Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

Tailored Care Improves Adherence to Glaucoma Therapy

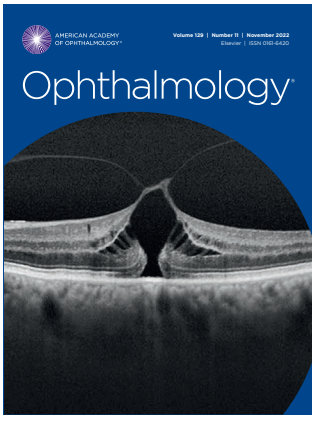
November 2022

Although many efforts to improve medication adherence in patients with glaucoma have been proposed, evidence of their relative effectiveness is lacking. **Ha et al.** conducted a network meta-analysis of randomized controlled trials (RCTs) to compare effectiveness for various interventions. They found that tailored care that included a face-to-face needs assessment and a personalized care plan was superior to standard of care (SOC) for improving adherence rates. When tailored care was combined with other initiatives, such as reminder devices and multimedia education, adherence improved even further.

For this work, the authors searched multiple databases to identify RCTs of strategies to improve medication adherence among adults with glaucoma or ocular hypertension. They then compared the efficacy of 11 interventions alone or in combination: basic SOC (control), enhanced SOC, short message service (SMS), telephone call, device reminder, incentives, motivational interview, multimedia education, physician education, tailored care, and provision of own medical records. Enhanced SOC was defined as basic SOC plus additional support, such as providing printed information. The main outcome measure was the mean adherence score following intervention. The standardized mean differences (SMDs) were analyzed by a random-effects model, and effectiveness was ranked by p score (the probability of being the best intervention).

Nineteen RCTs, representing 4,981 patients, qualified for the analysis. Tailored care, which included an in-person needs assessment and personalized care plan, was better than SOC for improving therapy adherence (SMD, 1.28; p = .810). Multifaceted interventions that included tailored care improved adherence even further: tailored care + multimedia education (SMD, 1.44; p = .850) and tailored care + multimedia education + device reminder (SMD, 1.6; p = .914). P scores (highest to lowest) for the other interventions were .606 for incentives, .535 for SMS, .458 for enhanced SOC, .430 for device reminder, .429 for multimedia education, .401 for telephone call, .391 for provision of own medical records, .281 for physician education, .230 for general SOC, and .165 for motivational interview.

Findings of this meta-analysis suggest that adherence to glaucoma medication is better with tailored care than with standard care. "A multifaceted approach might yield additional improvements," said the authors. They emphasized that a personalized approach may reduce barriers to adherence.



Laser Refractive Surgery May Improve Amblyopia

November 2022

For an Academy *Ophthalmic Technology Assessment,* **Cavuoto et al.** reviewed literature on the effectiveness and safety of laser refractive surgery for treating anisometropic amblyogenic refractive error in children. Although their analysis of relevant studies found variations in the ability of this surgery to address anisometropic amblyogenic refractive error, the magnitude of anisometropia was reduced. However, improvement of amblyopia did not necessarily correlate with refractive improvement. Most complications of the surgery were not serious.

For this review, the authors searched PubMed in October 2021 for all English-language publications on the topic. Of 137 potential results, 69 articles qualified for full-text review, and 12 met all criteria for inclusion. The panel methodologist assigned a level of evidence to each study using Academy guidelines. Each of the 12 studies represented evidence level 3. Ten were case series, and two were case-control studies. Six studies involved LASIK, two evaluated PRK, and one assessed refractive/small

incision lenticule extraction (ReLEx Smile). The others involved some combination of LASIK, PRK, laser epithelial keratomileusis, or ReLEx Smile. Five studies focused on anisometropic myopia, two concentrated on anisometropic hyperopia, and the remainder had a mix of patients with either condition.

Although VA improved in all 12 studies, the amount of improvement varied widely, as did the assessment parameters. The definition of successful outcome used in this review was residual refractive error within 1 D of the target refraction, which also was the most common metric among the 12 studies. The proportion of successful outcomes ranged from 27% to 89%, and the mean follow-up period ranged from four months to seven years. Despite these vast differences, the magnitude of anisometropia improved in every study. Regression of refractive error occurred more frequently—and to a greater degree—in younger children, in eyes with myopia, and in eyes with relatively longer follow-up. The only serious complications were two free flaps (in the same study). The most common adverse effects were striae and corneal haze.

"Laser refractive surgery may address amblyogenic refractive error in children," said the authors, who noted that it may decrease anisometropia. They acknowledged that large well-designed prospective studies are needed to fully clarify the role of refractive surgery in children and its potential effect on amblyopia.

Perioperative Multiuse Eyedrop Protocols Are Cost-Effective

November 2022

Berkowitz et al. explored the cost-effectiveness of multiuse eyedrop protocols in the perioperative setting. Their analysis of adults who had ophthalmic surgery requiring preoperative dilation and intravitreal injection showed that vast cost savings would be achieved if one bottle of mydriatic eyedrops was used for multiple patients. According to the study model, the five-year savings per institution would exceed $240,000. Moreover, multiuse protocols would minimize waste.

For this work, the authors used economic modeling with scenario analysis to estimate the economic value of using a bottle of mydriatic eyedrops for multiple patients as opposed to discarding the bottle after use in just one patient. According to the multiuse protocol for mydriatic drops, the same bottle would be used for multiple successive patients until it is empty or has expired. The authors conducted similar analyses for a povidone-iodine protocol to precede intravitreal injections. The multiuse protocol for povidone-iodine assumes two drops for each patient and use in successive patients until the vial is empty or expired. The authors applied sensitivity analyses to test baseline model assumptions for various degrees of waste and case volume.

Among 7,170 patients who required a full regimen of mydriatic drops during the five-year study, the multiuse protocol reduced the number of bottles needed by 97.1% (from 35,850 to 1,037). This represents a five-year estimated savings of roughly $240,000 per institution, assuming an average of 1,434 cases per year (base-case scenario). Similar results occurred with sensitivity analyses that accounted for practical limitations such as loss, expiration, or contamination of bottles used for multiple patients (savings range, 95%-97.5%). The size of mydriatic drops made little difference in the cost savings (range, 96.7%-99.2%). As for preinjection povidone-iodine, the multiuse protocol would reduce the number of vials per institution by 99.6% (from 41,954 to 153 bottles) in a five-year period, yielding a savings of approximately $41,800. Findings of the sensitivity analyses were similar. The combined per-institution savings could total more than $280,000 per five-year period, before adjusting for inflation.

This analysis suggests that multiuse protocols for mydriatic eyedrops would reduce the cost and environmental waste associated with surgeries requiring pupillary dilation. It also indicates that multiple-use povidone-iodine protocols could lower the cost of office procedures that require them. "Opportunities for cost and environmental waste reduction can help ensure financial viability of care in high-cost ophthalmology practices," said the authors.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Managing Complications Associated With the Port Delivery System

November 2022

The Port Delivery System (PDS) includes a permanent, indwelling, and refillable ocular implant that provides continuous release of a customized formulation of ranibizumab. It is approved for the treatment of neovascular age-related macular degeneration (AMD). **Awh et al.** set out to provide strategies for the management of key ocular adverse events that may be encountered with the PDS in everyday clinical practice.

This safety evaluation was based on two key studies of the PDS, the phase 2 Ladder and phase 3 Archway trials. Procedural videos and eye or implant images collected during the trials were systematically reviewed.

The researchers identified and described the following key adverse events that may arise after insertion of the PDS or the refill-exchange procedures: conjunctival retraction and conjunctival erosion; endophthalmitis; implant dislocation; conjunctival bleb and conjunctival filtering bleb leak; wound leak, hypotony, or choroidal detachment; vitreous hemorrhage; retinal detachment; cataracts; and septum dislodgment. For each category, they provided recommendations for patient examination and management.

Surgeons should be aware of these potential complications and take steps to identify them early in order to achieve optimal outcomes, the researchers said. They noted that patient selection is key—for instance, patients with thin or scarred conjunctiva are not ideal candidates for the PDS—and recommended careful assessment of the ocular surface before any planned PDS procedure. *—Summary by Jean Shaw*

Ophthalmology Science

Selected by Emily Y. Chew, MD

Topical Solution Shows Promise for Dry Eye Secondary to GvHD

September 2022

In a pilot trial, **Sugar et al.** evaluated the safety and tolerability of two concentrations of a topical ophthalmic solution for the treatment of dry eye disease secondary to graft-versus-host disease (GvHD). They found that the solution, known as CAM-101, was well tolerated and showed no significant toxicity.

CAM-101 is a fibrinogen-depleted human platelet lysate solution prepared from pooled human platelet apheresis products. For this phase 1/2 study, 64 participants from nine U.S. centers were randomized 1:1:1 to placebo control (n = 22) or to 10% (n = 20) or 30% (n = 22) CAM-101. Drops were administered four times daily, one drop in each eye, for 42 days. Primary outcomes were ocular and systemic adverse events and the number of participants with any abnormal clinically significant findings at day 42, as compared with baseline. Secondary outcomes were efficacy endpoints, including reductions in ocular discomfort from baseline to day 42 and findings on fluorescein corneal and lissamine green conjunctival staining and tear break-up time. Following this, those in the control group were offered 42 days of open-label treatment with CAM-101 30%.

Of the 64 participants initially enrolled in the trial, 54 completed the study according to the protocol. For the 10 who dropped out, the primary reason given for withdrawal was a change in systemic medications indicated by a change in their underlying GvHD.

Results showed that both concentrations of CAM-101 were safe and well tolerated, with no indications of toxicity. Statistically significant improvement in some dry eye symptoms were observed in those treated with the 30% concentration. The objective findings of corneal and conjunctival staining were not statistically significant, although there was improvement in tear break-up time. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Alert Systems May Curb Opioid Dosing

November 2022

Opioid alert systems have led to a decline in opioid prescriptions in some specialties, but data pertaining to ophthalmology are sparse. **Blaga et al.** looked at opioid prescribing trends in ophthalmology and explored the effect of an alert system on prescribing patterns. They found that demographics played a role in the prescribing of opioids and that an alert system could reduce the volume of opioid prescriptions in the eye care setting.

The study was retrospective in design and compared prescribing trends before and after implementation of an electronic opioid alert system. Study participants were adults who received prescriptions for opioid medication from an ophthalmologist within a tertiary care center during a period of approximately seven years. The mean morphine-equivalent daily dose (MEDD) per prescription was compared before and after instituting the alert system, whereby any prescription that exceeded a mean MEDD of 30 or a seven-day supply for an adult would prompt the system to signal an alert. In this study, the system applied only to prescriptions issued electronically at discharge to manage acute pain. Paper scripts were not included.

The study population included 8,014 patients and 9,055 separate prescriptions for an opioid. More than three-fourths of the prescriptions were for pain management following an ophthalmic surgery. After the alert system was implemented, the mean MEDD per prescription decreased by 15.17 ($p < .001$), from 40.05 to 24.88, indicating the system's effectiveness. The per-prescription MEDD was higher for male patients (33.53 vs. 32.55 for females; $p < .001$) and for Black individuals (33.93 vs. 32.80 for Whites; $p = .03$). Patients with a disorder of the eyelid, orbit, or lacrimal system had the highest proportion of opioid prescriptions (57.4% of the total), followed by patients with a disorder of the sclera, cornea, iris, or ciliary body (16%).

A unique aspect of this study is its emphasis on morphine equivalents specific to ophthalmology, said the authors. The authors recommend comparing these observed trends and dosages with those of other institutions, which may lay the groundwork for developing national opioid prescribing guidelines for ophthalmologists.

Intermittent Fasting May Lower AMD Risk

November 2022

Intermittent fasting has been successful in preventing and treating various conditions, primarily those of a metabolic and cardiovascular nature. Skipping breakfast is a popular form of intermittent fasting and has been investigated in several studies. **Choi et al.** used data from the nationwide Korean health and nutrition survey to explore the effect of skipping breakfast on the prevalence of age-related macular degeneration (AMD). They found that AMD risk was significantly lower for people who refrained from eating breakfast. The effect was most pronounced in those who were obese, were younger than age 70 years, and lived in urban areas.

For this cross-sectional study, the investigators gathered data from the Korean National Health and Nutrition Examination Survey (KNHANES). People older than 54 years who provided detailed information, including meal frequency and fundus images, were identified from the 2015-2018 KNHANES database. These individuals were assigned to one of two groups based on breakfast frequency in the preceding year: nearly zero times per week (intermittent fasting group) or five to seven times per week (nonfasting group). Multiple logistic regression analysis was performed to explore relationships between breakfast frequency and the AMD risk factors noted on fundus photographs. Subset analyses were performed on demographic and lifestyle factors.

The intermittent fasting group

included 4,003 participants, while only 183 people were in the nonfasting group. Those who skipped breakfast were somewhat younger and were less likely to have hypertension, dyslipidemia, or diabetes. Among the entire study population, AMD was identified in 25.1%. The proportion of participants with AMD was significantly lower for fasters (14.2% vs. 25.6%; p = .001), which translated to a lower risk of AMD development relative to nonfasters (adjusted odds ratio [aOR], 0.413), especially in those under 70 years of age (aOR, 0.357), those with obesity (aOR, 0.663), and residents of urban areas (aOR, 0.437). Independent risk factors for AMD were older age (aOR, 1.058) and elevated serum levels of high-density lipoprotein (aOR, 1.011). Smoking, anemia, and hepatitis B did not significantly affect AMD risk. Although some experts consider larger waist circumference to be a risk factor for AMD, it seemed to lower AMD risk in this study.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Predominantly Peripheral Lesions and DR Progression: Role of UWF-FA

October 2022

In a study from the DRCR.net, **Marcus et al.** aimed to determine whether detecting predominantly peripheral lesions (PPLs) on ultra-widefield imaging aids in predicting the progression of diabetic retinopathy (DR). They found that the presence of PPLs on ultra-widefield fluorescein angiography (UWF-FA) is associated with DR progression. A similar association was not found with UWF-color imaging.

For this prospective longitudinal study, known as Protocol AA, researchers at 37 clinical sites enrolled 388 participants who were at least 18 years old, had type 1 or 2 diabetes, and had at least one eye with nonproliferative DR (NPDR). The analysis cohort consisted of 544 study eyes of 367 participants.

Standard 7-field ETDRS images, UWF-color images, and UWF-FA images were taken at baseline. Following that, UWF-color images were taken during four years of follow-up, and UWF-FA images were taken at the one-year and four-year visits. The primary outcome measure was the progression of disease, defined as either worsening by 2 or more steps on the Diabetic Retinopathy Severity Score (DRSS) scale or receipt of treatment for DR during follow-up.

All told, 542 eyes had gradable color and FA images. Of these, PPLs were detected in both sets of images in 136 eyes (25%) and were absent in 210 eyes (39%). PPLs were evident only on UWF-color imaging in 85 eyes (16%) and only on UWF-FA in 111 (20%).

When all eyes were stratified by degree of disease at baseline, the four-year disease worsening rates were 45% for eyes with mild NPDR, 40% for eyes with moderate NPDR, 26% for eyes with moderately severe NPDR, and 43% for eyes with severe NPDR. Disease worsening was not associated with the presence of PPLs on UWF-color at baseline but was associated with their presence on UWF-FA at baseline. This association was present within DRSS subgroups and with multiple individual types of PPLs.

Based on these data, the researchers said, "findings on UWF-color are not interchangeable with findings on UWF-FA." Moreover, they said, the study results "support the use of UWF-FA for future DR staging systems and clinical care to more accurately determine prognosis in NPDR eyes." *(Also see companion study by Silva et al., as well as related commentary by Imran H. Usuf, MB ChB(Hons), MRes, MRCP, DPhil, FRCOphth, and Andrew J. Lotery, MD, FRCOphth, in the same issue.)*

Eyewear and COVID-19 Infection

October 2022

Does wearing eyeglasses or contacts protect against COVID-19 transmission? **Gregersen et al.** investigated this question and found inconclusive results.

This cohort study was conducted during the first wave of the COVID-19 pandemic in Denmark and Sweden. Employees of Falck, an international rescue corps, participated in voluntary COVID screenings every two weeks from June 22, 2020, to Aug. 13, 2020. The employees served in different job functions (including ambulance, health care, firefighting, and office staff positions), and 2,120 employees participated. Of these, 1,448 wore contacts or glasses, including reading glasses.

Participants filled out a questionnaire regarding their vision correction. To adjust for potential confounding factors, information on age, sex, job function, and number of contacts encountered during the workday were included. The primary outcome was the rate of COVID-19 infection before or during the study period.

In the Swedish cohort (n = 841), wearing glasses was inversely associated with COVID-19 infection (odds ratio [OR] .61; 95% confidence interval [CI], .37-.99; p = .047; seroprevalence, 9.3%). However, this did not hold true for the 1,279 employees in the Danish cohort (OR, 1.14; 95% CI, .53-2.45; p = .73; seroprevalence, 2.4%). Moreover, once the results for the Swedish cohort were adjusted for confounding factors, the effect size changed slightly and lost statistical significance.

The authors noted that while their analyses were inconclusive, the possibility that glasses provide protection against COVID "remains a biologically plausible, safe, and inexpensive additional protection, which should be considered in disease-preventive strategies." *(Also see related commentary by B. Michele Melia, ScM, in the same issue.)*

Visual Impairment at Time of Childhood Brain Tumor Dx

October 2022

Nuijts et al. set out to assess the prevalence and types of abnormal ophthalmic findings in children with a newly diagnosed brain tumor. They found a high prevalence of visual impairment, even in those children who did not present with visual symptoms at the time of diagnosis.

For this prospective cohort study, the researchers evaluated 170 young Dutch patients (median age, 8.3 years;

range, .2 to 17.8 years) who were diagnosed with a brain tumor between May 15, 2019, and Aug. 11, 2021. Infratentorial tumors were diagnosed in 82 of the children, while 88 had supratentorial tumors.

Overall, 101 of the children (59.4%) presented with visual symptoms at the time of diagnosis, most often diplopia (42 children), decreased vision (42), eye movement disorders (32), and visual field (VF) loss (23). In addition, 30 children initially presented to an ophthalmologist, after which a brain tumor diagnosis was established.

A complete ophthalmic examination was conducted at the time of diagnosis; this revealed abnormal ophthalmic findings in 134 of the patients (78.8%), notably papilledema (52.4%), gaze deficits (33.5%), VF defects (28.1%), nystagmus (24.8%), strabismus (19.9%), and decreased VA (8.6%). Of the 69 children who initially presented without visual symptoms, 24.4% had VF defects, and 9.8% had visual impairment in both eyes.

The findings support the need for a standardized ophthalmologic exam at the time of diagnosis, regardless of presenting visual symptoms, the researchers said. *—Summaries by Jean Shaw*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

IAT Improves Vision in Patients With CRAO

Graefe's Archive for Clinical and Experimental Ophthalmology
Published online Aug. 10, 2022

Intra-arterial thrombolysis (IAT) is a treatment option for central retinal artery occlusion (CRAO), but it has been linked to adverse events such as cerebral complications. Previous meta-analyses yielded inconsistent findings and were limited by relatively small sizes as well as differences in definitions of VA improvement among the analyzed studies. To better clarify the efficacy and safety of IAT for CRAO, **Huang et al.** performed a larger systematic review and meta-analysis. They found that VA improved significantly following IAT, but they cautioned that the treatment could have serious consequences that must be weighed against its advantages.

For this work, the investigators searched PubMed and Embase for potentially relevant studies published through early November 2021. For those that met the inclusion criteria, standard mean differences (SMDs) were pooled to determine baseline and final VA of patients who received IAT for CRAO. "Baseline VA" was defined as VA at time of admission, and "final VA" denoted VA at the end of follow-up. Improvement rates and odds ratios (ORs) were analyzed to compare VA outcomes between patients who underwent IAT and those who did not. Other variables of interest included time from symptom onset to IAT and the definition of VA improvement. Adverse effects were documented to assess safety.

In 15 studies that qualified for the meta-analysis, 507 patients with CRAO received IAT, and 296 were treated conservatively. The VA improvement rate was higher in the IAT group (56% vs. 32%; OR, 3.55) and was highest if IAT was performed within six hours of symptom onset (OR, 4.60 vs. 3.36 for later procedures). VA improvement of at least 3 Snellen lines was maintained (OR, 4.68) and was better in cases of incomplete occlusion. The serious adverse events ascribed to IAT were symptomatic intracranial hemorrhage (five patients) and ischemic stroke or transient ischemic (21 patients). Hemiparesis occurred in one patient treated conservatively.

These findings suggest that IAT enhances VA in patients with CRAO and is most successful if performed shortly after symptom onset, but the risks warrant consideration, the authors said.

Oxytocin and Secretin: Dual Neuropeptides for Dry Eye

Frontiers in Ophthalmology
Published online Aug. 1, 2022

Lopez et al. reviewed relevant literature to summarize evidence that oxytocin and secretin, as well as their receptors OXTR and SCTR, could be a foundation for novel treatments of dry eye syndrome (DES) and other pain-producing ocular conditions. Advantages of a potential dual-neuropeptide therapy for DES include promotion of tear production, reduction of nociceptive and neuropathic pain, and enhancement of anti-inflammatory activity.

For this review, the authors searched PubMed for English-language publications containing the following key terms: (oxytocin OR secretin) AND (inflammation OR anti-inflammatory OR pain OR nociception OR trigeminal neuralgia OR eye OR dry eye syndrome OR Sjögren syndrome).

Their summary is as follows:

Oxytocin and OXTR are found in the lacrimal gland and stimulate the release of tears; both typically are depleted in DES. Inflammatory responses caused by bacteria on the eye surface also appear to trigger DES symptoms and pain. The presence of lipopolysaccharides (LPS) in eyes of mice increases the expression of specific inflammatory mediators, some of which can be decreased by introducing oxytocin. In vitro studies of anterior pituitary cell cultures support oxytocin's ability to inhibit LPS and IL-1β stimulation of macrophages, T cells, and B cells, and to reduce IL-6 cytokine production. Oxytocin has a good safety profile and is most effective for treating DES symptoms when administered topically or intranasally rather than intravenously. Studies in rodents have shown that the presence of secretin influences oxytocin secretion as well as OXTR expression, potentiating the responses. Various nonpeptide analogs of oxytocin also appear to activate OXTR and SCTR responses.

A growing body of evidence supports the synergism of oxytocin and secretin in achieving ocular surface homeostasis. Given the coexistence of OXTR and SCTR in the human ocular surface, developing treatments that target them may be fundamental for alleviating the pain associated with DES. Oxytocin analogs, in conjunction with secretin, also warrant investigation as potential remedies for DES and other painful ocular disorders.

—Summaries by Lynda Seminara