

## *The State of Therapeutics In Eye Care – Part 2*

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### Financial Disclosure

Drs Ron Melton and Randall Thomas are consultants to, on the speakers bureau of, on the advisory committee of, or involved in research for the following companies: ICARE and B+L

### Qbrexza™ (glycopyrronium tosylate)

- In a class of anticholinergics – therefore can affect accommodation
- Indication: Primary Axillary Hyperhidrosis (excessive underarm sweating)
- Approved in 2018 as a medicated towelette applied directly to skin
- Prescription drug approved down to age 9.
- Potential ocular side-effects:
  - » Dilated pupils
  - » Dry eyes
  - » Blurred vision
  - » Angle closure (in anatomically narrow angles)
- Manufacturer: Demira, Inc. Menlo Park, CA

### Treatment for Thyroid-related Proptosis

- New breakthrough drug to reduce proptosis
- Tepezza™ (teprotumumab) Horizon Therapeutics
- 75% achieved ~2.5mm reduction in proptosis
- I.V. infusion every 3 weeks for 8 sessions
- Mild to moderate side effects:
  - » Muscle spasm
  - » Nausea
  - » Alopecia
  - » Diarrhea
  - » Fatigue
  - » Hyperglycemia
  - » Hearing loss
  - » Dry skin
  - » Dysgeusia
  - » Headache
- Cost is about \$100,000.00 for 6 month treatment

NEJM January 23, 2020

### Idiopathic Orbital Inflammatory Disease (Orbital Pseudotumor)

- Usually acute onset, unilateral, red eye
- Chemosis, lid edema and erythema
- Proptosis, EOM dysfunction - diplopia ±
- Systemic association rare if unilateral
- VA, exophthalmometry, IOP, CT or MRI
- Treatment is oral prednisone, high dose (1mg/kg/d initially) with taper

### Osteoporosis and the Eye

- “Bisphosphonates are the mainstay therapy in the prevention and treatment of osteoporosis in both men and post-menopausal women.”
  - These drugs inhibit osteoclast-induced bone resorption.
  - Potential side-effects include (in one or both eyes):
    - » Orbital inflammation
    - » Uveitis
    - » Scleritis
    - » Episcleritis
    - » Non-specific conjunctivitis
- These generally occur within 2 or 3 months
- Discontinuation generally allows for reversal of these ocular side-effects.

Modern Optometry, June 2019

## Idiopathic Orbital Inflammation

- Bisphosphonate generic drugs typically end in “ronate”
- Common brand/generic names are:
  - » Fosamax® - alendronate sodium
  - » Boniva® - ibandronate sodium
  - » Actonel® - risedronate sodium
  - » Reclast® - zoledronic acid

## The Eye and the ED

- Why people go to the ED with Eye problems
  - Most common ICD Diagnosis

Conjunctivitis	33%
Corneal injury	13%
Corneal F.B.	8%
Hordeolum	4%
- Mean ED charge \$989.30 for eye visit
- Eye visits: 1.5% of all visits
  - Vazini K, et al. Ophthalmology 2016;123(4):917-19*
- “About 400,000 patients per year present to U.S. emergency departments with eye injuries, and children represent up to one-third of those injured.”
  - JAMA Ophthal, August, 2018*

## Same Day Problem Work-Ins

- Average “Urgent Care” visit costs \$168.00
- ER visit is “over 10 times more expensive”
- Antibiotics for viral conjunctivitis is common practice in these settings
- “We’ve cultivated a culture of “yes”. If patients want or need to be seen, then they get an appointment.”
- “There are ways to provide same-day care. Such care is good medicine -- and it’s good for the practice.”

EyeNet October, 2019

## Acute Conjunctivitis and Antibiotic Use

- “Conjunctivitis is the most common cause of red or pink eye, but most (up to 80%) are viral.”
- “Topical antibiotics (for bacterial infection) provide only a very modest beneficial effect on clinical remission.”

Antibiotic Rx	Combo Rx
- OD’s – 44%	OD’s – 30%
- MD’s – 36%	MD’s – 23%
- Non-Eye Dr’s – 60%	Non-Eye Dr’s – 8%
- One-fifth of all Rx’s were for a combination antibiotic-steroid “which are contra-indicated in acute cases of conjunctivitis.” (Not True!)
- Use of AdenoPlus may reduce diagnostic uncertainty and increase comfort with deferring antibiotic therapy.

Ophthalmology, August, 2017

## Adenoviral Infections

- Common cause of “red eyes”
- Assume adenovirus until proven otherwise
- Often have pre-auricular node
- Non-purulent watery discharge
- Usually starts in one eye and spreads to fellow eye in a few days
- Always evert lids to survey tarsal conjunctiva
- With EKC, spotty sub-epithelial infiltration in 50 to 75% of untreated cases

## Povidone - Iodine 5% ophthalmic solution

- Broad spectrum microbicide
- Indicated for “irrigation of the ocular surface”
- “Off label” use: Tx adenoviral keratoconjunctivitis
  - Anesthetize with proparacaine
  - Instill 1 or 2 drops of NSAID
  - Instill several drops Betadine 5% in eye(s), close eye(s)
  - Swab or rub excess over eyelid margin
  - After 1 minute, irrigate with sterile saline
  - Instill 1 or 2 drops of NSAID
  - Rx steroid qid x 4 days
- No reports in clinical trials of adverse reactions.
- Avoid use if patient is allergic to iodine
- Marketed as Betadine 5% ophthalmic prep solution (30 ml opaque bottle) by Alcon surgical
- CPT 99070 supply code

## Perspective on Betadine

- “The instillation of 5% povidone iodine solution in the conjunctival sac to prevent endophthalmitis has been shown to be effective and has been widely used for decades.”
- “One in three ASC’s prepares the 5% solution by diluting commercially available 10% povidone-iodine with saline solution. This practice has been shown to be safe and effective despite the labeling ‘do not use in the eye’ present on the 10% Betadine solution.”

OSN 9-10-15

## Insights Into Povidone-Iodine (Betadine)

- 5% Betadine works well on the ocular surface
- Betadine is a broad spectrum antimicrobicide
- “Brief application of povidone iodine (PI), 5% - 10%, to the ocular surface is commonly used world wide since the 1980s.”
- Toxicity is concentration and duration dependent
- It is preoperative standard-of-care
- Effectively kills bacteria that are resistant to topical antibiotics
- “Dilute PI solution is widely available, easy to make, inexpensive, and has been studied extensively.”

Survey Ophthalmol, Nov-Dec, 2018

## Literature on Adenoviral Keratoconjunctivitis

- Pseudo-membranes are a frequent complication of EKC
- In untreated cases, 50% of corneas develop subepithelial infiltrates – a cellular immune reaction against viral antigens
- AdenoPlus® is highly sensitive, specific, simple and inexpensive
- Bacterial superinfection is rare
- “Topical steroids relieve symptoms, and 5% betadine kills the virus in tears, thus reducing the risk of disease spread.”
- Restasis does not affect the natural course of the disease.

Jhanji V, et al. Survey Ophthalmol. 2015;60(5):435-43

## Don't Get Sued: Key Points

- Study the optic nerve – Don't let a normal or low IOP fake you out!
- Always document your discussions with your patients, especially for follow-up evaluations.
- Truly care, and be clinically attentive
- These 3 basic fundamentals can prevent a lot of law suits.

## Relatively Few ODs are Actively Managing Glaucoma

Deciles of GL TRx Volume (10% per Decile)	# of ODs	% of ODs by Decile	Annual GL TRx Range*	Est. Mean # of Patients Treated Annually
	<b>42,300</b>			
10	178	0.4%	4300 - 27400	1321
9	372	0.9%	2500 - 4100	288
8	560	1.3%	1800 - 2600	183
7	770	1.8%	1400 - 1800	133
6	1,000	2.4%	1000 - 1400	100
5	1,325	3.1%	800 - 1000	75
4	1,750	4.1%	600 - 800	58
3	2,500	5.9%	400 - 600	42
2	4,000	9.5%	200 - 400	25
1	20,000	47.3%	1 - 200	8
0	10,000	23.6%	0	0

\*All Glaucoma Therapeutic Agents (Branded and Generic)  
Source: ASC Data (Nov-Dec 2018)

50% of GL Prescriptions in Optometry are written by <7% of ODs

80% of GL Prescriptions in Optometry are written by 20% of ODs

The other 80% of ODs are managing VERY FEW GL patients therapeutically

## Glaucoma Treatment Options

- Prostaglandin Analogs
- Beta-Adrenergic Blockers
- Prostaglandin / Beta-Blocker combinations
- Adrenergic Agonists
- Adrenergic Agonist / Beta-Blocker combination
- Carbonic Anhydrase Inhibitors (CAI's)
- CAI/Beta-Blocker combination
- Pilocarpine derivatives
- Epinephrine derivatives
- Laser Trabeculoplasty
- MIGS
- Surgical Trabeculectomy
- Nitric Oxide donating PGA
- Rho-kinase Inhibitor

### Prostaglandin Receptor Agonists

- Latanoprost (Xalatan and generic) 0.005%
- Travoprost (Travatan Z) 0.004%
- Bimatoprost (Lumigan) 0.01%
- Tafluprost (Zioptan) 0.0015%

### Latanoprostene Bunod 0.024%

- FDA approved in November 2017
- First nitric oxide – donating prostaglandin
- One molecule – two mechanisms of action
  - » Enhances uveoscleral outflow
  - » Enhances trabecular meshwork outflow
- Reduces IOP by 7.5 – 9.1 mm Hg
- Preserved with 0.2% BAK
- Used once daily in the evening (6% red eyes)
- Comes in a 2.5 and 5 ml opaque bottle
- Refrigerate until opened
- Marketed as Vyzulta by Bausch & Lomb

### Xelpros™ (0.005% latanoprost)

- Xelpros is non-BAK preserved latanoprost
- Preservative is 0.47% potassium sorbate
- (Zioptan® is the only preservative-free formulation of a prostaglandin)
- Not available in retail pharmacies
- Must be ordered through their contracted compounding pharmacies, and the requisite 3-month supply is shipped monthly directly to the patients
- See Xelpros.com (Sun Pharmaceuticals) for details
- Dosed once daily, exactly as any other latanoprost product

### Rhopressa (netarsudil 0.02%)

- FDA approved in December 2017
- First rho-kinase inhibitor
- MOA purported to be enhancement of conventional trabecular outflow
- Use once daily in the evening
- Reduces IOP about 4-5 mm Hg
- Preserved with 0.015% BAK
- Comes in a 2.5 ml bottle
- Potential Side Effects:
  - » In phase III, 53% experienced red eyes;
  - » Can cause subconjunctival hemorrhages
  - » Can cause an amiodarone-like vortex keratopathy
- Marketed by Aerie Pharmaceuticals

### Rocklatan™ Ophthalmic Solution

- A combination of netarsudil 0.02% (Rhopressa) and latanoprost 0.005%
- First combination drug of a prostaglandin and a rho-kinase inhibitor
- Both ingredient drugs are “once daily” administration
- As with new drugs, coupons may be essential to achieve cost-effectiveness
- Conjunctival hyperemia (59%) may be a limiting factor
- Marketed by Aerie Pharmaceuticals

### How important is “Preservative Free”?

- “Published studies have not demonstrated any clear benefits of the BAK-Free formulations.”
- “There is a lack of evidence of clinically significant harm from a small number of BAK preserved drops in patients without OSD. This means that generally more expensive PF glaucoma medications should only be recommended for those on poly pharmacy or those with OSD but are not necessarily required for all patients.”

*Br J Ophthalmol, July, 2018*

### Treatment Options - Ocular Allergy

- Artificial Tears
- Mild Vasoconstrictors
- Decongestant / Astringents
- Vasoconstrictor / Antihistamines
- Antihistamines
- Antihistamine / Mast Cell Stabilizers
- Mast Cell Stabilizers
- Non-steroidal Anti-inflammatories
- Mild Corticosteroids
- Systemic Antihistamines
- Potent Corticosteroids
- Homeopathic Formulations

### Antihistamine/Mast Cell Stabilizer

- Highly selective H1 receptor blockers with prolonged receptor binding
- Good mast cell stabilization
- All bid dosing, except Pataday and Lastacraft qd
 

Olopatadine 0.1%	(Patanol) (5 ml)
0.2%	(Pataday) qd (2.5 ml)
0.7%	(Pazeo) qd (2.5ml)
Bepotastine 1.5%	(Bepreve) (5, 10 ml)
Epinastine 0.05%	(Elestat and generic) 5 ml
Alcaftadine 0.25%	(Lastacraft) qd (3 ml)
Azelastine 0.05%	(Optivar and generic) (6 ml)
Ketotifen 0.025%	(generic and OTC)
	(Claritin Eye) (5 ml)
	(Zyrtec Itchy Eye) (5 ml)
	(Zaditor) (5 ml)
	(Alaway) (10 ml)
	(Refresh) (5ml)
	(TheraTears) (5 ml)

### Cetirizine 0.24% ophthalmic solution

- Now Indicated for ocular itching associated with allergic conjunctivitis
- Instill 1 drop in each affected eye BID (8 hr apart)
- Adverse Effects:
  - » Hyperemia (1-7%)
  - » Instillation site pain (1-7%)
  - » Reduced visual acuity (1-7%)
- Marketed by Eyevance as Zerviate ophthalmic solution

### FDA Approves Three Drugs for Nonprescription Use Through Rx-to-OTC Switch Process

For Immediate Release: February 14, 2020



The U.S. Food and Drug Administration today approved three drugs for nonprescription, or over-the-counter (OTC), use through a process called a prescription (Rx)-to-OTC switch. The FDA approved Voltaren Arthritis Pain (diclofenac sodium topical gel, 1%) for the temporary relief of arthritis pain; Pataday Twice Daily Relief (olopatadine HCl ophthalmic solution/drops, 0.1%) for the temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair or dander; and Pataday Once Daily Relief (olopatadine HCl ophthalmic solution/drops, 0.2%) for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair or dander, for nonprescription use.

### Treatment of Ocular Allergies



Antihistamine/  
Mast Cell  
Stabilizer

Loteprednol

### Anti-Viral Medicines

#### Topical

Trifluridine Viroptic  
Ganciclovir Zirgan

#### Oral

Acyclovir Zovirax  
Valacyclovir Valtrex  
Famciclovir Famvir

- These are anti-herpetic drugs and are ineffective against the various adenoviral serotypes -

## Finer Points to Antiviral Prescribing

- For lactose intolerant patients: valacyclovir
- For children, use the oral suspension: acyclovir
- For patients over 65, famciclovir is recommended

Reference: AAO Guideline: Herpes Simplex Viral Keratitis: A Treatment Guideline- 2014 Appendix IV. Am. Acad. Ophthalmol.

## Shingrix Replaces Zostavax®

- Shingrix is the 2nd vaccine to be FDA approved to help prevent shingles.
- Approved for people aged 50 and older
- A non-live vaccine (Zostavax is live, attenuated)
- Administered in 2 - I.M. doses (initially then 2-6 months later)
- About 90% effective and maintained over four years
- If the last Zostavax vaccine was at least 5 years ago, \_\_\_\_\_ can have Shingrix
- Marketed by GlaxoSmithKline

## Latest on Shingles

- Mean age of event: 52
- Patients who have had HZO should be examined "within several weeks before and after vaccination against herpes zoster" because they may be at risk for recurrent eye disease.
- We should "recommend strongly" that patients over 50 get Shingrix.
- Our advocacy could "play an important role in increasing vaccination rates."
- About 10% of people have a reaction to Shingrix, more after the second dose.

Reference: Ophthalmology, Nov 2018

## Update on Shingles

- Incidence is on the rise, and at increasingly earlier ages
- Postherpetic neuralgia occurs in about 30% of patients with HZO, mostly in older people
- Shingrix is about 90% effective
- "Although eye doctors often view recommending vaccinations as the job of the PCP, given the incredible toll that HZ can take on the eye, we must take responsibility for protecting our patients and recommending this preventive measure."

Reference: Ophthalmology, Nov 2018

## Herpes Zoster Ophthalmicus

- Acute vesicular eruption of ophthalmic division of 5th cranial nerve
- Etiology: varicella-zoster virus; more common after 50 or in the immuno-compromised
- Symptoms: skin pain most common
- Ocular involvement in 50%
  - » more common - zoster epithelial lesions, anterior uveitis, stromal keratitis, episcleritis
  - » Tx: valacyclovir 1000mg tid for 1 wk; famciclovir 500 mg tid for 1 wk; acyclovir 800mg 5x d for 1 wk
  - » If ocular involvement, treat with topical steroids

## Dry Eye Disease

- "Dry eye disease is a heterogeneous disorder of the ocular surface in which the common denominator is inflammation."
- "Topical corticosteroids also play an important role in breaking the inflammatory cycle." "Repeated short-term pulse therapy has produced a disease-free state for more than 1 year in a study of patients with Sjögren's syndrome."
- "When meibomian glands function correctly, the lipids secreted reduce ocular surface water evaporation and prevent dry eye. When these glands are reduced, absent or dysfunctional, the impact on the ocular surface can be immense."
- "Treatment of DED is based on minimizing inflammation and optimizing various components of the tear film."

## Dry Eye Disease

- “Inflammation is one of the major targets in treating DED, and breaking the cycle of inflammation is crucial in improving symptoms. All patients DED deserve a trial of anti-inflammatory therapy at some point during their treatment.”  
“Corticosteroids are one of the most effective and rapid therapies available for suppressing inflammation on the ocular surface.”
- “Omega-3 supplementation is a well-tolerated therapy to improve ocular surface health in nearly all forms of DED and is generally recommended to be used for all patients with no other medical contraindications.”

## Discordance Between Symptoms and Signs

- Patients with chronic pain syndromes (CPSs) had 30% greater symptoms than signs.
- Important CPSs are irritable bowel syndrome, fibromyalgia, chronic pelvic pain and osteoarthritis.
- There is “growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, indicating neuropathic ocular pain.”
- It is thought that “patients with atopy or allergy have a sensitized ocular surface because of inflammatory processes influencing corneal nerves, which can lead to symptoms of dry eye even when the homeostasis of the ocular surface is minimally compromised.”

*Ophthalmology, March 2017*

## Topical Therapies for Ocular Surface Dryness

- Aqueous-based PF artificial tears did little or nothing to alleviate symptoms.
- Adding a topical steroid, signs and symptoms were improved.
- The majority of dry eye sufferers use AT’s, yet many still experience exacerbations of irritation and ocular surface disease in low-humidity environments.

Moore QL, et al. Am J Ophthalmol 2015;160(1):135-42.

## Expert Perspective on DED Inflammation

“It is now well understood that inflammation is one of the most important aspects of DED pathogenesis, and no matter the trigger, untreated or undertreated, established disease can lead to severe refractory disease. At this time, there are three topical prescription therapies available to treat inflammation in DED: corticosteroids, topical cyclosporine A and lifitegrast. Oral essential fatty acid supplementation and tetracycline-class antibiotics are also commonly prescribed for inflammatory ocular conditions, including DED.”

*Sheppard J. Advanced Ocular Care, April 2017*

## Steroids and Dry Eye Disease (DED)

- “Because chronic inflammation at the ocular surface plays an essential role in the pathogenesis of DED, topical steroids have been commonly used in these patients.”
- “Although the pathogenesis of DED is multifactorial and not fully understood, inflammation has been recognized as a key mechanism in its development and propagation.”

*Am J Ophthalmol, June, 2018*

