

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

### Red-Light Therapy for Myopia Control

May 2022

Progressive myopia raises the risk of irreversible visual impairment, so prevention and control are crucial. As spending extra time outdoors in bright light has been found to reduce myopia risk, some researchers recommend glass walls and ceilings for schools. However, this strategy is costly and challenging. As an alternative, **Jiang et al.** proposed delivering light directly to the retina for short periods, through a device that emits red light at a wavelength of 650 nm. In a prospective multicenter trial, these investigators tested low-level exposure to red-light therapy as a method to control myopia. Their data showed that the treatment is effective, safe, and highly acceptable to users.

For this single-masked, parallel-group study, the authors enrolled myopic children (aged 8 to 13 years) with spherical equivalent refraction (SER) between  $-1$  and  $-5$  D, anisometropia of  $\leq 1.50$  D, astigmatism of  $\leq 2.50$  D, and BCVA of  $\geq 0.0$  logMAR. The children were assigned randomly to the intervention group (red light + single-vision spectacle [SVS]) or the control group (SVS only).

The red-light therapy was given at home and supervised by parents. A desktop device delivered the light at illuminance of roughly

1,600 lux and power of 0.29 mW for a 4-mm pupil (class I classification). For a 12-month period, the treatment was administered twice daily, five days per week. Each session lasted three minutes, and the interval between treatments was at least four hours.

Main outcomes were changes in axial length and SER from baseline to each follow-up visit (months 1, 3, 6, and 12). Children who had at least one follow-up visit were included in the efficacy analysis, which was conducted with longitudinal mixed models.

Of the 264 enrollees, 246 (93.2%) qualified for data analysis (117 treated patients plus 129 controls). Results showed a 12-month axial elongation and SER progression of 0.13 mm and  $-0.20$  D in those treated with red light, versus 0.38 mm and  $-0.79$  D in controls. There were no severe adverse events related to the red-light therapy, and no structural damage was seen on OCT scans. The median rate of treatment compliance was 75%.

The authors noted that double-masked, placebo-controlled studies of low-level red-light therapy are needed to evaluate long-term efficacy and safety, to look for possible rebound effects, and to determine optimal device settings and treatment regimens.

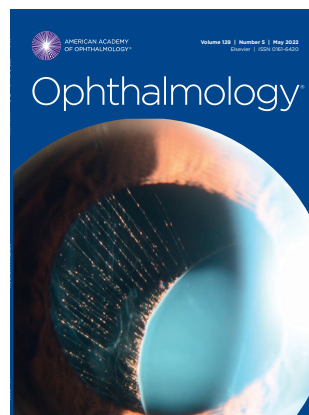
### Fungal Keratitis: Natamycin Superior to Chlorhexidine

May 2022

Fungal keratitis is challenging to manage, and treatment is often delayed in areas with limited access to care. Although natamycin has been the treatment of choice, it is costly, difficult to formulate, and not available globally. Recognizing the need for an affordable, accessible option, **Hoffman et al.**

compared chlorhexidine with natamycin in a noninferiority study. They found that natamycin produced better visual acuity and had fewer side effects than chlorhexidine. As a result, it should remain the preferred first-line therapy for fungal keratitis, they said.

For this single-masked, randomized, controlled trial, the investigators enrolled adults with filamentous fungal infection managed at a tertiary-level ophthalmic hospital in Nepal. The infection was confirmed by a smear test or confocal microscopy. Participants were assigned randomly to receive topical treatment with 0.2% chlorhexidine or 5% natamycin. The main outcome measure was logMAR BCVA at three months. Secondary outcomes included the incidence of perforation or therapeutic penetrating keratoplasty within 90 days. Cases of mixed fungal and bacterial infections were excluded from the primary analysis but included in secondary analyses.



The predetermined noninferiority threshold for efficacy was 0.15 logMAR.

During the 17-month enrollment period (June 2019–November 2020), there were 354 eligible participants. Of these, 178 received chlorhexidine, and 176 received natamycin. After excluding those for whom 90-day outcomes were not available and cases of mixed bacterial-fungal infections, 284 participants remained for the primary analysis (141 chlorhexidine, 143 natamycin).

The investigators found that outcomes in the natamycin-treated group were superior to those in the chlorhexidine-treated group. Patients treated with natamycin had significantly better BCVA at 90 days, after adjusting for baseline BCVA ( $p < .001$ ). BCVA was approximately 3 lines better in the natamycin group. Perforations and emergency corneal grafts were more common in those treated with chlorhexidine (13.7% vs. 5.8%;  $p = .018$ ), and natamycin-treated cases were less likely to experience perforation or require an emergency corneal graft, after adjusting for baseline ulcer depth (odds ratio, 0.34;  $p = .013$ ).

The authors suggest viewing these results in a global context. For example, if natamycin is not available, cautious use of chlorhexidine may be useful. Even so, this study highlights the need for natamycin to be readily available wherever fungal keratitis is a public health concern, said the authors. They recommend testing the safety of lower doses of chlorhexidine and exploring the possibility of a chlorhexidine-natamycin combination treatment for the disease.

### **Immediate Sequential Bilateral Cataract Surgery: Trends and Outcomes**

May 2022

Malwankar et al. used Medicare claims data to explore trends and outcomes of immediate sequential bilateral cataract surgery (ISBCS) in the United States. They found that even though ISBCS use remained low through 2019, the rates of endophthalmitis and cystoid macular edema (CME) were comparable for ISBCS and delayed sequential

bilateral cataract surgery (DSBCS). They recommend that similar reviews be conducted for the COVID-19 era to understand whether the pandemic has influenced acceptance of ISBCS.

For this study, the authors reviewed and compared data for Medicare patients who had ISBCS or DSBCS from 2011 through 2019. In addition, they used logistic regression to explore factors associated with ISBCS. Main outcomes included incidence of ISBCS and DSBCS; demographic, ocular, and medical factors relating to ISBCS use; and the rates of endophthalmitis and CME for both approaches.

Altogether, 1,944,979 patients were identified from the claims data. Of these, 4,014 patients (0.2%) underwent ISBCS; all others received DSBCS (1,940,965 [99.8%]). ISBCS was more common in patients of Black, Asian, and Native American races than in those who were White (respective odds ratios [ORs]: 2.31, 1.82, and 2.42). Patients in rural regions were more likely to undergo ISBCS than were residents of metropolitan areas (OR, 1.26). Surgery performed in a hospital, rather than an ambulatory surgery center, trended toward ISBCS (OR, 2.71). Bilateral cases that were deemed “complex” were more likely than non-complex cases to receive ISBCS (OR, 3.23). Patients with a Charlson comorbidity score of at least 1 were more apt to have ISBCS, whereas patients with glaucoma, macular degeneration, macular hole, or epiretinal membrane were more likely to have DSBCS. The difference in rates of endophthalmitis occurring within six weeks was not significant, nor was the difference in CME rates. —*Summaries by Lynda Seminara*

### **Ophthalmology Retina**

Selected by Andrew P. Schachat, MD

#### **Frequency of Anti-VEGF Injections and Mortality Rates**

May 2022

Reibaldi et al. set out to determine whether an intensive regimen of anti-VEGF injections is associated with a higher risk of mortality. They found no significant link between mortality risk

and treatment intensity.

For this meta-analysis, the researchers evaluated the results of 52 randomized trials with 13,099 and 9,691 patients at 12 and 24 months of follow-up, respectively. The primary outcome of interest was the relationship between the average number of injections in different study arms and the all-cause mortality rate. Separate regression analyses were conducted to investigate this relationship in selected subgroups of studies, including patients with different retinal diseases and receiving different anti-VEGF medications.

The median number of injections was 7.1 (interquartile range, 3.3-10.1) at 12 months and 11.6 (interquartile range, 5.9-20.6) at 24 months.

At 12 months, 134 of 13,099 patients (1.02%) in 46 studies had died. At 24 months, 326 deaths (3.36%) had occurred among 9,691 participants in 18 studies. Results of univariate regression analysis showed that a greater number of injections was not associated with an increase in mortality risk at 12 months (incidence rate ratio [IRR], 1.16%; 95% confidence interval [CI], .87-1.53;  $p = .31$ ) or at the 24-month mark (IRR, 1.05; 95% CI, .95-1.15;  $p = .03$ ). However, in a subgroup analysis of patients with diabetic macular edema, a slightly higher risk of mortality was observed at 24 months in five studies with 74 deaths (IRR, 1.17; 95% CI, 1.02-1.33,  $p = .03$ ).

The researchers noted that most of the studies in this analysis excluded patients with a history of stroke and myocardial infarction; thus, the results “should be interpreted cautiously in patients at high cardiovascular risk,” they said. —*Summary by Jean Shaw*

### **Ophthalmology Science**

Selected by Emily Y. Chew, MD

#### **Opioid Use Raises Risk of Retinal Vein Occlusion**

March 2022

McDermott et al. used the NIH’s All of Us database, which links to electronic medical records, to determine risk factors for retinal vein occlusion (RVO). They found a previously uncharacter-

ized association between opioid use and RVO.

For this retrospective case-control study, the researchers evaluated data from All of Us (<https://allofus.nih.gov>) on 691 participants with RVO (380 with branch and 311 with central RVO) and another 1,520 participants, who served as controls. All were 18 years of age or older, and controls were proportionally matched to the demographic distribution of the 2019 U.S. census. Data were extracted regarding demographics, comorbidities, income, housing, insurance, and substance abuse. The main outcome measure was development of RVO based on diagnostic codes.

Overall, patients with branch and central RVO shared medical risk factors, with traditional risk factors (e.g., glaucoma, hypertension, hyperlipidemia, and diabetes) linked to a greater risk of developing RVO. The results also indicated that older participants were at increased risk, as were those who were Black.

With regard to substance use, past marijuana use was associated with a decreased risk of developing RVO. However, those who had used opioids were at increased risk (branch RVO = odds ratio [OR], 1.98; 95% confidence interval [CI], 1.41-2.78; central RVO = OR, 2.32; 95% CI, 1.59-3.41;  $p < .001$  for both).

The researchers noted that the results of previous studies have suggested that opioids may induce local microvascular or systemic cardiovascular changes that could lead to RVO. However, they noted, further studies—ideally those with larger cohorts and a prospective design—are needed.

—*Summary by Jean Shaw*

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Long-Term Outcomes for Pediatric Intermediate Uveitis

May 2022

Albloushi et al. set out to better understand the course and outcomes of pediatric idiopathic intermediate uveitis

(IIU). Although the researchers noted a trend toward lifelong inflammatory complications, they found that good vision was retained long-term in most patients. In moderate cases, steroid-sparing immunomodulatory therapy (IMT) was somewhat protective against cystoid macular edema and ocular hypertension.

The study cohort included 125 children (221 eyes) under 17 years of age with IIU (per the Standardization of Uveitis Nomenclature [SUN] definition) but no systemic disease. The children, 56.8% of whom were boys, were treated at Moorfields Eye Hospital between 1992 and 2020. Main outcomes were VA, inflammation severity, and occurrence of sight-threatening complications.

At presentation, 29 of the children (23.2%) had unilateral uveitis, and 18 (14.4%) were asymptomatic. All eyes had vitreous involvement, and 35 had substantial vitreous haze (SUN score  $\geq 2$ ). In 11 eyes, BCVA was worse than 20/160. Second-line IMT was used in 41 children, 27 of whom received methotrexate. The most common irreversible structural findings were ocular hypertension, cataract, and macular edema (65 [29.4%], 41 [18.5%], and 29 [13.1%], respectively). The mean follow-up time was 72.4 months (median, 57 months).

At the final visit, no patient had a SUN score  $\geq 2$ , and 116 patients (92.8%) had BCVA of 20/40 or better and “quiet eyes.” Factors that raised the risk of new-onset macular edema were naivete to IMT (odds ratio [OR], 6.3;  $p < .001$ ) and glaucoma occurrence during the observation period (OR, 6.6;  $p < .001$ ). Secondary cataract was more common with longer follow-up.

This study affirms earlier reports of retinal detachment, cystoid macular edema, and cataract being common causes of poor BCVA in IIU. Elevated IOP was another key sight-threatening finding in this study. On a positive note, IMT may control inflammation in IIU and its troubling consequences while also limiting corticosteroid use, said the authors. Their suggestions for future research include identifying potential IIU subtypes and exploring

responses to the various IMTs used for management.

### Robot-Assisted Subretinal Drug Delivery in Humans

May 2022

Cehajic-Kapetanovic et al. conducted a first-in-human randomized controlled study of a robotic device designed to deliver drugs subretinally to patients undergoing vitreoretinal surgery for acute macular hemorrhage. They found that the robotic-assisted procedure was safe and well tolerated. Outcomes resembled those for the manual technique, indicating that robotic technology may have roles in gene and cell therapies that require a high level of precision.

The authors performed this dual-arm intervention trial between August 2016 and March 2020 at Oxford Eye Hospital in Oxford, United Kingdom. They recruited 12 patients who had acute loss of vision from subfoveal hemorrhage associated with neovascular age-related macular degeneration. After standard vitrectomy, tissue plasminogen activator (tPA) was injected in six patients subretinally using the Preceyes Surgical System (with the surgeon manipulating a handheld motion controller in four possible axes). The other six patients received tPA manually under OCT guidance. The robotic procedure involved advancement of a cannula through the retina and foot-controlled injection of up to 100 mL of the tPA solution. Safety was the primary outcome; the researchers also assessed surgical duration, surgical success, and tolerability of the procedure during local anesthesia.

In all patients, the procedures were safe and well tolerated; measurable outcomes were equivalent for both groups. The median number of retinotomy sites was 1 in the robotic arm and 2 in the manual arm. The median volumes of injected tPA were .05 and .100 mL, respectively, and the median durations of delivery were 5.9 and 4.3 minutes, respectively. The mean durations of surgery were 42.7 and 46.9 minutes, respectively. The number of retinal microtraumas, which was a

proxy for safety, did not differ significantly between the groups. One month post-op, the median gain in VA was 1.30 logMAR in the robotic group and 1.62 logMAR in the manual group.

The authors acknowledged the limitations of their study, including the small sample and surgeon inexperience with robotic technology. Nonetheless, this work shows proof of concept for robot-assisted subretinal drug delivery and highlights the promise of this technology in the management of retinal degenerative diseases.

—Summaries by Lynda Seminara

## JAMA Ophthalmology

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

### Topical Pilocarpine for Presbyopia

April 2022

Waring et al. evaluated the efficacy and safety of AGN-190584 (pilocarpine hydrochloride 1.25%) eyedrops, now sold as Vuity, in patients with presbyopia. They found that the drug was safe and effective.

For this randomized phase 3 study, known as Gemini 1, 323 participants with presbyopia were enrolled from Dec. 21, 2018, to Oct. 31, 2019, at 36 sites in the United States. All were 40 to 55 years old (mean, 49.6 years). The majority (n = 235, 72.8%) were female and White (n = 292, 90.4%). Their baseline mean distance-corrected near visual acuity (DCNVA) in mesopic (e.g., dim) lighting conditions was 29.2 letters. Effects of pilocarpine on night vision were not evaluated.

Participants were randomized to receive either Vuity (n = 163) or vehicle (n = 160) eyedrops, which were administered bilaterally once a day for 30 days. The main outcome measure was the proportion of participants with an improvement of 3 or more lines on day 30 at hours 3 and 6.

At hour 3 on day 30, 50 (30.7%) of those who received Vuity had improved by 3 or more lines in mesopic, high-contrast DCNVA, versus 13 (8.1%) of those who received vehicle. At hour 6 on day 30, those percentages were

18.4% and 8.8%, respectively. Overall, treatment with Vuity was well tolerated. (Also see related commentary by Kevin K. Ma, MD, and Jennifer Rose-Nussbaumer, MD, in the same issue.)

### Depression and Severity of Dry Eye Signs and Symptoms

April 2022

Zhou et al. investigated the association between depression and severity of dry eye disease (DED). They found that patients with depression had worse DED symptoms and more ocular discomfort than did those without depression.

For this cross-sectional study, the researchers performed a secondary analysis of data from the DREAM (Dry Eye Assessment and Management) study, which evaluated the efficacy of omega-3 fatty acid supplements for DED. The Ocular Surface Disease Index (OSDI) and Brief Ocular Discomfort Index (BODI) were used to assess DED symptoms. DED signs were assessed by tear film breakup time, Schirmer test, corneal and conjunctival staining, tear osmolarity, and meibomian gland dysfunction at baseline, six months, and 12 months, and a composite score was calculated. DED features were compared for participants with and without depression and adjusted for age, sex, race, visits, and baseline comorbidities. Markers of inflammation (e.g., proinflammatory cytokines) were measured for some trial participants. The Mental Component Summary (MCS) score of the 36-Item Short Form Health Survey was used to screen for depression.

The majority of the 535 participants were women (n = 434, 81%) and White (n = 398, 74.4%). All were age 18 years or older (mean, 58 years). A total of 84 participants (15.7%) had depression at baseline, compared to 82 at six months and 64 at 12 months.

Those who screened positive for depression had worse DED symptoms by OSDI (effect size = .45; p < .001), BODI (effect size = .46; p < .001), and composite DED sign score (effect size = .21; p = .006). A lower MCS score (which signifies a higher level of depression) was correlated with a higher OSDI score at baseline and at the six-

and 12-month marks. Inflammatory markers did not differ by depression status.

The findings support consideration of depression as a comorbidity when managing patients with DED, the authors said. (Also see related commentary by Anat Galor, MD, MSPH, in the same issue.)

### Strabismus and Mental Health in Children

April 2022

Lee et al. assessed the association between strabismus and mental illness in the pediatric population. They found that children with strabismus had higher odds of having anxiety, depression, bipolar disease, and schizophrenia than did those without eye diseases. However, the researchers did not find a similar association for substance use disorder.

For this cross-sectional study, the researchers used claims data from the OptumLabs Data Warehouse for more than 12 million children younger than 19 years (mean age at time of first claim, 8 years) between Jan. 1, 2007, and Dec. 31, 2017. The main outcome measure was the presence of claims for five types of mental health problems.

All told, 352,636 children had strabismus, while the remaining 11,652,553 had no eye disease diagnoses and served as the control group. Those with strabismus were slightly more likely to be female (50.1%, vs. 49.2% of controls) and White (51.6%, vs. 49.4% of controls).

The adjusted odds ratios (ORs) for the association of mental illnesses with strabismus were as follows: 2.01 (95% confidence interval [CI], 1.99-2.04) for anxiety disorder, 1.83 (95% CI, 1.76-1.90) for schizophrenia, 1.64 (95% CI, 1.59-1.70) for bipolar disorder, 1.61 (95% CI, 1.59-1.63) for depressive disorder, and .99 (95% CI, .97-1.02) for substance use disorder. When analyzed by type of strabismus, ORs ranged from 1.23 (95% CI, 1.17-1.29) for the association between esotropia and bipolar disorder to 2.70 (95% CI, 2.66-2.74) for the association between exotropia and anxiety disorder.

In their discussion, the authors

acknowledged that children with strabismus may be subject to negative social bias, which may raise their risk of developing mental health issues. They noted that additional studies on this topic are needed; for instance, they said, “it would be useful to study whether correction of strabismus can help mental illness.” They also recommended that ophthalmologists take two steps: 1) consider incorporating a mental health screening tool into their examinations of patients with strabismus, and 2) refer children with strabismus for a mental health evaluation. (Also see related commentary by S. Grace Prakashaporn, MD, MPH, Manpreet Kaur Singh, MD, MS, and Nathan Congdon, MD, MPH, in the same issue.)

—Summaries by Jean Shaw

## Other Journals

Selected by Prem S. Subramanian, MD, PhD

### High Myopia and Glaucoma Risk in Beijing Eye Study

*British Journal of Ophthalmology*  
Published online Feb. 22, 2022

Little is known about the long-term incidence of and risk factors for open-angle glaucoma (OAG) among Chinese people. Moreover, previous longitudinal studies in China and elsewhere had limitations such as timelines of just five years. Wang et al. aimed to learn more through an observational analysis of data from the 10-year Beijing Eye Study. They found high myopia to be a major risk factor for OAG.

Of the 4,439 participants aged 40 and older in the Beijing Eye Study at its inception in 2001, 2,695 (60.7%) were available for examination in 2011. Assessments included measuring IOP, vertical cup-to-disc ratio (VCDR), and uncorrected visual acuity; performing automatic refractometry; viewing the anterior segment by slit lamp; and imaging the macula and optic nerve head. Ocular biometry was used to measure central corneal thickness (CCT), corneal curvature radius, anterior chamber depth, lens thickness, and total axial length. IOP readings were corrected for dependence on CCT and central

corneal curvature radius using linear regression analysis. Demographic data, risk factors, and OAG incidence were documented. Incident glaucoma was defined as the absence of glaucoma at baseline with observation of structural glaucomatous changes in the optic nerve head and retinal nerve fiber layer in 2011. Refractive status was classified as emmetropia/hyperopia, minor myopia, moderate myopia, or high myopia based on respective axial lengths of <24 mm, 24-25 mm, 25.01-26 mm, and >26 mm.

Incident glaucoma was found in 75 of the 2,494 participants who did not have it at baseline. The 10-year incidence of OAG ranged from 1.8% for participants in their 40s to 5.9% for those older than 69 years (mean, 3.0%) and was greatest for those with high myopia (odds ratio [OR], 7.3), followed by moderate myopia (OR, 4.2) and low myopia (OR, 3.2). In the multivariable analysis, OAG was linked to older age (OR, 1.06), longer axial length (OR, 1.72), higher IOP in 2001 (OR, 1.18), higher VCDR (OR, 60.8), and thinner CCT (OR, 0.98). OAG was more common in men, but the gender difference was not significant.

The greatest risk factor for OAG in this analysis was high myopia; compared with emmetropic eyes, the risk was more than sevenfold. These findings may be relevant for clinical protocols and screening strategies, said the authors.

### Partial Monovision for Presbyopia

*Graefe's Archive for Clinical and Experimental Ophthalmology*  
Published online Feb. 17, 2022

Knecht et al. hypothesized that partial monovision (PMV) in presbyopic patients may be attained with a monofocal IOL in one eye and a multifocal lens in the other. In a retrospective pilot study, they compared PMV and monofocal correction and found that PMV produced good visual results with minimal photopic effects.

The two study groups were similar in distributions of age, gender, and type of surgery (cataract or clear lens

extraction). Patients with other ocular diseases affecting VA were excluded. The PMV group underwent implantation of a monofocal IOL in the dominant eye three months before placement of a multifocal lens in the nondominant eye. The monofocal correction group received monofocal IOLs in both eyes, with the intent to achieve slight anisometropia (0.0 D/−0.50 D).

Before and at least three months after IOL implantation, patients in both groups underwent assessment of uncorrected near, intermediate, and distance VA. Defocus curve and stereo acuity (Lang-Stereotest II) also were assessed. Refractive correction was used for contrast sensitivity testing. In addition, patients were asked to complete questionnaires on their quality of vision and visual function, and they were evaluated for spectacle independence and general satisfaction.

The researchers assessed 27 patients with PMV and 28 with bilateral monofocal correction. Outcomes in the PMV group were superior for uncorrected near VA ( $0.11 \pm 0.08$  vs.  $0.56 \pm 0.16$  logMAR) and defocus curves (between −2 and −4 D); the between-group differences were significant for both parameters ( $p < .001$ ). Uncorrected intermediate VA was slightly better in the PMV group ( $0.11 \pm 0.10$  vs.  $0.20 \pm 0.18$  logMAR). The differences in uncorrected distance VA and contrast sensitivity were not significant. PMV produced better stereo vision ( $p = .008$ ) and greater spectacle independence at all distances (near and intermediate,  $p < .001$ ; far,  $p = .012$ ). Responses to the visual function questionnaire indicated that PMV was superior ( $p < .001$ ). With regard to quality of vision, responses for frequency and severity of visual disturbances were similar for the two groups. Patient satisfaction was high in both groups.

Overall, these results suggest that PMV is well suited for patients who wish to avoid spectacles, said the authors. Vision outcomes are good, and the photopic effects typical of bilateral multifocal correction are less common with the PMV approach.

—Summaries by Lynda Seminara