Advances in Pharmacotherapy: What Every Optometrist Needs to Know

Greg A. Caldwell, O.D., F.A.A.O.
Barry J. Frauens, O.D., F.A.A.O.

2 hour course presentation

Course Description:

Every year the FDA approves numerous pharmaceuticals (AKA "Legend Drugs") for the management of diseases in many therapeutic categories. This course will review recently approved pharmaceuticals that are pertinent to optometric patient care. This course will review systemic and ocular complications of select pharmaceuticals.

Objectives:

- Review the recently approved pharmaceuticals for ocular usage
- Review the recently approved pharmaceuticals that impact optometric patient care
- Discuss marijuana and the ocular side effects
- Review potential systemic complications of ocular treatments
- Review potential ocular complications of systemic treatments
- Increase the optometrist's comfort level and knowledge in the various advances in pharmacotherapy

Outline:

1. Disclosures- Greg Caldwell, OD, FAAO
    a. Will mention many products, instruments and companies during our discussion
    b. I don't have any financial interest in any of these products, instruments or companies
    c. Pennsylvania Optometric Association –President 2010
    d. POA Board of Directors 2006-2011
    e. American Optometric Association, Trustee 2013-2016
    f. Thank you to the members and those who join
    g. I never used or will use my volunteer positions to further my lecturing career
    h. Lectured for: Shire, BioTech, Optovue, Allergan, Alcon, Aerie
    i. Advisory Board: Allergan
    j. Envolve: PA Medical Director
2. Disclosures- Barry J. Frauens, O.D., F.A.A.O.
3. Therapeutic Areas to be Covered
    a. Optometry
    b. Endocrinology
    c. Cardiology/Vascular Disease
    d. Hepatology (liver, pancreas, gall bladder)
    e. Neurology
    f. Dermatology
4. **Optometry**
5. Rhopressa (netarsudil ophthalmic solution)
    a. Aerie Pharmaceuticals

b. Approved December 2017
c. Treatment of glaucoma or ocular hypertension
d. Rho kinase inhibitor
    i. ROCK-NET Inhibitor
e. Once daily in the evening
    i. Twice a day dosing is not well tolerated and is not recommended
f. Side Effects
    i. Conjunctival hyperemia
    ii. Corneal verticillata
    iii. Instillation site pain
    iv. Conjunctival hemorrhage
g. Rhopressa (ROCK-NET Inhibitor) Triple-Action
h. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
i. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015. 24(1):51-4.
j. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900
k. 3 Identified IOP-Lowering Mechanisms
l. Netarsudil Causes Expansion of TM in Donor Eyes, Increases TM Outflow Facility in Clinic
m. Netarsudil Is Similarly Effective at Baseline IOPs
    i. <25 mmHg and ≥25 mmHg
n. Most Frequently Reported Systemic TEAEs
o. Netarsudil Once Daily Demonstrated Consistent Ocular Safety Profile with Four Phase 3 Studies
p. Ocular AEs Leading to Discontinuations
q. *Pooled Phase 3 Studies*
r. Conjunctival Hyperemia Was Sporadic and Severity Did Not Increase with Continued Dosing
s. Netarsudil Once-Daily Dosing Biomicroscopy Hyperemia Severity Did Not Increase Over Time *Netarsudil QD (N=839)*
t. Conjunctival Hemorrhage Was Sporadic and Severity Did Not Increase with Continued Dosing
u. Cornea Verticillata Observed in Phase 3 Studies
v. Cornea Verticillata Due to Phospholipidosis
w. Summary of the Most Common Netarsudil Ocular TEAEs
x. How Will I Use Netarsudil to Treat Glaucoma?

6. Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%
    a. Bausch & Lomb
    b. November 2, 2017; approved (previously Vesneo**™**)

    c. Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
    d. Once daily monotherapy
    e. Dual mechanism of action
    f. Uveoscleral pathway to increase aqueous humor outflow
    g. Butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
    h. Ocular adverse events
    i. Conjunctival hyperemia, eye irritation, eye pain and instillation site pain
    j. Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur
7. Zerviate (cetirizine) ophthalmic solution 0.24%
    a. NicOx
    b. Approved May 2017
    c. Treatment of ocular itching associated with allergic conjunctivitis
    d. Twice daily (approximately 8 hours apart)
    e. Second generation antihistamine (H1 receptor antagonist)
    f. Binds competitively to histamine receptor sites to reduce
        i. Swelling
        ii. Itching
        iii. Vasodilation
8. Luxturna (voretigene neparvovec)
    a. Spark Therapeutics
    b. Approved December 2017
    c. For the treatment of vision loss due to confirmed biallelic RPE65-mediated inherited retinal disease
    d. Gene therapy for mutations in the RPE65 gene
    e. Intraocular suspension for subretinal injection
    f. Administered to each eye on separate days
        i. Within a close interval, no fewer than 6 days apart
    g. Once inside the eye, the new genetic material enables patients to produce the protein that is missing as a result of their genetic mutation
9. Luxturna (voretigene neparvovec)
    a. *RPE65*-mediated Inherited Retinal Disease (IRD)
    b. Also known as inherited retinal dystrophies
    c. Leber's congenital amaurosis (LCA)
    d. Autosomal recessive retinitis pigmentosa (RP).
        i. Group of rare blinding conditions caused by one of more than 220 different genes
    e. Biallelic *RPE65*gene mutations often experience
        i. Night blindness (nyctalopia)
        ii. Nystagmus
        iii. Loss of peripheral vision
            1. Develop tunnel vision

2. Eventually, they may lose their central visionl
    a. Resulting in total blindness

10. Humira (adalimumab)
    a. Company: Abbvie
    b. Approved July 2016
    c. Indication: uveitis
        i. Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
    d. Dosage: subcutaneous injection
        i. Recommended dose is 80 mg initial dose
        ii. Followed by 40 mg every other week starting one week after initial dose
    e. The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for "off-label" uses.
    f. Monitoring parameters:
    g. Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to ACTIVE tuberculosis
    h. Once Humira is initiated, watch for any signs or symptoms of infection…if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.
        i. Non-infectious intermediate, posterior and panuveitis
            1. Reason for reduced acuity?
11. Xiidra (lifitegrast) 5%
    a. Company: Shire
    b. Approved July 2016
    c. Specific treatments/indication: dry eye disease
        i. Signs and symptoms of dry eye
    d. Dosage: one drop twice daily in each eye, 12 hours apart
        i. Dysgeusia, site irritation, blurred vision
    e. Relief as soon as 2 weeks with symptoms
        i. Eye Dryness Score
    f. Signs improve as soon as 12 weeks
        i. Inferior cornea staining
    g. Mechanism of Action
    h. Lymphocyte function-associated antigen-1 antagonist
        i. LFA-1 is found on the T-cell
        ii. Blocks ICAM-1/LFA-1 interaction
            1. Intercellular adhesion molecule-1
        iii. ICAM is overexpressed in dry eye
            1. Cornea, conjunctiva, lacrimal gland
    i. Anti-inflammatory by inhibiting
        i. T-cell activation
        ii. T-cell migration
        iii. Cytokine Release
    j. Xiidra or Restasis? Or BOTH?

i. We need more longitudinal data from post-marketing surveillance to determine efficacy and toxicity as an individual drug, as well as efficacy and toxicity as compared to Restasis, but Xiidra data is very promising!
ii. Both fairly expensive – Medicare will hopefully cover soon…

k. Only pharmaceutical indicated for signs and symptoms of dry eye disease
l. First 5 Rx don't count
m. Works within 2 weeks for moderate DED, 6 weeks for mild, and cornea staining takes 12 weeks
n. Use it as a diagnostic
o. 30 million USA adults with DED
p. BID means 12 hours apart
q. Get in front of the dysgeusia
r. Works great for GPC and SAC. Look for post IOL patient

12. Hetlioz (tasimelton)
    a. Company: Vanda Pharmaceuticals
        i. Approved January 2014
        ii. Specific treatments: non-24-hour sleep-wake disorder in the totally blind
            1. "As seen on TV"…circadian rhythm disorders in patients who are blind
        iii. Dosage: 20 mg per day, taken before bedtime
            1. $10,000 PER MONTH!!!
            2. Compared to placebo, it increases sleep by 28 minutes!
        iv. Other specialties: neurology, sleep
13. Marijuana
    a. Marijuana Active ingredients:
        i. Cannibis sativa
            1. Tetrahydrocannibinol (Δ^1-THC)
            2. Cannabidiol (CBD)
            3. High THC/CBD ratio $\cong$ 1
    b. Marijuana Ocular effects
        i. Inhaled
            1. Decrease in IOP
                a. 25% reduction in IOP lasting 3-4 hours
                    i. Not all experience this reduction
            2. Systemic Toxicity
                a. Emphysema-like lung changes
                b. Altered mental status
                c. Orthostatic hypotension
            3. Conjunctival vasodilation
                a. Conjunctival hyperemia
            4. Pupillary constriction
            5. Narrowing of the palpebral fissure
            6. Reduction in tear secretion

14. Endocrinology-Incretin System
15. Endocrinology
    a. New/updated Type 2 diabetes guidelines suggest use of insulin and/or agents that act as agonists on the incretin system!
    b. Many, MANY manufacturers are starting to make new combination drugs that contain both
        i. Benefit? Fewer injections per day!
        ii. Risk? The patient's wallet, and increased risk of hypoglycemia!
16. Endocrinology
    a. Ozempic (semaglutide)
        i. Approved 2017 – Novo Nordisk
        ii. GLP-1 Agonist
        iii. Type 2 diabetes
    b. Soliqua 100/33 (insulin glargine and lixisenatide injection)
        i. Approved November 2016
        ii. Long-Acting insulin + GLP-1 Agonist
        iii. Inadequately controlled type 2 diabetes
17. Endocrinology
    a. Synjardy (empagliflozin and metformin hydrochloride)
        i. Approved August 2015
        ii. SGLT-2 inhibitor + biguanide (ORAL)
        iii. Type 2 diabetes
    b. ALERT! Watch for even NEWER guideline updates to include the "flozins" (above and Invokana/canagliflozin) due to new data that shows improvement in CV risks in HIGH RISK patients!
18. Endocrinology – Ribociclib (Kisqali)
    a. Kinase inhibitor used in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
    b. Approved 2017 – Novartis Pharmaceuticals
    c. Adverse drug reactions: mainly neutropenia, QT prolongation, hepatobiliary toxicity
19. Cardiology/Vascular Disease
    a. Byvalson (nebivolol and valsartan)
        i. Approved June 2016
        ii. Cardioselective beta-blocker + angiotensin receptor blocker (ARB)
        iii. Hypertension
    b. Prestalia (perindopril arginine and amlodipine besilate)
        i. Approved January 2015
        ii. ACE-inhibitor + dihydropyridine calciuim channel blocker
        iii. Hypertension
20. Cardiology/Vascular Disease
    a. Yosprala (aspirin and omeprazole)

i. Approved September 2016
ii. Prevention of cardiovascular and cerebrovascular events
iii. Adds "built-in" stomach protection with omeprazole…but that may not be a good thing
1. Fractures, anemias, gut infections…

21. Cardiology/Vascular Disease
a. Repatha (evolocumab)
i. Approved August 2015
ii. Heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease
b. Praluent (alirocumab)
i. Approved 2015
ii. Heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease
c. Both subcutaneous injections…used when "statins" don't work!
i. Stay tuned for myopathy issues…
1. "statins on steroids" – diplopia, etc.

22. Hepatology (liver, pancreas, gall bladder)
a. Vemlidy (tenofovir alafenamide)
i. Approved November 2016
ii. Chronic hepatitis B
b. Epclusa (sofosbuvir and velpatasvir)
i. Approved June 2016
ii. Hepatitis C
iii. You will see many new hepatitis B and C meds, as now these patients can be CURED!

23. Neurology
a. Zinbryta (daclizumab)
i. Approved May 2016
ii. Injectable interleukin-2 receptor blocker
iii. Relapsing multiple sclerosis
b. Troxyca ER (oxycodone and naltrexone)
i. Approved August 2016
ii. Pure opioid agonist + pure opioid antagonist…another in a long line of "me-too" drugs!
iii. Severe pain

24. **Dermatology** – Doxycycline
a. Doryx (enteric coated hyclate pellet), Adoxa (monohydrate), Oracea (monohydrate – 75% immedidate release + 10% delayed release)
i. Approved 2005
b. Good 'ol doxy…being reborn AGAIN!
c. Did you know?
i. At normal doses, the monohydrate and hyclate salts have equal efficacy?

ii. At normal dose, the monohydrate salt MIGHT have a decrease in GI side effects.
iii. ALL doxy products can generally be taken with food to decrease GI upset.
1. Don't get caught in the web of "sexy doxy" formulations

25. Dermatology –Delafloxacin (Baxdela)
    a. A fluoroquinolone antibiotic for acute bacterial skin and skin structure infections
    b. Approved 2017 – Melinta Therapeutics
    c. Available orally and intravenously
    d. Adverse effects: SO NEW…but in clinical trials, the only ophthalmic side effects that were noted = blurred vision!
        i. Only time will tell if retinal detachment is something to worry about with this new FQ!

26. Systemic Medicines with Ocular Side Effects or Ocular Medicines with Systemic Side Effects

27. Antibiotics
    a. Fluoroquinolones
        i. Levaquin (levofloxacin)
        ii. Cipro (ciprofloxacin)
        iii. Retinal detachment
            1. 1 in 2,500 will experience (compared to 1 in 1,000 who will experience tendinitis)
28. Antibiotics (anti-inflammatory)
    a. Tetracycline analogs
    b. Doxycycline
    c. Minocycline
    d. Enhances the effects of
        i. Coumadin
        ii. Digoxin
    e. Idiopathic intracranial hypertension
    f. Pseudotumor cerebri
    g. Hyperpigmentation
    h. Benign intracranial hypertension
    "It's not rare if it's in your chair"
29. Alpha 1 Blockers
    a. Floppy iris syndrome!
    b. Treatment of enlarged prostate:
        i. Uroxatrol (Alfuzosin)
        ii. Flomax (Tamsulosin)
            1. 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
30. Treatment of CHF and/or hypertension
    a. Coreg (Carvedilol)
        i. Alpha1/beta 2 blocker

31. Treatment of refractory hypertension:
    a. Hytrin (Terazosin)
        i. Alpha 1 blocker
32. Alpha 1 Blockers
    a. Floppy iris syndrome and miosis!
    b. After 4 rounds of phenylephrine, tropicamide, and cyclopentolate, if poor dilation
    c. Iris hooks
    d. What happens at the time of making the incision?
    e. Tricks with different viscoelastic agents
    f. Post op day 1, IOP 43
    g. What's the caution?
33. Anti-arrhythmics
    a. Treatment of cardiac arrhythmia
        i. Cordarone (amiodarone)
        ii. Corneal deposits
        iii. Optic neuritis
    b. 65 year old woman
    c. Patient reports decreasing vision over past 6-9 months. Especially at near
    d. Vision 20/50 OU
    e. Topography
    f. Topography
    g. 6 Months Later
    h. 6 Months Later
    i. 67 year old man complains of vision slowly deteriorating over the past 8 months
    j. History of NA-ION 10 months ago OD
    k. Patient sees family physician for physical due to recent NA-ION
    l. Patient has not been to PCP for 35 years
    m. Patient started Cardarone
    n. VA 20/80 OD 20/25 OS (9 months ago)
    o. VA 20/400 OD 20/200 OS (today)
    p. CF: severe constriction OU
    q. SLE: vortex corneal whorls OU
    r. Amiodarone Optic Neuropathy
34. Osteoporosis Medications
    a. Bisphosphonates:
        i. Fosamax (Alendronate)
        ii. Actonel (Risedronate)
            1. Episcleritis
            2. Uveitis
            3. Iritis
    b. Typically, the benefit of using these agents outweigh the risks for ocular side effects

c. Encourage patients to get regular ophthalmic exams and to report any acute changes!

35. COX-2 Specific Inhibitors
    a. Celebrex (celecoxib)
        i. Cataracts
        ii. Glaucoma
        iii. Conjunctival hemorrhage
        iv. Vitreous floaters
    b. Hey Celebrex, where did your brothers Vioxx and Bextra go?!?! Oh how we miss them…
36. Anticonvulsants
    a. Sabril (vigabatrin)
        i. Uncommon agent used in infantile spasms and in refractory partial complex seizures
        ii. FDA mandated BLACK BOX WARNING:
        iii. Optic atrophy
        iv. Optic neuritis
        v. Peripheral constriction of visual field
        vi. Decrease in visual acuity
37. Autoimmune Agents
    a. Treatment of Multiple Sclerosis
        i. Gilenya (fingolimod)
            1. FDA-approved oral agent for the treatment of relapsing forms of multiple sclerosis (MS) in September 2010.
            2. Macular edema
                a. FAME - Fingolimod-Associated Macular Edema
    b. 52 year old woman
        i. History of MS was switched from Tysabri (natalizumab) to Gilenya (fingolimod)
        ii. Blurred vision in her left eye, BVA 20/40
        iii. Noticed blurred vision 7-8 weeks after starting Gilenya
    c. Gilenya (fingolimod) & FAME
        i. Prior to starting medication
        ii. Follow up in 3-6 months after medication started
        iii. Be aware of FAME
        iv. If FAME occurs
            1. Stopping Gilenya typically will reverse edema
            2. May need topical NSAID and/or steroid
    d. Another Gilenya (fingolimod) and FAME
38. Autoimmune Agents
    a. Treatment of rheumatologic conditions
        i. Rheumatoid arthritis, systemic lupus erythmatosis
    b. Plaquenil (hydroxychloroquine)
        i. Bull's eye maculopathy

39. Immunosuppressive Medications
40. PLAQUENIL
    a. Hydroxychloroquine (Plaquenil) - Anti-malarial
    b. Ophthalmic side effects (infrequent with current dosing ranges):
        i. Irreversible retinal damage has been observed ("chloroquine retinopathy").
        ii. 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
    c. Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy
    d. Recommendations were 2002 by the American Academy of Ophthalmology
    zImproved screening tools and new knowledge about prevalence of toxicity have prompt the change
    e. <u>1% after 5-7 years of use or a cumulative dose of 1000 grams (Plaquenil)</u>
    f. There is no treatment for this condition
        i. Therefore must be caught early
    g. Screening for the earliest hints of functional or anatomic change
    h. Plaquenil toxicity is not well understood
    i. Revised Again
    j. 71 yo woman
        i. With Lupus and hypertension
        ii. Medications:
            1. Clonazepam
        iii. Plaquenil 200 mg BID, 15 years
        iv. 81 mg ASA
        v. Prednisone
        vi. Losartan
        vii. VA 20/25 OD/OS (mild cataracts)
        viii. Patient was told to see an ophthalmologist in 2013
        ix. 2016
41. Thank You!
42. Questions