Complications of Pharmaceuticals Every Optometrist Should Know!

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Tracy Offerdahl, PharmD, FAAO
Heart of America
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Disclosures - Greg Caldwell, OD, FAAO

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru
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- Healthcare Registries – Chairman of Advisory Council for Diabetes
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Disclosures- Tracy Offerdahl, PharmD, FAAO

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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.
Thoughts

Always check the medication list
  - Review it with the patient (techs don’t always update)

Medications to H.A.T.E in neuro-op (Andy Lee, MD)
  - Hydroxychloroquine / chloroquine retinopathy
  - Amiodarone optic neuropathy - Anterior ischemic optic neuropathy
  - Tetracycline: pseudotumor cerebri
  - Ethambutol optic neuropathy

The Erectile dysfunction agents (Viagra) - Anterior ischemic optic neuropathy
Antibiotics

Fluoroquinolones

- **Levaquin™** (levofloxacin)
- **Cipro™** (ciprofloxacin)

- Tendon rupture
- Retinal detachment
  - 1 in 2,500 will experience (compared to 1 in 1,000 who will experience tendinitis)
Oral fluoroquinolone not associated with retinal detachment

Primary Care Optometry News, December 2018

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.

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.
Antibiotic Fluoroquinolones
Dropless Cataract Surgery
Antibiotic Fluoroquinolones
Dropless Cataract Surgery
**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
Benign intracranial hypertension

“It’s not rare if it’s in your chair”
PTC VS. IIH
(THANKS DR. JOE SOWKA)

• **Pseudotumor Cerebri (PTC)**
  • Increased intracranial pressure in the absence of an intracranial mass lesion
  • Many causative agents have been identified

• **Idiopathic Intracranial Hypertension (IIH)**
  • Increased intracranial pressure without an identifiable cause
  • Young, obese females are at risk

• **Primary PTC**
  • IIH

• **Poor CFS drainage**
Minocycline Optic Nerve Edema
Minocycline Optic Nerve Edema
6 Months Later
1 Year Later
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
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?
Anti-arrhythmics

- Treatment of cardiac arrhythmia
  - Cordarone™ (amiodarone)
  - Corneal deposits
  - Optic neuritis
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Punctate opacities in a horizontal linear pattern in the inferior cornea</td>
</tr>
<tr>
<td>II</td>
<td>More aligned deposits in a linear pattern that extend into the inferior pupillary margin toward the limbus</td>
</tr>
<tr>
<td>III</td>
<td>Increased numbers of branching patterns in the inferior pupillary area into the visual axis</td>
</tr>
<tr>
<td>IV</td>
<td>Deposits form additional clumps compared with grade III</td>
</tr>
</tbody>
</table>
65-year-old woman

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

20/25 BVA
6 Months Later

20/25 BVA
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
Amiodarone Optic Neuropathy
(Toxic Optic Neuropathy)
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
Rhoprossa™ 0.02% (netarsudil)
Causes Expansion of TM in Donor Eyes
Increases TM Outflow Facility in Clinic

<table>
<thead>
<tr>
<th>Change (%)</th>
<th>Control</th>
<th>+ Netarsudil</th>
</tr>
</thead>
</table>
| TM Outflow Facility (Healthy Volunteers)


TM: Trabecular Meshwork; SC: Schlemm’s Canal; Control: buffered saline solution; ESV: Episcleral Vein
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)

<table>
<thead>
<tr>
<th>Baseline IOP &gt;20 to &lt;25 mmHg</th>
<th>Netarsudil QD</th>
<th>Timolol BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-4.2</td>
<td>-4.3</td>
</tr>
<tr>
<td>Mean</td>
<td>-4.1</td>
<td>-4.3</td>
</tr>
<tr>
<td>Max</td>
<td>-10.7</td>
<td>-10.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline IOP ≥25 to &lt;30 mmHg</th>
<th>Netarsudil QD</th>
<th>Timolol BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-3.7</td>
<td>-5.3</td>
</tr>
<tr>
<td>Mean</td>
<td>-3.7</td>
<td>-5.3</td>
</tr>
<tr>
<td>Max</td>
<td>-12.3</td>
<td>-12.0</td>
</tr>
</tbody>
</table>
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

1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing information. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].
Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Netarsudil 0.02% QD (N=839) n (%)</th>
<th>Timolol 0.5% BID (N=839) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE Conjunctival Hemorrhage</td>
<td>144 (17.2)</td>
<td>15 (1.8)</td>
</tr>
<tr>
<td>AE Resulting in Discontinuation</td>
<td>8 (1.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

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
**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*

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)

Images were taken from netarsudil subjects
Source: Courtesy of study investigators  AR-13324-CS302
My Experience
OD treated OS gtts
### Summary of the Most Common Netarsudil Ocular TEAEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>TEAE %</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival Hyperemia</td>
<td>54.4%</td>
<td>TEAE, Severity did not increased with continued dosing, Sporadic</td>
</tr>
<tr>
<td>Cornea Verticillata</td>
<td>20.9%</td>
<td>Asymptomatic, 7.4% experienced reduced visual acuity (not clear to a directly associated), all resolved after 13 weeks of D/C</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>17.2%</td>
<td>TEAE, Mild in severity and transient, Self-resolving with continued dosing</td>
</tr>
</tbody>
</table>
Toxic Optic Neuropathy

**Causes**
- Ethambutol (TB)
- Isoniazid
- Antimicrobials
  - chloramphenicol, streptomycin, penicillamine
- Halogenated hydroxyquinolones
- Vigabatrin
- Disulfiram
- Tamoxifen
- Sildenafil

**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)
Ethambutol

- Toxic optic neuropathy
- 2 cases in the past 12 months (2019)
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
3/13/19 20/30, 20/100, 20/25
4/29/19 20/25, 20/50, 20/20
7/29/19 20/20, 20/25, 20/20
Progression
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!
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…
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
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
Autoimmune Agents

ꔾ Treatment of Multiple Sclerosis

★ Gilenya™ (fingolimod)

✓ FDA-approved oral agent for the treatment of relapsing forms of multiple sclerosis (MS) in September 2010

 nomine Macular edema

– FAME - Fingolimod-Associated Macular Edema
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™
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
Another Gilenya™ (fingolimod) and FAME

Courtesy of Joe Shovlin, OD, FAAO
After D/C Gilenya™ (fingolimod)
Autoimmune Agents

- Treatment of rheumatologic conditions
  - Rheumatoid arthritis, systemic lupus erythematosus
- Plaquenil™ (hydroxychloroquine)
  - Bull’s eye maculopathy
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™)
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
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 Statement

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

Michael F. Marmor, MD,1 Ulrich Kellner, MD,2 Timothy Y.Y. Lai, MD, FRCOphth,3 Ronald B. Melles, MD,4 William F. Mieler, MD,5 for the American Academy of Ophthalmology

Background: The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

Pattern of Retinopathy: Although the locus of toxic damage is parafoveal in many eyes, Asian patients often show an extramacular pattern of damage.

Dose: We recommend a maximum daily HCQ use of ≤5.0 mg/kg real weight, which correlates better with risk than ideal weight. There are no similar demographic data for CQ, but dose comparisons in older literature suggest using ≤2.3 mg/kg real weight.

Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

Major Risk Factors: High dose and long duration of use are the most significant risks. Other major factors are concomitant renal disease, or use of tamoxifen.

Screening Schedule: A baseline fundus examination should be performed to rule out preexisting maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

Screening Tests: The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients. The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus.

Toxicity: Retinopathy is not reversible, and there is no present therapy. Recognition at an early stage (before any RPE loss) is important to prevent central visual loss. However, questionable test results should be repeated or validated with additional procedures to avoid unnecessary cessation of valuable medication.

Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose levels, and the importance of regular annual screening. Ophthalmology 2016;123:1386-1394 © 2016 by the American Academy of Ophthalmology.

Retinal toxicity from chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) has been recognized for many years. Chloroquine toxicity remains a problem in many parts of the world, but is seen less frequently in the United States where the drug largely has been replaced by HCQ. Hydroxychloroquine is used widely for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis, and related inflammatory and dermatologic conditions. It is now being considered for new applications in diabetes mellitus, heart disease, and adjunct cancer therapy. Thus, it is important for ophthalmologists and other physicians to understand the prevalence and risk factors for retinopathy.
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WITH ALL TESTING FOR PLAQUENIL TOXICITY...FOCUS ON THE "1.0-1.5 MM RADIUS PLAQUENIL ZONE"
Figure 1 The flying saucer sign representing compromise of the perifoveal retinal tissue with maintenance of the foveal retinal tissue. From Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the “flying saucer” sign). Clin Ophthalmol. 2010; 4: 1151–1158. Published online 2010 October 21. doi: 10.2147/OPTH.S14257
BILATERAL COMPROMISE OF THE PIL (WHITE ARROWS) AFTER COLLAPSE OF PERIFOVEAL RETINA (RED DASHED ARROWS) WITH FLYING SAUCER ATTACK (BLUE ARROWS)
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
Plaquenil Toxicity

Courtesy of Joe Shovlin, OD, FAAO
Antivirals
Beside the dosing frequencies...

What is different about the oral antivirals?

🔗 Main reason for early discontinuation of oral acyclovir in HEDS
🔗 Gastrointestinal side effects
🔗 Rash

Many patients on oral acyclovir have GI symptoms
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&amp;C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of the L-valyl ester of the antiviral drug acyclovir. VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&amp;C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>FAMVIR tablets contain 125 mg, 250 mg, or 500 mg of famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.</td>
</tr>
</tbody>
</table>

Generics available in the US contain lactose

* In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)
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 experience CNS side effects with acyclovir or valacyclovir.

- Other major concern with elderly patients is age-related reduced kidney function.
Questions?

Thank You!
Tracy and Greg