

The State of Therapeutics In Eye Care – Part 1

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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

JAMA Ophthalmology Perspective on “Disclosure”

“Since this study shows that current disclosure policies and laws have not been associated with a decrease in ethically questionable physician-industry relationships and may instead have created a permissive atmosphere for physician-industry relationships, perhaps disclosure policies and laws should be reconsidered.”

JAMA Ophthalmology, March, 2019

Refractionist or Doctor

- A new world of vision testing and eye wear sales is dawning now that refractions and prescription fulfillment are being offered online.
- These developments may not be a negative for ophthalmology practices and patients.
- Websites:
 - Visibly
 - EyeNetra
 - MyVisionPod
 - Smart Vision Labs
 - Vmax Vision
 - Warby Parker
- Optometrists: Expand your scope of patient care services to protect your future!
- The AOA is aggressively fighting for optometry: Join the AOA!!

Eyenet, Aug 2017.

“Remotely” Performed Eye Exams

- Now you can allegedly “perform remote comprehensive eye examinations during day, evenings, or weekends from your home, office or other location of your choice.”
- Such examinations are being “performed remotely by licensed optometrists.”
- “Generate Prescriptions for Eyeglasses and Contact Lenses Remotely.”
- Examine: www.digitalsoptometrics.com
- Also see www.for2020now.com!
- Be aware that technology is poised to radically change how eye care is delivered.

Optometric Perspective on Refraction

- “I rarely refract anymore as our technicians have become very adept at doing so. More importantly, the aging American demographic in conjunction with meteoric changes in technology, have really put a premium on our time. Given that I have limited time – and cognitive resources – I figure I better be expanding both in the most productive way! Much better things to be doing with our patients than refracting.”

Remote Diagnosis Imaging

- There is a rapidly increasing interest in providing ocular diagnoses by remote image acquisition. This can easily bypass optometric participation.
- Combining photos and OCT (captured by lay office personnel in primary care offices) can be highly effective.
- In the V.A., their “Technology-based Eye Care Services”, veterans can receive basic eye care services in their primary care clinics. Such services include “multiple diagnostic tests such as retinal photography, including vision, refraction, IOP, and pachymetry.” “Accuracy rate and patient satisfaction is high.”

JAMA Ophthalmol., July, 2019

OCT Failure in TECS Model

- “OCT did not seem to improve the diagnostic accuracy of the TECS protocol when compared with a face-to-face examination.”
- “OCT did not seem to improve the accuracy of glaucoma or retinal disease detection when added to the standard TECS protocol.”
- M+T: We have no doubt that technology will continue to evolve, but, at least for now, if you want optimum care, see an Optometrist!

Remote Patient Monitoring

- A new and engaging way of involving patients with their chronic disease monitoring
- Via the ICARE HOME tonometer, select patients can help monitor their glaucoma in between their scheduled office visits
- Since January 2019, these types of “remote patient monitoring” are insurance reimbursable.
- Such remote patient monitoring is yet another vehicle by which artificial intelligence will influence patient care.
- For more details, visit www.icare-usa.com

Eye Glasses From 3-D Printing Technology

- The (unintended) assault on traditional optometric practice continues
- 3-D printing technology can make a lightweight (7 grams), customized pair of eye glasses in 14 hours at a cost of about \$160.00
- We believe that a variety of technologies will steadily replace the need for traditional optometric care.
- Embrace medical eye care, or you might devolve into a dinosaur!

Clin Exp Optom, May, 2018

Eye Drops for Presbyopia

- EVO6 (Novartis) – new agent designed to restore crystalline lens flexibility
 - Prodrug with lipoic acid choline ester 1.5% - converts to dihydrolipoic acid – breaks down disulfide bonds in lens – improved flexibility
 - Goal is to maintain and possibly reverse lens hardening and allow lens to maintain or regain accommodation
- Review of Optometry, June 15, 2017*
- Liquid Vision drops – temporary presbyopia-correcting therapy lasting five hours or longer
 - In Phase II a trials – combines aceclidine (miotic) with tropicamide (cycloplegic) to create super pinhole effect and moderate accommodation
 - Developed by Presbyopia Therapies
- Review of Optometry, June 15, 2017*

“Topical Treatments for Presbyopia on the Horizon”

- “Topical agents that temporarily treat presbyopia without affecting other aspects of vision are on the cusp of becoming approved and available for widespread use.”
- “There are a number of new pharmaceutical agents currently being investigated for the treatment of this condition.”
- “The landscape is changing for the medical treatment of presbyopia. They appear safe, effective, and easy to use in early studies.”

Eye Care News, October 14, 2019

What Makes a Happy Patient

“Time spent with the physician and ease of scheduling an appointment are the 2 most important factors in determining whether or not a patient will recommend a particular practice to others. Even practices that provide the highest-quality care will not be successful if patients have trouble making appointments and do not get what is perceived to be adequate time with the practitioner”

Long C, et al. Ophthalmology 2016;123:242-7

Dress For Success

- True optometric physicians need to dress like the doctors we are.
- “Patients preferred to see their physicians dressed formally with white coats. They saw these physicians as more knowledgeable, trustworthy, caring and approachable than physicians dressed in other ways; patients also felt more comfortable with physicians dressed formally with white coats.”

Br Med J, May, 2018

Oxervate (cenegermin) 0.002% solution for Neurotrophic Keratitis

- FDA-approved in August 2018
- Eye drop delivery of human nerve growth factor
- Dosage: 6 x D (2 hour intervals) for 8 weeks
- Do Not Shake – Very complex administration protocol
- 70% “complete healing” in 8 weeks
- “Orphan Drug” – marketed by Dompe U.S., Boston

Regener-Eyes for DED

- First in class “biologic” eye drop
- Contains numerous anti-inflammatory cytokines and growth factors from placental-derived tissue
- Hyaluronic acid for lubrication
- Enhances the lipid layer
- Helps the body to regenerate itself
- Available in a 2.5 ml sterile bottle
- See mydryeyes.org

The “Drug Wars” in Historical Perspective

- Early to Mid-1990’s “The Beta-blocker Wars”
- Late 1990’s “The Antihistamine Wars”
- Early 2000’s “The Prostaglandin Wars”
- Late 2010’s “The Steroid Wars”
- Good drugs always garner competition!
- Sure wish such competition lowered costs!

Loteprednol Etabonate

- Only ester-based, site-specific steroid
- Works at target tissues, and then is quickly metabolized into inert compounds
- LE has high intrinsic activity when applied locally
- 0.5% loteprednol similar in therapeutic equivalence to 1% prednisolone acetate, yet causes little, if any, increase in IOP
- Available as 0.2% (Alrex) ophthalmic suspension, 0.5% Lotemax ointment and 0.5% Lotemax Gel

Literature Perspective on Steroids and Elevated IOP

- "IOP elevation is much more common with older steroids such as dexamethasone, prednisolone and fluorometholone, compared to newer steroids such as loteprednol, difluprednate or rimexolone."
- A note about difluprednate: "Though the occurrence of increased IOP is about 3%, the IOP elevation may be significantly higher compared to the other newer steroids." Only about 2% of patients experience "a clinically significant IOP increase" with loteprednol.
- "Post-operatively, loteprednol did not induce a significant IOP elevation and when used as a replacement for older steroids led to a significant IOP reduction in known steroid responders."

Survey Ophthalmol. March/April 2020

Inveltys (loteprednol 1%) suspension

- "Treatment of post-operative inflammation and pain following ocular surgery"
- FDA-approved in August 2018
- Approved for BID administration
- Uses micro-particles to extend duration of efficacy
- Marketed by Kala Pharmaceuticals (2.8ml)

Lotemax SM (loteprednol 0.38%) Gel

- "Treatment of post-operative inflammation and pain associated with ocular surgery"
- Approved for TID administration
- Delivers a submicron particle size for faster drug dissolution in tears
- Provides two times greater penetration to the aqueous humor compared to Lotemax Gel
- Lowest % of preservatives in a loteprednol formulation
- Marketed by B + L (5ml)

Off label

- "An estimated 50 percent of medications used routinely in ophthalmic practice are used off-label."
- "Clinical practice should be guided by the best interest of the patient."
- "In many instances, off-label treatments may be the best, or the only, available treatment, and withholding treatment would be unethical."

Reference: EyeNet. April 2011

Dextenza®

(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

FDA Approves Dextenza Intracanalicular Insert to Treat Ocular Pain After Surgery

- Approval based on:
 - efficacy in two randomized, vehicle-controlled phase 3 studies that showed statistically significantly higher incidence of subjects were pain free at day 8 post-cataract surgery compared to vehicle (Study one: 80% vs 43%; $P < .001$; Study two: 77% vs 59%; $P = .025$)
 - safety in the two phase 3 studies
 - third randomized, vehicle-controlled phase 2 study

HOW DEXTENZA® WORKS

DEXTENZA is dexamethasone delivered via hydrogel technology^{1,2}



ACTIVATES^{1,2}

- With moisture
- Swells to fit comfortably and securely in the canaliculus

RELEASES^{1,2}

- Dexamethasone for up to 30 days

RESORBBS^{1,2}

- Slowly through the course of treatment
- Clears via the nasolacrimal duct

¹ DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutic, Inc; 2018.

² Walters T et al. J Clin Exp Ophthalmol. 2016;7(4):1-11.

Perspective on Posterior Vitreous Detachment

- Occurs mostly between ages 50 and 70 (peak incidence 62)
- No association with refractive error, except patients with $-3.00D$ or more go to P.V.D. 5-10 years earlier
- 80-90% of breaks associated with P.V.D. are in the superior quadrants

Acute PVD and Retinal Tears

- The rate of an acute retinal tear associated with an acute symptomatic PVD is about 8% at the initial visit, and 1.5% of eyes without a tear on the initial visit are found to have a tear on follow-up examination.

Ophthalmology, January 2018

What About Scleral Depression

- "An examination using a 28 diopter lens with scleral depression did not provide any additional benefit to an examination without depression during indirect ophthalmoscopy."
- "In many areas around the world ophthalmologists have progressively shifted from indirect ophthalmoscopy with 28 diopter-type lenses to new fundus lenses at the slit lamp to improve the comfort of the patient without scleral depression."

Am J Ophthalmol. November 2018

PVD - Glaucoma Suspect

- 40 yowf with hx of 2 wks ago seeing floaters OD; checked by her optician at mall and given glasses Rx; still seeing floaters OD and wanted second opinion; no flashes; $-7.00 D$ myope OU; family hx mother glaucoma
- VA: OD 20/30, OS 20/30
- Pupils: normal OU; CVF: full OU
- IOP 19, 19 @ 7:24 am; CCT: 504, 508
- SLE: normal, no Shafer's sign OD
- DFE: -OD .7H x .75V no notching, no hem; OS .7H x .75V, tilted disc;
-Partial PVD without signs of tear or RD; macula normal; periphery normal OU;
- Plan: -Patient education of PVD; if experiences curtain over vision, flashes, or significant increase in floaters call immediately;
-OCT RNFL and macula today; F/U 1 month for DFE OD with IOP, VF 24-2 SF, gonio, CCT, and DFE of OD for f/u of PVD OD;

PVD - RD 1 week later

- CC: 2 days ago started seeing film in bottom of vision OD; no flashes of light with floaters less than before
- VA: OD 20/30, OS 20/30
- Pupils: normal; CVF: OD infer ?
- IOP: 21, 20 @ 2:40pm
- SLE: Positive Shafer's Sign OD
- DFE: Superior Retinal Detachment with large horseshoe tear
- Plan: Consult with retinal specialist for surgical intervention; f/u after released for further investigation as glaucoma suspect;



Protecting Sight. Empowering Lives.™

Posterior Vitreous Detachment, Retinal Breaks, and Lattice Degeneration Preferred Practice Pattern®

Patients presenting with an acute PVD and no retinal breaks have a small chance (~2%) of developing retinal breaks in the weeks that follow. Selected patients, particularly those with any degree of vitreous pigment, vitreous or retinal hemorrhage, or visible vitreoretinal traction, should be asked to return for a second examination promptly if they have new symptoms or within 6 weeks following the onset of PVD symptoms.

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AAO Preferred Practice Pattern®
AAO.org

Treatment of Vitreous Floaters

- Treatment options:
 - » Live with them
 - » Vitrectomy
 - » Vitreolysis
- YAG laser – angle of focus can be changed to reach floaters; special vitreous lenses allow the laser beam to focus on floater
- Advantages: simple, noninvasive, no pain or discomfort
- Disadvantages: healthy eyes getting elective surgery, risk of retinal detachment, possibly worsening of symptoms
- Clear visualization of floaters key to successful treatment
- Treatment may require more than one laser session; symptomatic vitreous opacifications (SVO); only SVO's > 4mm from retina treated
- Patient decision on benefits vs risks *CRST, May 2016 (Stonecipher)*

Timing and RD Repair: Is there a hurry?

- Preoperative VA is the strongest predictor of postoperative VA
- When central vision is affected, about 30% of patients ultimately achieve 20/40 or better
- "There is no difference in VA outcomes among patients who underwent repair within the first week of onset."
- VA can improve for months to years after surgical repair
- There was no association between duration of macular detachment and postoperative VA
- "Clinical evidence suggests that the duration of macular detachment has a minor, if any, effect on visual outcome when repair is performed within about one week. Similarly, many fovea-sparing RD's can likely be deferred for a short period without affecting visual outcomes."

JAMA Oph. November 2013

Visual Recovery After Retinal Detachment with Macula-Off

- After 10 days, no rush for up to 30 days
- Enhanced result if surgery is done within the first 3 days

BJO, 2016; 100 (11)

Risk of Progression in Macula-On Retinal Detachment

- A "bullous configuration" of a macula-on rhegmatogenous RD portends a higher risk of macular detachment. This study suggests "prompt surgery in patients diagnosed with bullous macula-on rhegmatogenous RD."

Clinical and Experimental Ophthalmology, August, 2017

Malpractice Risks Regarding Retinal Detachments

- Uptick in legal claims for diagnostic errors
 - » Especially retinal detachments
- "And by far the most frequently missed diagnosis in our entire study was RD– nothing else came close."
- 85% of these missed RD's presented with risk factors specific to RD
- "The primary pathogenic mechanism– and the biggest risk factor– for RD is PVD."
- Comprehensive ophthalmologists (and optometrists) should have a low threshold for referral to a retinal subspecialist."

Reference: EyeNet, April, 2018

FDA Pregnancy Categories

- A- Controlled studies show no risk
- B- No evidence of risk in humans
 - » Either animal studies show risk, human studies do not; or if no human studies, animal studies negative
- C- Risk cannot be ruled out.
 - » Human studies lacking, and animal studies positive for fetal risk or lacking. Potential benefits may justify potential risks
- D- Positive evidence of risk post-marketing data show risk to fetus. If needed in life-threatening
 - » Investigational or situation or serious disease, drug may be acceptable if safer drugs cannot be used
- X- Contraindicated in pregnancy
 - » Fetal risk clearly outweighs any benefit to patient

Treating During Pregnancy

- 6.3 million pregnancies reported in US each year
- Pregnancy creates a natural reduction in IOP (19.6% reduction is normal; 24.4% decrease in OH)
- Past FDA Pregnancy Categories no longer apply for drugs approved after June 30, 2015; Doctor must now read the package inserts and analyze the safety data to make an informed decision.
- Until new drugs are approved, use the more familiar pregnancy category labeling
- In glaucoma, brimonidine only category B (avoid during lactation- linked to CNS depression)
- Consult patient's OB/GYN or PCP prior to treatment

Primary HSV Infection

- Vesicular eruptions on the eyelid skin and/or eyelid margin
- Can be limited to the skin or can also result in follicular conjunctivitis and/or corneal epithelial disease
- Treatment: - PO ACV 400 mg 5 x D x 1W
- PO Valtrex 500 mg tid x 1W
- Vesicles resolve without scarring

Non-ophthalmic steroid: ointment/cream/lotion

- Triamcinolone - moderate potency steroid
- Available in cream, ointment and lotion (0.5%, 0.1%, 0.025%)
- Our favorite: the 0.1% cream

Reference: *Drug Facts and Comparisons*

Moore et al. *Journal of Ophthalmic Inflammation and Infection* (2017) 7:15
DOI 10.1186/s12348-017-0033-4

Journal of Ophthalmic
Inflammation and Infection

ORIGINAL RESEARCH Open Access

Neomycin, polymyxin B, and
dexamethasone allergic reactions following
periocular surgery

Nicholas A. Moore^{1*}, Craig N. Cyle^{2,3}, Tracy D. Carter², Jill A. Foster⁴ and Kenneth V. Cahill⁵

Abstract
Background: The aim of this study was to evaluate the rate of periocular allergic skin reactions to topical neomycin, polymyxin B, and dexamethasone (NPD) ophthalmic ointment.
Methods: A consecutive patient prospective study was performed. A total of 522 patients who had a procedure involving incision of the periocular skin with subsequent postoperative application of NPD ophthalmic ointment were included. Patients were evaluated for signs of allergy at 1 week postoperatively or prior if the patient had complaints. A periocular allergic reaction was defined as any periocular skin pruritus, erythema, edematous papules, vesicles, or plaques at the site of ointment application beyond that of the typical postprocedure presentation. The patients continued to be monitored for 30 days postoperatively.
Results: Of the 522 patients who completed the study, eight (1.5%) had a definitive periocular allergic contact dermatitis to the NPD ophthalmic ointment. Allergic presentation ranged from postoperative day 3 to 14.
Conclusions: The rate of periocular allergic reactions to NPD ophthalmic ointment is significantly lower than reported in the literature for other topical preparations of neomycin and polymyxin B. The low rate of allergy in this study suggests that NPD ophthalmic ointment can safely be applied to the periocular skin with a very minimal risk of inciting an allergic reaction.

Systemic Prednisone

- Most common Rx'd systemic corticosteroid
- Common initial dosage 40-60 mg
- Available generically in both tablets and DosePaks (5 or 10 mg at 6 or 12 day course)
- Questions to ask before prescribing?
 - » Diabetic?
 - » Peptic Ulcer Disease?
 - » Tuberculosis?
 - » Pregnant?

Perspective on Oral Prednisolone

- Using oral prednisolone at 1,250 mg/day is equivalent to 1,000 mg of I.V. methylprednisolone sodium succinate (Solu-Medrol®) for 3 days in treating acute optic neuritis.
- "There was no significant difference in adverse events between the groups."
- And,... we are concerned about using 40 – 60 mg/day!?!

JAMA Neurology, June, 2018