

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Foveal Development in Preterm Infants Treated for ROP

March 2018

Vogel et al. studied foveal development and cystoid macular changes (CMCs) in preterm infants, including the potential effects of treatment with intravitreal bevacizumab or laser photocoagulation. They found that outer retinal thickening at the foveal center occurs faster with bevacizumab—and that laser treatment produces earlier extrusion of inner retinal layers and delayed development of the ellipsoid zone at the foveal center.

This observational case series included 131 preterm infants who underwent screening for retinopathy of prematurity (ROP). Of these, 108 did not receive treatment, 9 had intravitreal bevacizumab only, 10 had laser only, and 4 received both treatments.

Handheld optical coherence tomography was performed longitudinally for all participants. Thickness of the inner and outer retinal layers was measured at the foveal center and the nasal and temporal foveal rims. Treated and untreated eyes were compared, with adjustments made for confounding variables. Correction for distortions and measurement errors caused by off-axis scans was accomplished by rescaling images to their native anatomic aspect ratio (this is important because off-axis scans are more common when nonsedated infants are imaged). The

main outcome measures were 1) weekly changes in thickness of the inner and outer retinal layers and 2) the presence of inner retinal layers, the ellipsoid zone, and CMCs.

Results showed that foveal center thickness increased 3.1 μm per week in untreated eyes and 7.2 μm per week in bevacizumab-treated eyes ($p = .038$). Laser-treated eyes were less likely than untreated eyes to have all inner retinal layers present at the foveal center (odds ratio, 0.04; $p = .001$) and to have an ellipsoid zone at the foveal center (odds ratio, 0.07; $p = .024$). CMCs were observed in 53% of patients and 22% of imaging sessions.

A strength of this study is the large sample size, resulting in data for 744 imaging sessions. Long-term follow-up and additional studies are needed to determine the anatomic and functional significance of the findings. Such knowledge may help guide treatment decisions for infants with ROP.

Prescribing Patterns and the Cost of Brand Medications

March 2018

Prescription drugs are the fastest-growing sector of health care spending. Newman-Casey et al. conducted research to quantify the costs of



ophthalmic medications prescribed by eye care providers, compare prescribing patterns between these and other providers, and estimate savings from negotiating prices and substituting generic/therapeutic alternatives for brand medications. They found that, among all providers, eye care specialists prescribe the highest proportion of brand name drugs by volume.

The study used data from the 2013 Medicare Part D prescriber public use file and summary file (released in 2015) to calculate medication costs by specialty and drug. Potential savings from substituting generic or therapeutic options for brand drugs were calculated. Potential savings were estimated using drug prices negotiated by the U.S. Veterans Health Administration.

Eye care providers (ophthalmologists and optometrists) accounted for \$2.4 billion of the \$103 billion total Medicare Part D costs for prescription drugs and produced the highest percentage of claims for brand medications among all specialties. Medications accounted for a significantly higher proportion of monthly supplies by volume as well as by total cost for eye care providers relative to other providers (38% vs. 23% by volume; 79% vs. 56% by total cost).

As for medication type, glaucoma drugs accounted for the largest proportion of costs generated by eye care providers (\$1.2 billion; 54% of total cost; 72% of total volume), followed by

Subretinal Air and tPA for Submacular Hemorrhage: First U.S. Results

March 2018

At present, there is no consensus on the optimal management of submacular hemorrhage (SMH), which is a rare but potentially devastating complication of choroidal neovascularization. **Sharma and Kumar et al.** set out to determine whether massive SMHs can be managed with subretinal injections of tPA (tissue plasminogen activator) and air. They found that the combination was successful, resulting in consistent displacement of SMH out of the fovea as well as improved visual acuity (VA) and retinal thickness.

This retrospective interventional case series included 24 patients with SMH from 5 sites in the United States. The patients' mean age was 79.1 years (range, 62-92 years). The underlying cause of SMH was polypoidal choroidal vasculopathy ($n = 4$) and age-related macular degeneration ($n = 20$). In addition, 13 (54%) of the patients were on anticoagulation therapy for stroke prevention ($n = 9$), stroke history ($n = 3$), or atrial fibrillation ($n = 1$). Main outcome measures included

drugs for dry eye syndrome. Restasis, which currently has no generic alternative, was responsible for nearly 99% (\$371 million) of drug expenditures in the dry eye category (17% of total cost; 4% of total volume). The Medicare Part D average payment for a monthly supply of Restasis was \$293, higher than the amount for any other drug.

If generics could be substituted for brand drugs, savings of approximately 7% (\$148 million) would be realized. The combination of generic and therapeutic substitutions would yield savings of 42% (\$882 million). If Medicare could attain Veterans Health Administration rates for medications, the resulting savings would be 53% (\$1.09 billion).

Efforts to reduce drug expenditures associated with eye care professionals should focus on greater use of generic and therapeutic options. Policy changes enabling Medicare to negotiate lower prices for prescription drugs could yield substantial savings for the program.

New Visual Disturbances by Site of Laser Peripheral Iridotomy

March 2018

In a multicenter study, **Srinivasan et al.** aimed to determine whether the site of laser peripheral iridotomy (LPI) has any bearing on the emergence of postoperative visual symptoms. They found that the incidence of new visual dysphotopsias is similar for the superior and nasal/temporal locations.

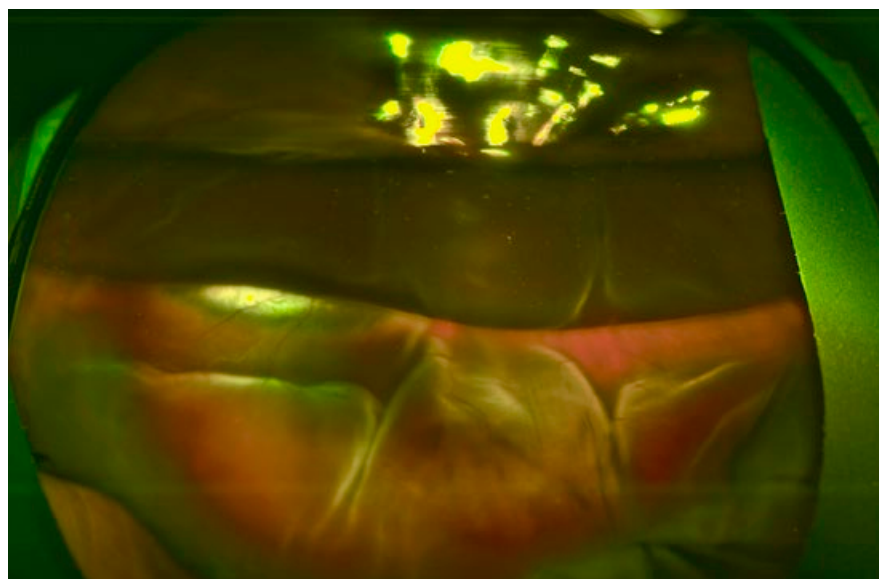
For this prospective randomized, single-masked trial, the authors included 559 South Indian adults who were primary angle-closure suspects (PACS) or had a diagnosis of primary angle closure (PAC) or primary angle-closure glaucoma (PACG) in both eyes. Participants were assigned randomly to receive bilateral superior LPI ($n = 285$) or bilateral nasal/temporal LPI ($n = 274$) and were matched for age, gender, and PACS/PAC/PACG distribution. The main outcome measure was occurrence of new-onset dysphotopsia symptoms. Visual disturbances were assessed preoperatively and 2 weeks post-LPI, utilizing a survey based on the 7-symptom dysphotopsia questionnaire used by Spaeth et al. in 2005.

Laser energy settings were similar for both LPI groups, but superior LPI involved more shots and greater total energy. There were no significant between-group differences in postoperative anterior chamber reaction or LPI area. The proportion of patients with at least 1 symptom before LPI was similar (superior, 15.8%; nasal/temporal, 13.9%), as was the incidence of each symptom.

After LPI, 8.9% of the study population reported 1 or more new symptoms; the most common were linear dysphotopsias (2.7%), glare (4.3%), and blurring (4.3%). Patients who underwent superior LPI did not report more new-onset dysphotopsia symptoms than those who had nasal/temporal LPI (8.4% vs. 9.5%), and the incidence of any new individual symptom was comparable. None of the following influenced the odds of new dysphotopsia symptoms postoperatively: location of LPI, size of LPI area, or quantity of laser energy.

Although dysphotopsia symptoms emerged after LPI in a large portion of the study population, the overall frequency of dysphotopsias did not increase. LPI site selection should be based on individual factors, such as location of the optimal crypt in patients with a thick iris.

—Summaries by Lynda Seminara



DISPLACED HEMORRHAGE. This wide-field image taken on postop day 1 shows an inferiorly displaced SMH, with partial gas fill in the vitreous cavity to prevent the subretinal air from migrating superiorly.

frequency and extent of SMH displacement and postoperative VA, retinal thickness, and complications.

Based on image review, SMH was considered subretinal in 5 patients, sub-RPE (retinal pigment epithelium) in 2, and both subretinal and sub-RPE in 17. Hemorrhage size was small (does not reach arcades) in 6 patients, large (extending to the arcades) in 2, extensive (extending past the arcades) in 9, and massive (extending to 2 quadrants and/or past the equator) in 7. With regard to retinal thickness, the hemorrhages were $< 500 \mu\text{m}$ in 7 patients and $> 500 \mu\text{m}$ in 17.

All patients underwent pars plana vitrectomy (with induction of a posterior vitreous detachment, if necessary), followed by subretinal injection of tPA and filtered air. Most ($n = 23$) of the patients also received bevacizumab as part of the surgery or treatment. They were then followed for an average of 12.5 months (range, 3-28 months).

At 3 months postoperatively, there was complete displacement of SMH in all eyes. Although 13 eyes experienced no complications, 5 had a recurrent subretinal SMH that was successfully displaced with the same treatment. The remaining 6 eyes had a nonclearing vitreous hemorrhage ($n = 3$), retinal detachments ($n = 2$), or macular hole ($n = 1$). Mean retinal thickness improved from $463.7 \mu\text{m}$ preoperatively to $311.3 \mu\text{m}$ postoperatively, and VA improved in 23 eyes and remained stable in 1.

—*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Choroidal Thickness Changes in Patients With Glaucoma

February 2018

The peripapillary choroid is of interest to researchers because its branches lend vital support to the prelaminar region of the optic nerve head, a primary site of glaucomatous optic neuropathy. Although the link between glaucoma and the choroid has been studied using optical coherence tomography, findings have been inconsistent. **Mundae et al.**

performed spectral-domain optical coherence tomography (SD-OCT) in patients with glaucoma and healthy controls to compare rates of peripapillary choroidal thinning. Their results showed no significant difference between the study groups.

The authors' research included participants of the multicenter African Descent and Glaucoma Evaluation Study and the Diagnostic Innovations in Glaucoma Study. The testing protocols of those studies were identical.

The healthy group (68 patients) contributed 132 eyes, and the glaucoma group (115 patients) consisted of 165 eyes. At baseline, the global mean peripapillary choroidal thickness (PCT) was significantly greater for healthy controls: $155.7 \pm 64.8 \mu\text{m}$ vs. $141.7 \pm 66.3 \mu\text{m}$ for patients with glaucoma ($p < .001$). However, when age was factored into the model, the difference was not significant ($p = .38$). Every eye was imaged by SD-OCT on at least 3 days. The San Diego Automated Layer Segmentation Algorithm was used to automatically segment and measure PCT from circle scans centered on the optic nerve head. Mixed-effects models were applied to calculate the rate of PCT thinning. The median follow-up time was 2.6 years.

In both study groups, PCT decreased significantly over time: $-2.18 \mu\text{m}$ per year in controls and $-1.88 \mu\text{m}$ per year in patients with glaucoma. Similarly, both groups had significant decreases in PCT percentage over time: -3.32% for controls and -2.85% for patients with glaucoma. However, the mean rate of PCT change over time was similar for the study groups, as was the change in PCT percentage.

Despite the observed similarities, the authors emphasized that longer follow-up is needed to determine with certainty whether monitoring the rate of PCT change has a role in glaucoma management.

Do Experts Agree on the Diagnoses Assigned to Uveitis Cases?

February 2018

Jabs et al. conducted an interobserver study to ascertain the level of expert

agreement on diagnoses assigned to cases of uveitis. They found that independent assessment yielded only moderate agreement, which improved greatly after conference calls with colleagues.

For their study, 5 committees (each with 9 uveitis experts) reviewed a total of 5,766 cases from a preliminary database representing 25 uveitic diseases. Initially, the experts voted online, independently, on whether each case coincided with its assigned diagnosis. The agreement statistic (κ) was calculated for 36 pairwise comparisons per disease, and the mean κ was calculated for each disease. After independent voting, committees held consensus conference calls to discuss the cases that lacked supermajority agreement, defined as $> 75\%$. Nominal group techniques were applied to attempt to reach the targeted level of agreement.

The mean κ achieved from independent voting was 0.39, denoting moderate agreement. Disease-specific variation ranged from 0.23 (for toxoplasmic retinitis) to 0.79 (for cytomegalovirus anterior uveitis). After the conference calls, supermajority agreement was attained for approximately 99% of cases, with disease-specific variations ranging from 96% to 100%. The remaining cases (approximately 1%) were permanently "tabled." Ultimately, 71% of the cases evaluated were accepted into the final database and 28% were rejected. Acceptance rates ranged from 42% for herpes simplex anterior uveitis to 92% for serpiginous-like tuberculous chorioiditis. Throughout the study, perfect agreement ($\kappa = 1.00$) was achieved by only 1 pair of experts. For several diseases, the agreement of at least 1 pair of experts was essentially "chance alone."

Although diagnostic agreement was only moderate early in the study, it was improved by collaborative discussion. Only during the conference calls did many essential disease-specific acceptance/rejection criteria begin to emerge. The obstacles to consensus that arose in this study indicate the need for clear, validated, widely accepted classification criteria for uveitic conditions. With better criteria, the data derived from case series, cohort studies, and

multicenter trials should become more homogeneous and thus more useful for establishing accurate diagnoses.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected by Neil M. Bressler, MD, and Deputy Editors

Risk of Intraocular Bleeding With Novel Antithrombotics

February 2018

Novel oral anticoagulation and antiplatelet therapies have become popular in the treatment of thromboembolic disease, but their ocular safety profiles are uncertain. Uyhazi et al. compared the risk of intraocular hemorrhage between novel and traditional antithrombotic agents and found that bleeding rates were no worse with the newer medications.

For their retrospective study, the authors utilized a large national insurance claims database to generate 2 parallel analyses. First, incident use of dabigatran etexilate or rivaroxaban was compared with incident use of warfarin sodium. For the second analysis, new use of prasugrel hydrochloride was compared with new use of clopidogrel bisulfate. Patients with previous intraocular hemorrhage or a prescription for the comparator drug were excluded from the study. The main outcome measure was the incidence of intraocular hemorrhage within 90 days and 365 days. Multivariate regression models were applied to compare hazard ratios for developing intraocular hemorrhage.

Data were compared for 146,137 patients who took warfarin (mean age, 69.8 years) and 64,291 patients who took dabigatran or rivaroxaban (mean age, 67.6 years). The hazard ratio for hemorrhage development was lower with dabigatran or rivaroxaban versus warfarin at 365 days (0.75) but not at 90 days (0.73). Data for the 103,796 patients taking clopidogrel (mean age, 68.0 years) and the 8,386 patients taking prasugrel (mean age, 61.0 years) did not show a greater risk of intraocular hemorrhage with prasugrel at either 90 or 365 days.

The authors emphasized that the

growing use of novel antithrombotics for coronary conditions requires greater understanding of ocular safety profiles. Their findings suggest that the risk of intraocular hemorrhage is lower with dabigatran etexilate and rivaroxaban than with warfarin and is similar for prasugrel hydrochloride and clopidogrel bisulfate. Additional studies are needed to fully characterize the ocular safety profiles of the new antithrombotic agents. (Also see related commentary by Daniel Caldeira, MD, PhD, in the same issue.)

Ophthalmologists' Adoption and Perceptions of EHRs

February 2018

Lim et al. looked at rates of electronic health record (EHR) use among ophthalmologists and gathered EHR-related financial and clinical opinions from these specialists. They found that, although EHR adoption has increased in recent years, ophthalmologists continue to express concerns about the systems.

For their study, the authors used a population-based, cross-sectional, random sample of 2,000 ophthalmologists. The sample was obtained from the Academy's 2015 active membership database (U.S. members), and the research was conducted in 2015 and 2016. A survey was emailed to each ophthalmologist to inquire about adoption of the EHR, perceptions of financial and clinical productivity related to EHRs, and involvement in Medicare/Medicaid programs that offer incentives for EHR use.

Among the 348 ophthalmologists who responded, 72.1% were currently using an EHR system. This rate is substantially higher than in a 2011 survey (47% adoption rate) and is similar to that for primary care physicians (79% adoption rate). Most respondents believe that EHR use contributed to declines in productivity and net revenue and to higher practice-related costs. Of the respondents who attested to stage 1 of the EHR meaningful use incentive program, 83% planned to attest to stage 2.

Most respondents are of the opinion that EHR use has not affected the ability to capture charges for office visits,

procedures, and tests. One-fourth of the surveyed specialists believe the EHR system has improved their ability to provide quality care, but 35% suspect that paper records are more conducive to delivering quality care. Most respondents noted that patients' attitudes toward the EHR are either positive or neutral. Subanalyses of data by the number of years in practice showed no statistically significant differences between junior and senior ophthalmologists.

These results suggest that the EHR system needs modification to optimize its value for ophthalmologists. Ideally, the utility of the record itself should be improved, and the government's requirements for using it meaningfully should be clarified and incorporated. (Also see related commentary by Jennifer S. Weizer, MD, Joshua R. Ehrlich, MD, MPH, and Paul P. Lee, MD, JD, in the same issue.)

Binocular Video Game for Unilateral Amblyopia

February 2018

Binocular treatment of amblyopia by contrast-rebalanced stimuli has shown promise in laboratory studies and is being investigated in real-world settings. Gao et al. compared a binocular video game with a placebo version. They found that the binocular game was not superior for improving visual function.

The multicenter, double-masked, randomized clinical trial included 115 participants aged 7 to 55 years (mean, 21.5 years). All had unilateral amblyopia caused by anisometropia, strabismus, or both; the visual acuity of the amblyopic eye was 0.30 to 1.00 logMAR (Snellen equivalent, 20/40 to 20/200). Eighty-nine participants (77.4%) had previously undergone occlusion or penalization therapy. Patients were classified by age group and were assigned randomly to play the active-treatment (binocular) video game or the placebo game.

The Falling Blocks game was used in both study arms and was played at home on an iPod Touch. The active-treatment game split visual elements between the eyes, with a dichoptic con-

trast offset, whereas the placebo game presented identical images to both eyes. Patients were instructed to play the game for 1 hour a day for 6 weeks. The main outcome measure was change in visual acuity of the amblyopic eye from baseline through week 6. Secondary outcomes included compliance, stereoacuity, and interocular suppression.

The mean (SD) visual acuity of the amblyopic eye improved 0.06 (0.12) logMAR (3 letters) from baseline in the active-treatment group and 0.07 (0.10) logMAR (3.5 letters) in the placebo group. Compliance with at least 25% of prescribed play was achieved by 64% of the active-treatment group and by 83% of the placebo group. By 6 weeks, fellow-eye contrast > 0.9 was attained in 36 active-arm participants (64%). There were 3 reports of asthenopia (2 in the active-treatment group), which was transient, and no reports of diplopia. There were no significant differences between groups for any primary or secondary outcomes.

Various requisites presumably should be satisfied before binocular video games are ready for clinical use. These include robust effectiveness data from randomized trials; sophisticated methods to monitor compliance; and development of more engaging games, aimed at improving compliance and effectiveness. (*Also see related commentary by Jonathan M. Holmes, BM, BCh, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Visual Structure and Function of Athletes in Collision Sports

Journal of Neuro-Ophthalmology
Published online Sept. 6, 2017

Vision-based measures are known markers for Alzheimer disease, multiple sclerosis, and Parkinson disease, and they may aid in understanding associations between repetitive head trauma and neurodegenerative sequelae. In a comparison study of athletes in collision sports and matched controls, **Leong et al.** noted substantial retinal axonal and neuronal loss in the athletes,

along with reduced visual function and quality of life (QOL). Patterns were similar to those of the above-mentioned neurologic diseases.

In their cross-sectional study, the authors compared 46 professional athletes (active or retired) with 104 age/race-matched healthy controls who had not participated in collision sports. All study participants received spectral-domain optical coherence tomography (SD-OCT) to measure thickness of the peripapillary retinal nerve fiber layer (RNFL) and the macular ganglion cell complex. High-contrast visual acuity (100% level) and low-contrast letter acuity (1.25% and 2.5% levels) were determined, and the King-Devick test of rapid number naming was administered. Vision-specific measures of QOL also were assessed.

On average, the RNFL of athletes (14 boxers, 29 football players, and 3 ice hockey players) was 4.8 μm thinner than that of controls. RNFL thinning was highest for boxers (10.8 μm vs. controls). Binocular and monocular low-contrast letter acuity at 2.5% contrast, as well as vision-specific QOL, differed significantly between athletes and controls. Performance time for rapid number naming was similar for the study groups.

Trauma-related vision changes that are detectable in vivo represent a unique opportunity to study related mechanisms of neurodegeneration. In future research, the authors plan to assess fluid biomarkers and apply imaging and cognitive measures of evaluation. Longitudinal examination will help determine whether structural and functional deficiencies signal neurodegeneration. Such knowledge will be important for establishing outcome measures in trials of drugs that target neuroprotection.

Galcanezumab for Episodic Migraine

JAMA Neurology
Published online Dec. 18, 2017

Current medications for migraine have variable efficacy, low adherence, and considerable adverse events (AEs). Recent studies have shown that calci-

tonin gene-related peptide is involved in migraine pathophysiology, which has prompted interest in monoclonal antibodies such as galcanezumab as preventive therapy. In a phase 2b trial, **Skljarevski et al.** compared various monthly doses of galcanezumab with placebo and found that the 120-mg dose of the drug was well tolerated and reduced migraine frequency.

The trial was conducted in 2014 and 2015 by 37 physicians in the United States. It consisted of 4 periods: screening/washout, prospective baseline (to determine migraine headache days [MHDs]), double-blind treatment, and post-treatment. The primary endpoint was superiority to placebo, evidenced by reduction in MHDs, from baseline to 9 or 12 weeks. Short-term migraine treatments—excluding opioids and barbiturates—were permitted during the trial.

The 410 enrollees (83% female) had onset of episodic migraine before 50 years of age and were experiencing 4 to 14 MHDs per month. Participants were assigned randomly (2:1:1:1) to receive monthly subcutaneous injection of placebo or galcanezumab (5, 50, 120, or 300 mg) for 3 months.

Period 3 of the trial was completed by 375 patients (galcanezumab, n = 249; placebo, n = 126). By month 3 of treatment, the 120-mg dose of galcanezumab had significantly reduced MHDs (–4.8 MHDs; –5.4 to –4.2 MHDs) versus placebo (–3.7 MHDs; –4.1 to –3.2 MHDs). From baseline to month 3, both the 120- and 300-mg doses of galcanezumab were more effective than placebo in reducing the overall number of MHDs. The frequency of treatment-emergent AEs was comparable for active-treatment groups. The most common AEs were upper respiratory tract infection, pain at the injection site, nasopharyngitis, nausea, and dysmenorrhea.

The authors cautioned that the small sample size precludes definitive conclusions about the safety of galcanezumab. However, they encouraged phase 3 investigation of varying doses of the drug to further assess its safety and efficacy for episodic migraine.

—Summaries by Lynda Seminara