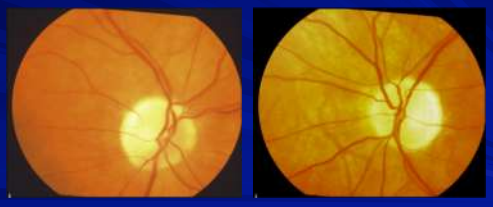
Amiodarone Optic Neuropathy
(Toxic Optic Neuropathy)



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Rhopressa™ 0.02%
(netarsudil ophthalmic solution)

- Aerie Pharmaceuticals
  - Approved December 2017
  - Treatment of glaucoma or ocular hypertension
  - Rho kinase inhibitor
    - ROCK-NET Inhibitor
  - Once daily in the evening
    - Twice a day dosing is not well tolerated and is not recommended
  - Side Effects
    - Conjunctival hyperemia
    - Corneal verticillata
    - Conjunctival hemorrhage

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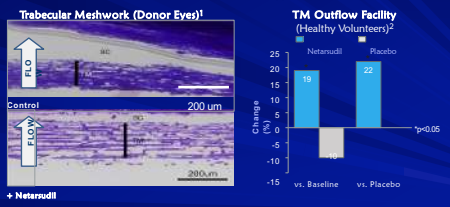
Rhopressa™ 0.02% (netarsudil)
Causes Expansion of TM in Donor Eyes
Increases TM Outflow Facility in Clinic



TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein
1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at AGS 2017.

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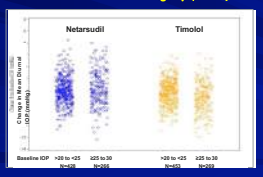
Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)



Baseline IOP ≥20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.1	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

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Rhopressa™ 0.02%

- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
  - Blood Pressure
    - Changes were generally small and not clinically relevant in both groups
  - Heart Rate
    - Timolol caused statistically significant reduction in the phase 3 studies by an average of 2-3 beats per month

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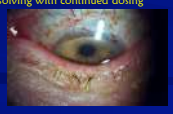
Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

- Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe
- Self-resolving with continued dosing



Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS301, -CS302

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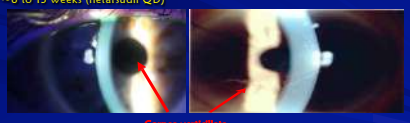
Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)



AR-13324-CS302 netarsudil QD subject

AR-13324-CS302 netarsudil BID subject

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS302

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Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07
* Ralzman MB et al. Surv. Ophthalmol. 2017;62:286-301

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Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia	Cornea Verticillata	Conjunctival Hemorrhage
• 54.4% TEAE	• 20.9% TEAE	• 17.2% TEAE
• Severity did not increased with continued dosing	• Asymptomatic	• Mild in severity and transient
• Sporadic	• Did not impact visual function	• Self-resolving with continued dosing

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Toxic Optic Neuropathy

- Causes
  - Ethambutol (TB)
  - Isoniazid
  - Antimicrobials
    - chloramphenicol, streptomycin, penicillamine
  - Halogenated hydroxyquinolones
  - Vigabatrin
  - Disulfiram
  - Linezolid
- Causes
  - Methanol
  - Heavy metals
  - Fumes
  - Solvents
  - Alcohol abuse
  - Tobacco abuse

Clinical Pearl: When you encounter a pt with these pharmaceuticals, consider and evaluate for toxic optic neuropathy (TON)

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Ethambutol

- Toxic optic neuropathy
- 2 cases in the past 12 months (2019)

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81 year old woman

- Calls the office reporting decreased vision (3-13-19)
  - Was warned vision could decrease due her medications
  - Glaucoma patient
- Mycobacterium avium infection
- Ethambutol, rifampin, and azithromycin
  - Ethambutol started October 2017
- Glaucoma patient
  - Was on latanoprost and Rhopressa
  - Had KDB
    - No glaucoma drops currently

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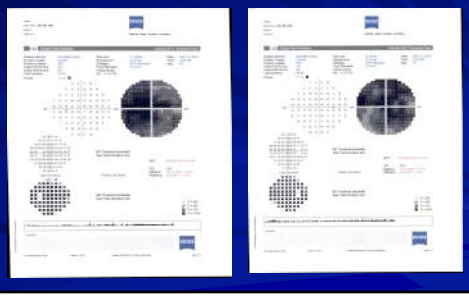
3/13/19 20/30, 20/100, 20/25



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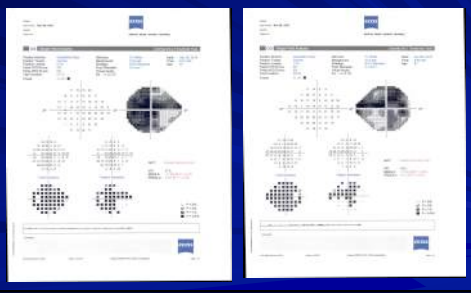
4/29/19 20/25, 20/50, 20/20



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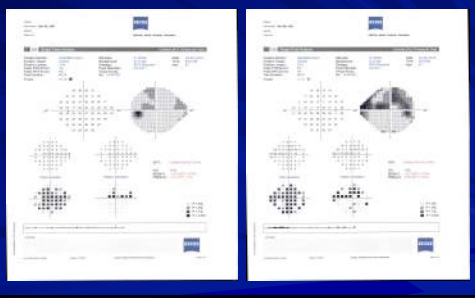
7/29/19 20/20, 20/25, 20/20



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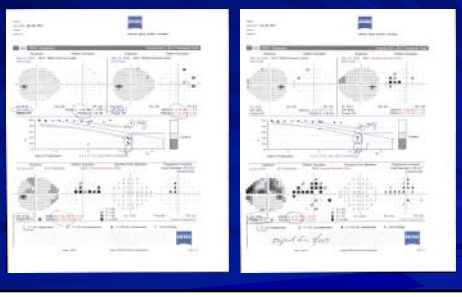
Progression



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Osteoporosis Medications

- Bisphosphonates:
  - Fosamax™ (Alendronate)
  - Actonel™ (Risedronate)
    - Episcleritis
    - Uveitis
    - Iritis
- Typically, the benefit of using these agents outweigh the risks for ocular side effects
- Encourage patients to get regular ophthalmic exams and to report any acute changes!

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COX-2 Specific Inhibitors

- Celebrex™ (celecoxib)
  - Cataracts
  - Glaucoma
  - Conjunctival hemorrhage
  - Vitreous floaters
- Hey Celebrex™, where did your brothers **Vioxx**™ and **Bextra**™ go?!?! Oh how we miss them…

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Anticonvulsants

- Sabril™ (vigabatrin)
  - Uncommon agent used in infantile spasms and in refractory partial complex seizures
  - FDA mandated BLACK BOX WARNING:
    - Optic atrophy
    - Optic neuritis
    - Peripheral constriction of visual field
    - Decrease in visual acuity

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Sabril™ (vigabatrin)

- Toxic Optic Neuropathy
- Selective, irreversible, inhibitor of GABA transaminase for refractory complex partial seizures and infantile spasms
- Clearly been shown to cause a dose-dependent, permanent peripheral field constriction.
- The earliest reports of toxicity were after 11 months of exposure
  - The vision loss is usually asymptomatic and spares the macula
  - Sub-clinical depression of macular function and color vision deficits have been reported
- Mechanism has not yet been fully demonstrated
  - Most likely involves toxicity to both retinal photoreceptors and ganglion cells
- Possibly induces a taurine deficiency that leads to toxicity
  - Taurine supplementation may prevent toxicity

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Autoimmune Agents

- Treatment of Multiple Sclerosis
  - Gilenya™ (fingolimod)
    - FDA-approved oral agent for the treatment of relapsing forms of multiple sclerosis (MS) in September 2010
    - Macular edema
      - FAME - Fingolimod-Associated Macular Edema

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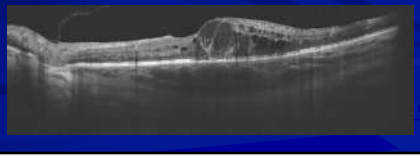
52-year-old woman

- History of MS was switched from Tysabri™(natalizumab) to Gilenya™ (fingolimod)
- Blurred vision in her left eye, BVA 20/40
  - Noticed blurred vision 7-8 weeks after starting Gilenya™



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Gilenya™ (fingolimod) & FAME

- Prior to starting medication
  - Follow up in 3-6 months after medication started
- Be aware of FAME
- If FAME occurs
  - Stopping Gilenya typically will reverse edema
    - May need topical NSAID and/or steroid

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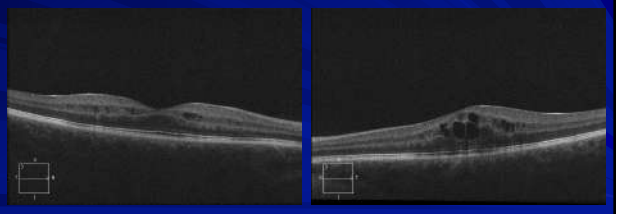
Another Gilenya™(fingolimod) and FAME



Courtesy of Joe Shovlin, OD, FAAO

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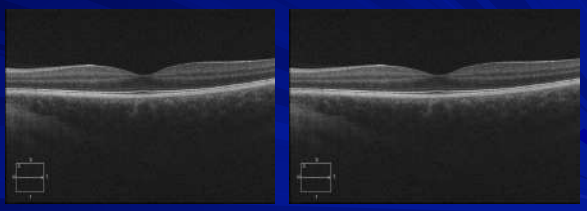
After D/C Gilenya™(fingolimod)



Courtesy of Joe Shovlin, OD, FAAO

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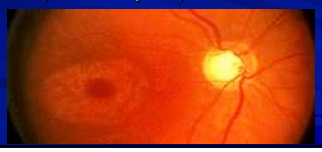
Autoimmune Agents

- Treatment of rheumatologic conditions
  - Rheumatoid arthritis, systemic lupus erythmatosis
- Plaquenil™ (hydroxychloroquine)
  - Bull's eye maculopathy



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Immunosuppressive Medications

Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Traditional Meds and Biologics

Methotrexate +/-
Hydroxychloroquine (Plaquenil™)

↓

Tumor Necrosis Factor α Inhibitors
- Adalimumab (Humira™)
- Infliximab (Remicade™)
- Etanercept (Enbrel™)
- Certolizumab (Cimzia™)

↓

Additional Agents
- Abatacept (Orencia™)
- Tocilizumab (Actemra™)
- Tofacitinib (Xeljanz™)
- Rituximab (Rituxan™)

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Plaquenil™

Hydroxychloroquine (Plaquenil™) - Anti-malarial

- Ophthalmic side effects (infrequent with current dosing ranges):
  - Irreversible retinal damage has been observed ("chloroquine retinopathy").
  - If there are any indications of abnormality in the color vision, visual acuity, visual field, or retinal macular areas, or any visual symptoms (eg. light flashes or streaks), d/c drug stat

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Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- Recommendations were 2002 by the American Academy of Ophthalmology
- Improved screening tools and new knowledge about prevalence of toxicity have prompt the change
  - 1% after 5-7 years of use or a cumulative dose of 1000 grams (Plaquenil)
- There is no treatment for this condition
  - Therefore must be caught early
- Screening for the earliest hints of functional or anatomic change
- Plaquenil toxicity is not well understood

American Academy of Ophthalmology Update

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

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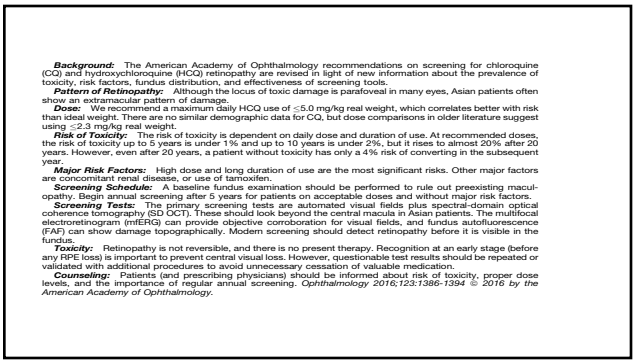

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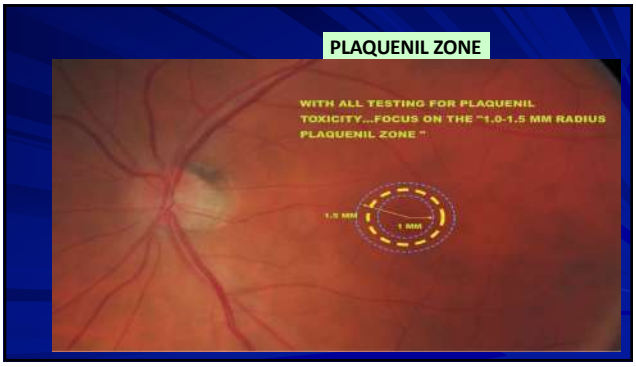

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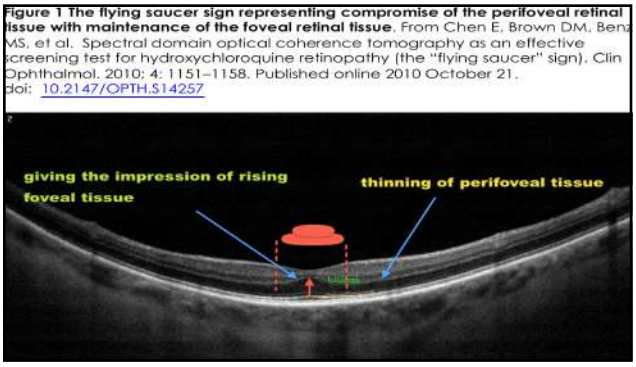

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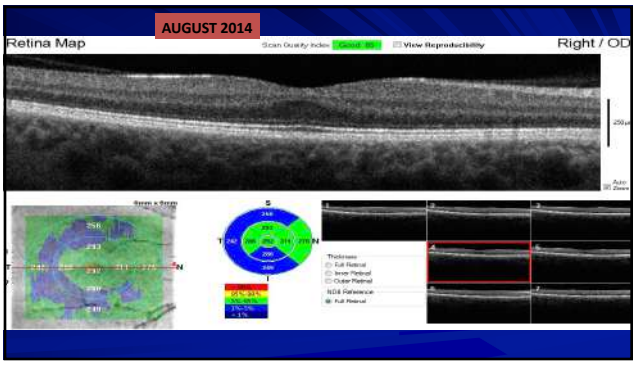

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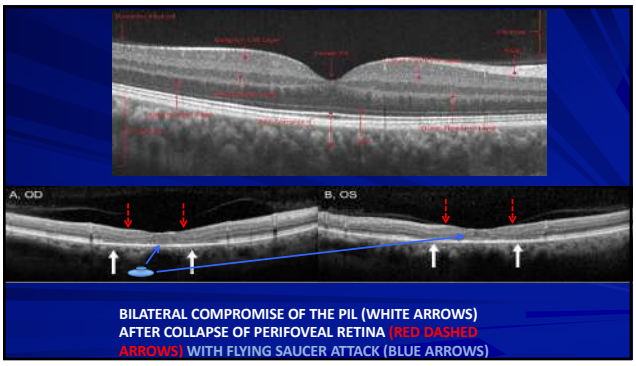

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71 yo woman

- With Lupus and hypertension
- Medications:
  - Clonazepam™
  - Plaquenil™ 200 mg BID, 15 years
  - 81 mg ASA
  - Prednisone
  - Losartan™
- VA 20/25 OD/OS (mild cataracts)
- Patient was told to see an ophthalmologist in 2013

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2016

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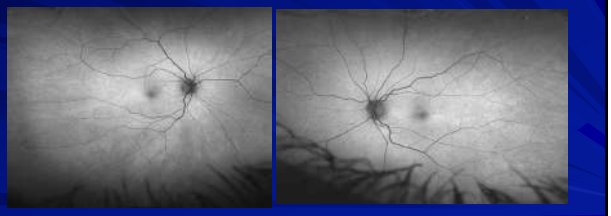
2016



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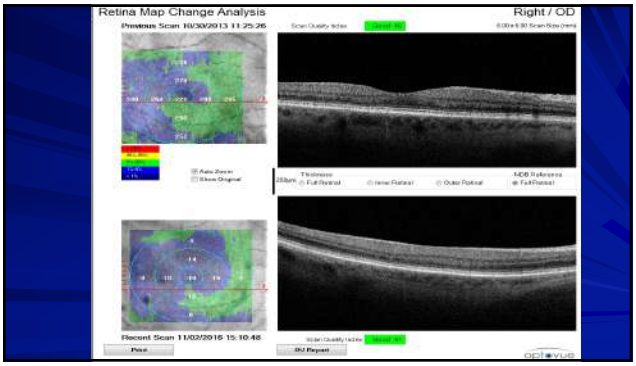

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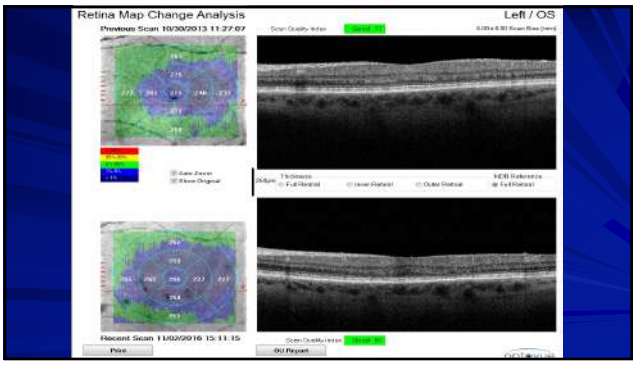

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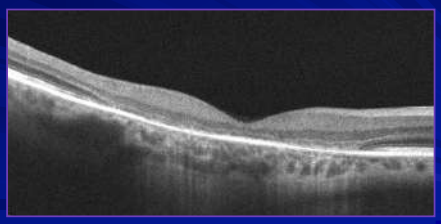
Plaquenil Toxicity



Courtesy of Joe Shovlin, OD, FAAO

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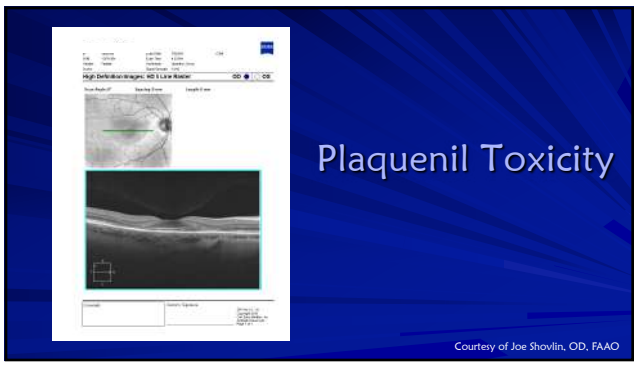

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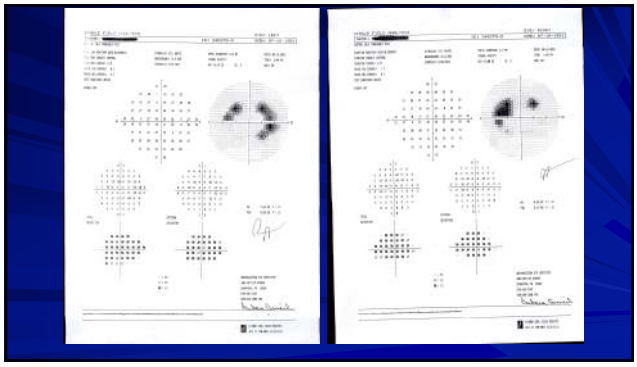

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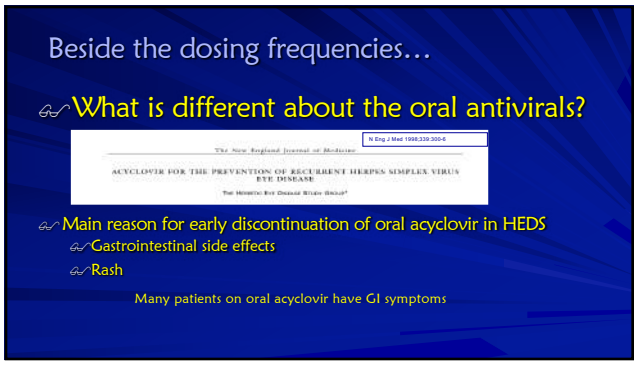

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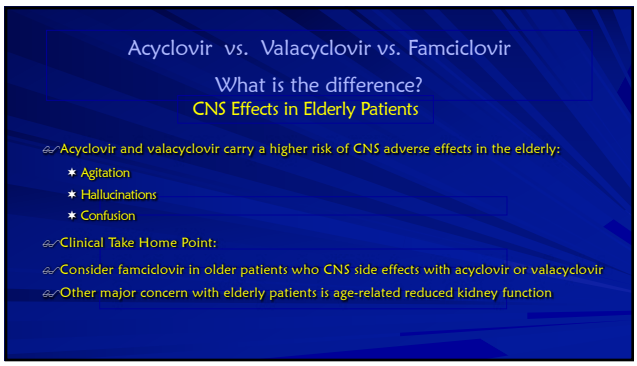
Acyclovir vs. Valacyclovir vs. Famciclovir
What is the difference?
CNS Effects in Elderly Patients
Acyclovir and valacyclovir carry a higher risk of CNS adverse effects in the elderly:
Agitation
Hallucinations
Confusion
Clinical Take Home Point:
Consider famciclovir in older patients who CNS side effects with acyclovir or valacyclovir
Other major concern with elderly patients is age-related reduced kidney function

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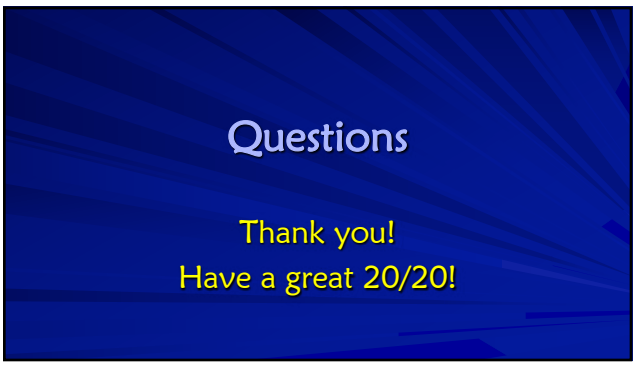
Questions
Thank you!
Have a great 20/20!

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