

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Access to Laser Capsulotomy in Oklahoma: Ophthalmologists and Optometrists

September 2017

Access to eye care in rural areas is presented as justification for expanding the responsibilities of optometrists to include laser procedures in some states. In Oklahoma, laser privileges were granted to these providers in 1998, including Nd:YAG posterior capsulotomy. Mahr et al. calculated the proximity of Medicare beneficiaries to their capsulotomy provider and found no meaningful geographic difference between optometrists and ophthalmologists.

Oklahoma Medicare data sets (100% and 5%) for 2014 were used in the cross-sectional study, along with travel distances and approximate driving times generated from a Google Maps programming interface. The shortest travel distance and associated driving time from the patient's residence to his or her laser provider were documented.

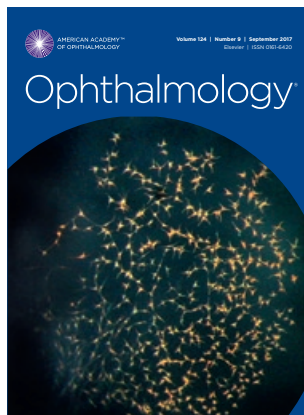
In 2014, 90 (57%) of 157 Oklahoma ophthalmologists submitted a total of 7,521 claims to Medicare for Nd:YAG laser capsulotomy. During this same period, 65 (13%) of the 506 Oklahoma optometrists submitted a total of 3,751 claims for the procedure. Six (9%) of the 65 optometrists shared their office address with an ophthalmologist. Seven ophthalmologists and 15 optometrists had a secondary location.

Analysis of the Medicare Limited 5% data set showed no meaningful difference in driving distance between beneficiaries who received laser capsulotomy from an ophthalmologist (median, 39 miles) and those who received it from an optometrist (median, 46 miles). Similarly, the driving time to an ophthalmologist (median, 47 minutes) was comparable to that for an optometrist (median, 50 minutes). If the beneficiary did not receive the Nd:YAG laser capsulotomy from his or her current optometrist, the additional travel distance to the closest laser-providing ophthalmologist's office from the laser-providing optometrist's office was a median of 2 miles (interquartile range, 1-26 miles; mean, 17 ± 29 miles).

fMRI Assessment of Neurobehavioral Impact of Dysphotopsia With Multifocal IOLs

September 2017

Dysphotopsia manifestations are a source of patient dissatisfaction with multifocal intraocular lenses (IOLs), leading to explantation in some cases. Studies of optical parameters have shed little light on the pathophysiology of these effects. However, Rosa et



al. observed an association between subjective visual symptoms and functional magnetic resonance imaging (fMRI) findings, indicating that neuroadaptive mechanisms play a role.

Their cross-sectional study involved 30 patients (mean age, 61 years; 16 women) who had undergone bilateral cataract surgery and implantation of diffractive IOLs 3 to 4 weeks earlier (patient group) and a control

group of 15 age- and sex-matched subjects with no previous intraocular surgery. All participants underwent fMRI while viewing low-contrast grating stimuli, which, in half the runs, were surrounded by a light source to induce glare. The main outcome measure was activity in the primary visual cortex and higher-level brain areas, including the attention network. The researchers also evaluated psychophysical factors, visual acuity, wavefront, and scores on the Quality of Vision (QoV) questionnaire.

When patients viewed low-contrast stimuli with glare, substantial activation of the frontal, middle frontal, parietal frontal, and postcentral gyrus was observed. Under the same conditions, control subjects demonstrated deactivation only of visual areas in the occipital lobe and middle occipital gyrus. Relative to controls, patients exhibited stronger recruitment of the cortical areas involved in learning, task planning, and problem solving.

Patients who were “more bothered” by the dysphotopic symptoms from stimuli with glare showed significant recruitment of the frontal and parietal lobes, cingulate gyrus, and caudate nucleus. No correlation was found, in either group, between QoV scores and optical properties such as total and higher-order aberrations, modulation transfer function, and Strehl ratio.

The authors concluded that an association exists between patient-reported difficulties and fMRI findings, independent of optical parameters and psychophysical performance. The increased activity in the cortical areas devoted to attention, learning, cognitive control, and task planning may suggest that neuroadaptation to the IOL is under way.

CXL for Treatment of Corneal Ectasia After Refractive Surgery

October 2017

Corneal ectasia remains one of the most visually significant complications of excimer laser surgery. Hersh et al. demonstrated that collagen cross-linking (CXL), which can stabilize corneal architecture in patients with keratoconus, also is effective and safe for managing corneal ectasia after refractive surgery.

The authors conducted 2 clinical trials concurrently at 11 sites, enrolling 179 patients with ectasia after refractive surgery (mean age, 43 years). Patients were assigned randomly to receive standard ultraviolet A–riboflavin 0.1% CXL (n = 91 eyes) or sham treatment (riboflavin alone, no removal of epithelium; n = 88 eyes). Efficacy was assessed by examining between-group differences in maximum K change from baseline (preoperative state) to 1 year postoperatively. A difference of ≥ 1 D was considered clinically significant. Secondary endpoints included corrected and uncorrected distance visual acuity (DVA) and adverse events.

The CXL group had a significant decrease in mean maximum K value from baseline to 12 months postoperatively (0.7 ± 2.1 D; $p < .05$), whereas the sham control group had a significant increase (0.6 ± 2.1 D; $p < .05$).

The between-group difference was 1.3 D ($p < .0001$). Of the 76 CXL-treated eyes for which 12-month maximum K data were available, 14 eyes decreased ≥ 2 D and 3 eyes increased ≥ 2 D. Mean corrected DVA improved by 5 logMAR letters in the CXL group; 23 eyes gained ≥ 10 logMAR letters and 3 eyes lost ≥ 10 letters. Among the latter 3 eyes, there was no obvious clinical cause for the decline. Uncorrected DVA improved by 4.6 letters with CXL treatment. The most common adverse effect of CXL was corneal haze, which persisted in 5 eyes at 1 year.

The authors concluded that CXL generally reduces the progression of corneal ectasia and appears to have an excellent safety profile. Variability in the results suggest that careful patient selection may optimize outcomes.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

AMD Meta-Analysis: Adverse Events With Bevacizumab and Ranibizumab

September/October 2017

Ten years into the anti-VEGF era, Maguire et al. reviewed data on the efficacy and safety of bevacizumab and ranibizumab in patients who received intravitreal injections of the drugs for neovascular age-related macular degeneration (AMD). They found no substantial difference in the risk of serious systemic adverse events (AEs) between the 2 medications.

For this meta-analysis, the authors identified 6 large-scale multicenter clinical trials and requested individual patient data on serious AEs, assigned drug and dosing regimen, and baseline prognostic factors from the investigators. A 2-stage approach was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) from Cox proportional hazards models adjusting for baseline prognostic factors. The primary outcome measure was the development of ≥ 1 serious systemic AE; secondary outcome measures included risk of arteriothrombotic events and death.

Data were received from 5 trials, for a total of 3,052 patients. Of these, 1,513 received bevacizumab, while 1,539 were given ranibizumab. All told, 403 (26.6%) of the bevacizumab group and 366 (23.8%) of the ranibizumab group experienced ≥ 1 serious AE. The adjusted RR (95% CI) for bevacizumab relative to ranibizumab was 1.06 for ≥ 1 serious AE. For secondary outcomes, adjusted RRs were 0.99 for death, 0.89 for arteriothrombotic events, 1.10 for events related to anti-VEGF treatment, and 1.11 for events not related to anti-VEGF treatment.

At this point in time, the authors wrote, it is unlikely that there will be any additional head-to-head clinical trials of the 2 drugs. Thus, they said, further investigation of differential risk between anti-VEGF drugs will likely be achieved via postmarketing surveillance or in-depth examination of health care databases. —Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Socioeconomic Disparity in the Global Burden of Cataract

September 2017

Although cataract is easy to treat, it remains a leading cause of blindness worldwide. Lou et al. analyzed 2013 data pertaining to the burden of cataract and examined trends since 1990. They found that the general global progress in cataract management has been uneven, in large part because of substantial socioeconomic disparities between countries.

Using disability-adjusted life year (DALY) data, the authors determined socioeconomic differences in the global burden of cataract. Their international comparative study entailed collecting published national age-standardized DALY rates attributed to cataract, as well as human development index (HDI) composite statistics. All data were examined longitudinally for 1990–2013, and the relationship between age-standardized DALY rates and HDI in 2013 was analyzed. Health-related Gini coefficients and concentration

indexes were calculated to determine between-country trends in cataract burden from 1990 to 2013.

HDI data for 2013 were available for 183 countries: 47 with very high HDI, 51 with high HDI, 42 with medium HDI, and 43 with low HDI. Multiple comparisons demonstrated that countries with lower HDIs had higher age-standardized DALY rates for cataract. According to linear regression analysis, age-standardized DALY rates correlated inversely with HDI. Global age-standardized DALY rates decreased from 1990 to 2013, and Gini coefficients increased during the same period (from 0.409 to 0.439). Concentration indexes showed that socioeconomic inequality declined in the 1990s but grew thereafter.

The investigators concluded that, unfortunately, the global health progress achieved in cataract management coincides with broadening socioeconomic inequality. Cataract burden is greatest in countries with the lowest socioeconomic status. These findings emphasize the need for more cataract services in developing countries and the importance of addressing barriers to cataract surgery among disadvantaged populations.

Corneal and Lens Clarity in Children With Type 1 Diabetes September 2017

Diabetic retinopathy (DR) is the chief ocular defect in patients with type 1 diabetes mellitus (DM). However, vision-threatening DR is rare in children, regardless of control or duration of diabetes. Tekin et al. sought to determine whether the impaired glucose metabolism intrinsic to diabetes is associated with effects on corneal or lens clarity in children with type 1 disease. They found that, relative to healthy subjects, children with type 1 DM had poorer lens clarity and greater lens thickness.

For this multicenter cross-sectional study, the researchers included 56 patients with well-controlled type 1 DM (mean age, 13.1 years) and 51 healthy controls (mean age, 12.2 years). Children with lens opacities or cataract were excluded. Duration of disease and

hemoglobin A_{1c} levels were documented for patients with DM. The Pentacam HR imaging system was utilized to obtain corneal densitometry measurements for all participants. Lens densitometry and thickness were measured using the same device, after pupillary dilation.

In all concentric zones and layers, corneal densitometry values were similar for the 2 study groups. Significant between-group differences were noted in mean values for average and maximum lens densitometry and in mean lens thickness. Among children with DM, the mean disease duration was 7.05 years and the mean hemoglobin A_{1c} level was 6.36%. Lens densitometry values correlated strongly with DM duration but not with hemoglobin A_{1c} level.

The authors speculated that swelling of the lens, due to elevated activity of the polyol pathway and nonenzymatic glycation of lens proteins, may contribute to the deficient lens clarity and unusual lens thickness in children with type 1 DM. Therefore, it is reasonable to surmise that diabetes plays a role in these lens abnormalities. Comprehensive longitudinal studies are warranted to fully elucidate the lens defects linked to type 1 DM.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Validation of the CHOP Model of ROP

August 2017

The retinopathy of prematurity (ROP) model of the Children's Hospital of Philadelphia (CHOP) uses factors such as gestational age, birth weight, and rate of weight gain to predict ROP severity. Binenbaum et al. tested the model's utility in a population of sufficient size to determine sensitivity for detecting ROP that requires treatment. The model proved valid for clinical use and may help clinicians refine ROP screening guidelines.

The investigation was a secondary analysis of longitudinal data from the

Postnatal Growth and ROP Study, which involved 30 hospitals throughout the United States and Canada. The study cohort comprised 7,483 premature infants at risk for ROP with a known ROP outcome. Median gestational age was 28 weeks (range, 22-35 weeks), and median birth weight was 1,070 g (range, 310-3,000 g). The CHOP ROP model was applied weekly to assess its ability to predict ROP risk. If the risk was deemed high, examinations were provided. If the risk was considered low, examinations were not performed. In another test scenario, low-risk infants received fewer exams rather than none.

The model accurately identified 452 of the 459 infants found to have type 1 ROP (98.5% sensitivity). If exams were given only to infants with high ROP risk, the proportion of infants requiring exams would be reduced by 34.3%. Lowering the cutpoint to capture all cases of type 1 ROP (100% sensitivity) would result in examining all but 6.8% of infants. However, if low-risk infants were evaluated at 37 weeks' postmenstrual age and monitored only if ROP was present at that time, all cases of type 1 ROP would be captured, and the number of exams among infants born after 27 weeks' gestation would be reduced by 28.4%.

In conclusion, the sensitivity of the CHOP ROP model was high but shy of 100%. However, the model reduces the frequency of examinations and may guide development of improved ROP screening guidelines, allowing resources to be directed to the infants in greatest need of them.

Risk of Intraocular Bleeding With Warfarin Versus Novel Oral Anticoagulants

August 2017

Intraocular hemorrhage is a rare but well-documented effect of warfarin and other antithrombotic agents. Novel oral anticoagulants (NOACs) have shown antithrombotic efficacy equivalent or superior to that of warfarin and are less likely to cause intracranial hemorrhage. Sun et al. performed a systematic review and meta-analysis demonstrating

that the risk of intraocular hemorrhage was lower with NOACs than with warfarin.

The authors searched Medline, ClinicalTrials.gov, and article bibliographies for phase 3 randomized controlled trials published before August 2016 that involved patients with atrial fibrillation or venous thromboembolism who received warfarin or a NOAC (i.e., rivaroxaban, apixaban, edoxaban, or dabigatran). Two independent investigators selected the trials to be analyzed. All chosen studies contained data on intraocular bleeding, which were pooled using inverse-variance, weighted, fixed-effects meta-analysis. The primary outcome measures were intraocular bleeding events and associated risk ratio for NOACs versus warfarin. In secondary analyses, the trials were stratified by indication for anticoagulation and type of NOAC.

Twelve trials (7 on atrial fibrillation, 5 on thromboembolism) involving 102,627 patients were included in the analysis. The reduction in intraocular bleeding was 22% lower for NOACs. No significant heterogeneity was observed among the trials. In subgroup analyses, the risk of intraocular bleeding also proved lower for NOACs, and there was no significant difference in the indication for anticoagulation or the type of NOAC used. Summary effects did not differ materially.

In conclusion, the risk of intraocular bleeding was substantially lower with NOACs than with warfarin. Benefits were observed across indications for anticoagulation and types of NOAC. The findings are particularly relevant for patients at increased risk for spontaneous retinal bleeding and may have implications for perioperative care. Future research efforts should be directed at optimizing the management of patients with concomitant ocular disease and cardiovascular disorders.

Effect of Premature Birth on Later Rod and Cone Function August 2017

Although advances in neonatal care have improved survival rates for premature infants, major morbidities are

common among survivors, including severe retinopathy. Even in full-term infants, the retina is immature and continues developing for several years. The effect of premature birth on rod and cone function during childhood was examined by **Molnar et al.**, who compared retinal function of children born very prematurely with that of children born at term. They found that children born prematurely exhibited reduced function of rods and cones.

Binocular full-field electroretinographic (ffERG) recordings were obtained in 6.5-year-old children born both before 27 weeks' gestation (n = 52) and at full term (n = 45). The recordings were analyzed for associations with gestational age and retinopathy of prematurity (ROP).

Relative to the full-term group, the preterm group had lower amplitudes of combined rod and cone responses and of the isolated cone response. The implicit time of the combined rod and cone responses was longer in the preterm group, as was the isolated cone response time. No association was observed between ffERG findings and ROP or gestational age in the preterm group.

The reduced rod and cone function suggests that extremely premature birth is a major reason for retinal dysfunction later in life. The researchers recommended long-term follow-up of patients born prematurely to detect and treat disorders resulting from rod or cone dysfunction, including photophobia, reduced visual field, and inadequate night vision. (*Also see related commentary by M. Elizabeth Hartnett, MD, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Targeting Complement Factor D Reduces Progression of AMD-Related Geographic Atrophy
Science Translational Medicine
Published online June 21, 2017

Genetic studies of patients with age-related macular degeneration (AMD) have implicated dysregulation of the

alternative complement pathway in the pathogenesis of geographic atrophy (GA). **Yaspan et al.** conducted a clinical trial of lampalizumab, an inhibitor of complement factor D, and noted a potential therapeutic effect on GA.

For this phase 2 study, the researchers compared lampalizumab to sham treatment in patients with GA secondary to AMD. Lampalizumab was administered by intravitreal injection monthly (n = 42) or every other month (n = 41); sham treatment was given at the same intervals (pooled control group, n = 40). The primary efficacy variable was the mean change in lesion area from baseline to 18 months, measured from fundus autofluorescence images.

Monthly treatment with lampalizumab demonstrated a reduction in lesion-area progression of 20% relative to sham treatment, indicating that the study's prespecified significance level was achieved. Efficacy in the monthly lampalizumab arm was noted as early as month 6 and continued thereafter. Monthly lampalizumab treatment reduced progression of the GA area regardless of lesion size at baseline. In contrast, the area of GA enlarged in the pooled sham group.

In a subgroup of complement factor I (CFI) risk-allele carriers (representing 57% of all patients analyzed), monthly active treatment produced a 44% reduction in progression of the atrophic area; no treatment effect was apparent in risk-negative patients. Overall, lampalizumab demonstrated an acceptable safety profile throughout the 18-month study.

Efficacy and Safety of Propranolol for Infantile Hemangioma
JAMA Dermatology
2017;153:529-536

Kim et al. conducted a randomized trial to assess the utility of propranolol as first-line treatment for infantile hemangioma (IH). This agent proved noninferior to prednisolone in therapeutic effect, and the drugs' safety profiles were similar.

The research was performed at an academic hospital in Seoul, South Ko-

rea. Eligible participants for the noninferiority study were diagnosed with IH between June 2013 and October 2014, had normal heart function, and had not received treatment for IH. Enrollees were assigned randomly to receive powdered propranolol (2 mg/kg/d, divided into 3 daily oral administrations) or prednisolone syrup (1 mg/mL syrup; 2 mg/kg/d), each for 16 weeks.

Patients in the propranolol group (n = 17) were admitted, observed for adverse effects during the first 3 days, and treated as outpatients for the remaining time. Patients in the steroid group (n = 17) were treated as outpatients for the entire duration of treatment. The primary efficacy variable was change in hemangioma volume from baseline to week 16, determined from magnetic resonance images. Adverse events (AEs) were monitored throughout the study.

Of the 34 patients randomized (mean age, 3.3 months), 31 completed the entire study. The intent-to-treat analysis, which included multiple imputations, showed a treatment response rate of 95.65% in the propranolol group and 91.94% in the steroid group. The difference of 3.71% indicated that propranolol was not inferior to prednisolone. Sensitivity analyses produced similar results. Although tumor volume reduction was greater in the propranolol group (55.87% vs. 46.52% reduction), the difference was not significant.

After the initial dose, the following parameters were significantly lower for propranolol recipients: heart rate (131.88 bpm vs. 147.63 bpm), body temperature (36.66°C vs. 36.96°C), and blood glucose level (103 mg/dL vs. 121 mg/dL). There were no serious AEs. Two patients in the steroid group had growth disability. The rates of overall and other AEs were comparable for the 2 groups. No AE was attributed to propranolol.

The authors concluded that propranolol is not inferior to prednisolone in terms of efficacy, and they added that larger studies are warranted to validate this finding, examine costs of propranolol, and comprehensively evaluate safety.

—Summaries by Lynda Seminara

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